Volume 32, Issue 15S, Part I of II

May 20, 2014

# Journal of Clinical Oncology

Official Journal of the
American Society of Clinical Oncology

ASCO 50 YEARS 1964-2014

## 2014 ASCO Annual Meeting Proceedings

50th Annual Meeting
May 30-June 3, 2014
McCormick Place
Chicago, IL

www.jco.org

ASCO

# 50th
# Annual Meeting of the American Society of Clinical Oncology May 30-June 3, 2014

Chicago, Illinois

*2014 Annual Meeting Proceedings Part I*

(a supplement to the *Journal of Clinical Oncology*)

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# JOURNAL OF CLINICAL ONCOLOGY

Official Journal of the American Society of Clinical Oncology

ASCO 50 YEARS 1964-2014

## CONTENTS

### 2014 ASCO ANNUAL MEETING PROCEEDINGS



*continued on following page*

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# American Society of Clinical Oncology
# 50th Annual Meeting

# 2014 Abstracts

## Descriptions of Scientific Sessions

***Plenary Session***
The Plenary Session includes abstracts selected by the Scientific Program Committee as having practice-changing findings of the highest scientific merit.

***Oral Abstract Sessions***
Oral Abstract Sessions include didactic presentations of abstracts of the highest scientific merit, as determined by the Scientific Program Committee. Experts in the field serve as Discussants and provide comprehensive themed discussions of the findings from the abstracts.

***Clinical Science Symposia***
Clinical Science Symposia provide a forum for science in oncology, combining didactic lectures on a specific topic with the presentation of abstracts. Experts in the field serve as discussants to place studies in the appropriate context and critically discuss the conclusions in terms of their applicability to clinical practice.

***Poster Highlights Sessions***
Poster Highlights Sessions feature selected abstracts of clinical research in poster format. The posters are grouped by topic and are on display for a specified time with opportunities for networking, followed by a discussion session in which experts provide commentary on the research findings.

***General Poster Sessions***
General Poster Sessions include selected abstracts of clinical research in poster format. The posters are grouped by topic and are on display for a specified time. Trials in Progress abstract presentations are presented within each track, and are designed to facilitate awareness of open, ongoing clinical trials of any phase.

***Publication-Only Abstracts***
Publication-only abstracts were selected to be published online in conjunction with the Annual Meeting, but not to be presented at the Meeting.

*All presented and publication-only abstracts are citable to this* Journal of Clinical Oncology *supplement. For citation examples, please see the Letter from the Editor.*

**This publication contains abstracts selected by the ASCO Scientific Program Committee for presentation at the 2014 Annual Meeting. Abstracts selected for electronic publication only are available in full-text versions online through ASCO.org and JCO.org. The type of session, the day, and the session start/end times are located to the right of the abstract number for scheduled presentations. To determine the location of the abstract session, refer to the Annual Meeting Program or the iPlanner, the online version of the Annual Meeting Program, available at am.asco.org.**

**Dates and times are subject to change.**
**All modifications will be posted on am.asco.org.**

The deadline for abstract submission for the 2015 Annual Meeting is
Tuesday, February 3, 2015, at 11:59 PM (EST).

# Letter from the Editor

The *2014 ASCO Annual Meeting Proceedings Part I* (a supplement to the *Journal of Clinical Oncology*) is an enduring record of the more than 2,900 abstracts selected by the ASCO Scientific Program Committee for presentation at the 50th ASCO Annual Meeting. Accepted abstracts not presented at the meeting are included in the online supplement to the May 20 issue of *Journal of Clinical Oncology* at JCO.org.

The majority of abstracts selected for presentation are included here in full and are categorized by scientific track. After the Annual Meeting, abstracts can be accessed online through ASCO University's Meeting Library (meetinglibrary.asco.org/abstracts). Online abstracts include the full list of abstract authors and their disclosure information.

Late-Breaking Abstracts are represented here by abstract title and presenting author only. The full-text versions of these abstracts will be publicly released through ASCO.org during the Annual Meeting. Late-Breaking Abstracts will also be included in the *2014 ASCO Annual Meeting Proceedings Part II*, an online supplement to the June 20 issue of *Journal of Clinical Oncology* on JCO.org. Print versions of these abstracts will be available onsite at the Annual Meeting in the *ASCO Daily News*.

All abstracts carry *Journal of Clinical Oncology* citations. The following are citation examples for print and electronic abstracts:

J Clin Oncol 32:5s, 2014 (suppl; abstr LBA1)

J Clin Oncol 32, 2014 (suppl; abstr e12000)

Should you have any questions or comments about this publication, we encourage you to provide feedback by contacting us at abstracts@asco.org.

Michael A. Carducci, MD
Editor, *2014 ASCO Annual Meeting Proceedings*

# JOURNAL OF CLINICAL ONCOLOGY

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# ASCO Abstracts Policy

## Public Release of Abstracts

ASCO has implemented changes to its abstract distribution to ensure simultaneous public release of important scientific information. Please note the new release schedule.

The abstracts published in the *2014 ASCO Annual Meeting Proceedings Part I,* including those abstracts published but not presented at the Meeting, were publicly released by ASCO at 5:00 PM (EDT) on Wednesday, May 14, 2014. These abstracts are publicly available online through ASCO.org, the official website of the Society. Late-Breaking Abstracts, which include all Plenary Abstracts, will be publicly released according to the following schedule:

- Late-Breaking Abstracts presented in a press briefing or scientific presentation (whichever comes first) on Friday, May 30, will be publicly released Friday, May 30, through ASCO.org at 2:00 PM (EDT). These abstracts will also be available in Section D of *ASCO Daily News* on the day of their scientific presentation.
- Late-Breaking Abstracts presented in a press briefing or scientific presentation (whichever comes first) on Saturday, May 31, will be publicly released Saturday, May 31, through ASCO.org at 7:30 AM (EDT). These abstracts will also be available in Section D of *ASCO Daily News* on the day of their scientific presentation.
- Late-Breaking Abstracts presented in a press briefing or scientific presentation (whichever comes first) on Sunday, June 1, will be publicly released Sunday, June 1, through ASCO.org at 7:30 AM (EDT). These abstracts will also be available in Section D of *ASCO Daily News* on the day of their scientific presentation.
- Late-Breaking Abstracts presented in a press briefing or scientific presentation (whichever comes first) on Monday, June 2, or Tuesday, June 3, will be publicly released Monday, June 2, through ASCO.org at 7:30 AM (EDT). These abstracts will also be available in Section D of *ASCO Daily News* on the day of their scientific presentation.

In the unlikely event that ASCO publicly releases an abstract in advance of the scheduled time, the release will be publicly announced on ASCO.org.

## Abstract Notice

All abstracts presented at and published in conjunction with the Annual Meeting are included in online supplements to the *Journal of Clinical Oncology*. The abstracts released on May 14, 2014, are included in the May 20 (Vol. 32, No. 15S) issue (*2014 Annual Meeting Proceedings Part I*), and the Late-Breaking Abstracts, released on a daily basis during the Meeting, are included in the June 20 (Vol. 32, No. 18S) issue (*2014 Annual Meeting Proceedings Part II*).

# ASCO Conflict of Interest Policy and PI Exceptions

In compliance with standards established by the ASCO Conflict of Interest Policy (*J Clin Oncol*. 2006; 24[3]:519–521) and the Accreditation Council for Continuing Medical Information (ACCME), ASCO strives to promote balance, independence, objectivity, and scientific rigor through disclosure of financial and other interests, and identification and management of potential conflicts. According to the Society's Conflict of Interest Policy, the following financial and other relationships must be disclosed: employment or leadership position, advisory role, stock ownership, honoraria, research funding, expert testimony, and other remuneration (*J Clin Oncol*. 2006;24[3]:520).

The ASCO Conflict of Interest Policy requirements apply to all abstract authors. Per the ASCO Conflict of Interest Policy Implementation Plan for CME Activities, all Oral Abstract Presenters will be subject to the same disclosure review and management strategies as faculty who participate in ASCO CME activities.

For clinical trials that began accrual on or after April 29, 2004, the Conflict of Interest Policy places some restrictions on the financial relationships between a trial's Principal Investigator(s) (PI) and the trial's company sponsor (*J Clin Oncol*. 2006;24[3]:521). If a PI holds any restricted relationships, his or her abstract may be ineligible for placement in the 2014 Annual Meeting unless the Ethics Committee grants an exception. Exceptions are generally not granted for PIs who have employment relationships with their trial's company sponsor or stock in the company sponsor. Abstracts that receive exceptions will be subject to additional management strategies, including but not limited to additional peer review, advance slide review, and session audits. ASCO will collect information on accrual initiation date, financial relationships of the principal investigator, and National Institutes of Health (NIH) funding upon abstract submission. NIH-funded trials are exempt from the PI restrictions in the Conflict of Interest Policy. Abstracts for which authors have been granted an exception in accordance with ASCO's Policy are designated with a caret symbol ( ) in the *Annual Meeting Proceedings*.

For more information on the ASCO Conflict of Interest Policy, the Conflict of Interest Policy Implementation Plan for CME Activities, and the restrictions on PIs, please visit asco.org/rwc.

# ABSTRACTS
# American Society of Clinical Oncology
# 50th Annual Meeting
# May 30–June 3, 2014
# McCormick Place
# Chicago, IL

## SPECIAL AWARD LECTURE ABSTRACTS

### David A. Karnofsky Memorial Award and Lecture
### Saturday, May 31, 9:30 AM

**Understanding.**

*H. M. (Bob) Pinedo, MD, PhD; VUmc Cancer Center, Amsterdam, Netherlands*

Translational research assists us in taking treatments from bench to bedside, and vice versa, and in understanding at a molecular level what changes are taking place in our patients. In recent decades, clinical oncology has developed into a multidisciplinary profession with specialists working in harmony when treating the patient, but also when performing translational research. We are witnessing today that we can treat patients better by using the biologic and molecular properties of their cancer cells and their tumor. Sequential biopsies, modern imaging, proteomics, and genomics are becoming essential guides to personalized therapies. Society should get prepared for targeted treatment. Periods of heavy chemotherapy are being replaced with less onerous treatment, while cancer is becoming a chronic disease. Our translational research, conducted over the past decades, will be illustrated by reviewing biologic and molecular studies in various domains of cancer treatment, including drug resistance, angiogenesis, radiosensitization, epigenetics, and immunotherapy. Notwithstanding all these developments, the oncologist must know his or her patient. David Karnofsky is our example par excellence in understanding the disease and his patient, and being available day and night to guarantee continuity of care.

### Science of Oncology Award and Lecture
### Sunday, June 1, 1:00 PM

**Do some human cancers originate from infections transmitted from domestic animals?**

*Harald zur Hausen, MD; German Cancer Research Center, Heidelberg, Germany*

A number of viral, bacterial, and parasitic diseases originate from transmissions of these infections by contact with animals or their products, among them rabies, hemorrhagic fevers, borreliosis, brucellosis, and several helminth infections. Conversely, latent and persistent infections with several agents prevalent in human populations do not or only rarely cause symptoms in the human host. Some of them, however, such as the polyomaviruses BK and JC, specific types of adenoviruses, and Epstein-Barr virus are relatively effective inducers of malignant tumors in rodents or new world primates, commonly in species in which they are unable to replicate. This prompted the consideration of whether similar agents exist in our domestic animals, not tumorigenic in their native hosts, but potentially causing cancer in a nonpermissive host, specifically after infection of humans. This resulted in an analysis of human cancers linked to dietary habits. In particular, cancer of the colon stands out, being linked to the consumption of red meat and processed red meat. The global epidemiology suggests a remarkable geographic correlation of these dietary habits with the distribution of domestic cattle (*Bos taurus*). This will be discussed in more detail. Chemical carcinogens arising in the preparatory steps for meat consumption have been incriminated in the past, although they are also produced in similarly prepared poultry or fish. Long-time consumption of the latter two does not increase the risk for colon cancer. For this reason, a potentially oncogenic infectious factor was postulated in beef, probably interacting synergistically with some of the chemical carcinogens. This resulted in the analysis of sera from healthy cattle for the presence of infectious agents interacting with human cells. The available results will be presented.

### ASCO–American Cancer Society Award and Lecture
### Sunday, June 1, 8:00 AM

**Carpe diem: Time to seize the opportunity for cancer prevention.**

*Graham A. Colditz, MD, DrPH; Siteman Cancer Center and Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St. Louis, MO*

The United States and other high-income nations have long developed a "cancer culture"—one marked by lifestyle profiles that together greatly increase cancer risk. There is immense potential to reduce the cancer burden by focusing prevention resources in a relatively small number of key areas. At least half of the roughly 1.6 million new cases of cancer diagnosed each year in the United States could be prevented using knowledge that we already have. Available strategies for cancer prevention include vaccination and safe sexual practices, smoking cessation, physical activity, healthy body weight, healthy diet, moderate or no alcohol intake, sun protection and avoidance of indoor tanning, and screening. Yet budget realities remain focused on areas other than prevention. To address the burden of cancer as effectively and efficiently as possible, prevention and control must become a true resource priority, with funding on par with other key areas. We need the political will to allocate resources, prioritize incentives and rewards, and implement regulations that reinforce behaviors that will prevent cancer.

## B. J. Kennedy Award and Lecture for Scientific Excellence in Geriatric Oncology
## Saturday, May 31, 4:45 PM

**Adventures in geriatric oncology: Inspirations, lessons learned, and hopes for the future.**
*Stuart M. Lichtman, MD, FACP; Memorial Sloan Kettering Cancer Center, New York, NY*

The field of geriatric oncology is now well within its third decade. B. J. Kennedy in his presidential address of 1988 laid out in great detail the importance of focusing on the older patient with cancer. He discussed the epidemiologic shift with the resultant aging of the population, the increased number of older patients with cancer, and relative shortage of physicians to address this need. The issues he anticipated have come true. Fortunately, he stimulated the interest of many to pursue this study. My adventures in geriatric oncology have paralleled the development of the field. The encouragement and foresight of the original investigators stimulated my interest. Inspiration came not only from colleagues, but also the older patients who provided their unique perspective on aging. Geriatric oncology in its infancy was a disparate group of clinicians, geriatrics, and investigators. In its adolescence there was the development of studies in the cooperative groups and a few institutions leading to the participation of national and international organizations. Our European colleagues, in particular, led this advance. Geriatric oncology now is not yet middle-aged. In this maturation of the field, there are thriving organizations (International Society of Geriatric Oncology, SIOG; Cancer and Aging Research Group), a unique journal: the *Journal of Geriatric Oncology,* and the strong commitment by ASCO. By witnessing and participating in this development, many lessons have been learned, which will be discussed. The current young investigators are leading the charge for geriatric oncology as an increasingly productive area of study, and they will help realize B. J. Kennedy's hope for the future to improve the care of the older patient with cancer.

## Pediatric Oncology Award and Lecture
## Saturday, May 31, 1:15 PM

**Childhood cancer survivors: A lifetime of risk and responsibility.**
*Leslie L. Robison, PhD; Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, TN*

Population-based statistics demonstrate that 83% of patients diagnosed with cancer in the first two decades of life survive five or more years. Among these five-year survivors, 95% are projected to be living 15 years following their cancer diagnosis. It is estimated that the prevalence of pediatric cancer survivors in the United States now exceeds 420,000. This growing population of cancer survivors represents a group at high-risk for experiencing long-term treatment-related morbidity and mortality. Results from large cohorts show that when compared to the general population, five-year survivors have an 8- to 10-fold increased risk of dying from a subsequent malignancy, cardiac event, or pulmonary cause. Clinical cohorts are now documenting that 80% of adult survivors of childhood cancer will have at least one serious/disabling or life-threatening chronic health condition by age 45. Knowledge relating to the prevalence of, and risk factors for, adverse health-related and quality-of life outcomes is increasing at a rapid rate with the expanding research base from established survivor cohorts. The challenge is to critically evaluate this information and rapidly translate it into clinical care guidelines for the long-term follow-up of childhood cancer survivors to facilitate early detection and treatment of therapy-related late effects, with the objective of minimizing excess morbidity and early mortality. Beyond the formulation and dissemination of clinical care guidelines, it is now important to also focus greater attention on translating knowledge from observational research to the development and the testing of intervention-based approaches, which are designed to avoid or ameliorate adverse outcomes. There is a role not only for researchers and health care providers, but also for survivors and their families, governing bodies, and advocacy groups in helping to understand and overcome the barriers that prevent survivors from receiving optimal care to minimize adverse health-related outcomes and to maximize quality-of-life outcomes.

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**LBA1** **Plenary Session, Sun, 1:00 PM-4:00 PM**

**Randomized comparison of adjuvant treatment with aromatase inhibitor (AI) exemestane (E) plus ovarian function suppression (OFS) versus tamoxifen (T) plus OFS in premenopausal women with hormone receptor-positive (HR+) early breast cancer (BC): Joint analysis of IBCSG TEXT and SOFT trials.** *Presenting Author: Olivia Pagani, Institute of Oncology of Southern Switzerland, SAKK & IBCSG, Lugano Viganello, Switzerland*

**The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Sunday, June 1, 2014, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2014, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Sunday edition of the *ASCO Daily News*.**

**LBA2** **Plenary Session, Sun, 1:00 PM-4:00 PM**

**Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPrCa): An ECOG-led phase III randomized trial.** *Presenting Author: Christopher Sweeney, Dana-Farber Cancer Institute, Boston, MA*

**The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Sunday, June 1, 2014, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2014, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Sunday edition of the *ASCO Daily News*.**

**LBA3** **Plenary Session, Sun, 1:00 PM-4:00 PM**

**CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC).** *Presenting Author: Alan P. Venook, University of California, San Francisco, San Francisco, CA*

**The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Sunday, June 1, 2014, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2014, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Sunday edition of the *ASCO Daily News*.**

**LBA4** **Plenary Session, Sun, 1:00 PM-4:00 PM**

**First results from the phase III ALTTO trial (BIG 2-06; NCCTG [Alliance] N063D) comparing one year of anti-HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T→L), or their combination (T+L) in the adjuvant treatment of HER2-positive early breast cancer (EBC).** *Presenting Author: Martine J. Piccart-Gebhart, Jules Bordet Institute, Breast International Group, Brussels, Belgium*

**The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Sunday, June 1, 2014, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2014, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Sunday edition of the *ASCO Daily News*.**

**500** **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

**Bevacizumab (Bv) in the adjuvant treatment of HER2-negative breast cancer: Final results from Eastern Cooperative Oncology Group E5103.** *Presenting Author: Kathy Miller, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN*

**Background:** Bv improves progression-free survival (PFS) but not overall survival (OS) in MBC. E5103 added Bv to adjuvant therapy in patients (pts) with HER2- disease. **Methods:** Pts were assigned 1:2:2 to one of three treatment arms. In addition to doxorubicin and cyclophosphamide followed by wkly paclitaxel, pts received either placebo (Arm A – AC>T), Bv during chemo (Arm B - BvAC>BvT), or Bv during chemo -> Bv monotherapy for 10 cycles (Arm C – BvAC>BvT>Bv). Randomization was stratified and Bv dose adjusted for choice of AC schedule. Radiation and hormonal therapy were administered concurrently with Bv in Arm C. The primary endpoint was invasive disease free survival (IDFS) requiring 426 IDFS events across Arms C and A to detect hazard ratio (HR) of 0.75 with 80% power using a one-sided 2.5% (two-sided 5%) stratified log rank test. **Results:** 4,994 pts were enrolled. Median age 52; 64% ER+, 27% LN-; 80% received ddAC. Chemotherapy associated adverse events (AEs) including myelosuppression (Grade 4 neutropenia 17/20/21%) and neuropathy (Grade > 3 - 8/8/9%) were similar across all arms. Grade > 3 hypertension/thrombosis/proteinuria/hemorrhage was reported by 8/3/<1/<1% of Bv-treated pts. The cumulative incidence of clinical CHF at 15 mos. was 1.0/1.9/3.0%. Emergent unblinding was uncommon and similar among all arms (3/4/4% respectively) but Bv exposure was less than anticipated with ~24% of pts in Arm B and ~55% of pts in Arm C discontinuing Bv before completing planned therapy. With a median follow-up of 47.5 mos. and 430 IDFS events across Arms C and A, 5-yr IDFS (95%CI) was 77%(70.9%-81.2%/76%(71.5%-79.8%)/80%(77%-82.5%) respectively. **Conclusions:** Incorporation of Bv into anthracycline and taxane containing adjuvant therapy does not improve IDFS or OS in pts with high risk HER2- breast cancer. Bv did increase AEs but no unexpected AEs were encountered. Longer duration therapy is unlikely to be feasible given the high rate of early discontinuation due to all causes. Clinical trial information: NCT00433511.

| | C vs A HR (0.95 CI) | Two-sided P-value |
|---|---|---|
| **IDFS overall** | 0.87 (0.70-1.08) | 0.17 |
| **ER/PgR +** | 0.93 (0.77-1.22) | 0.61 |
| **ER/PgR -** | 0.77 (0.57-1.03) | 0.08 |
| **OS Overall** | 0.89 (0.68-1.17) | 0.41 |
| **ER/PgR +** | 1.01 (0.67-1.53) | 0.97 |
| **ER/PgR -** | 0.77 (0.53-1.12) | 0.17 |

**501** **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

**Arobase: A phase III trial of exemestane (Exe) and bevacizumab (BEV) as maintenance therapy in patients (pts) with metastatic breast cancer (MBC) treated in first line with paclitaxel (P) and BEV—A Gineco study.** *Presenting Author: Olivier Tredan, Département d'Oncologie Médicale, Centre Léon Bérard, Lyon, France*

**Background:** Combination of P+BEV significantly improves progression-free survival (PFS) in MBC pts, but is associated with adverse events (AEs), mainly neuropathy and fatigue worsening over time. Endocrine therapy (ET) combined to BEV has been proven tolerable and may be a option as maintenance therapy after P+BEV. **Methods:** in this prospective, randomized, open label, phase III study, pts with histologically confirmed ER+ HER2- locally advanced or MBC, who had not progressed after 16-24 weeks of 1st-line P+BEV therapy, were randomized to P+BEV continuation vs ET+BEV (Exe 25 mg/d+BEV 15 mg/kg q3w). Primary endpoint was PFS. To demonstrate an improvement in the 6-month PFS rate (PFS-6m) from 50% with P+BEV to 65% with ET+BEV (2-sided $\alpha$=5%) with 80% power, 141 events were requiered and 198 pts were planned. An interim analysis (IA) was planned after 40% of required events. Secondary endpoints included overall survival (OS) and toxicity. **Results:** At the cut-off date for the IA (May 2013), 113 pts were included, 98 were analyzable. Median age was 55 (range 35-86). ET was given as adjuvant therapy in 64% of pts and in the metastatic setting in 24%. Median follow up was 9.7 months (range 0.8-28.3). PFS-6m was 70% (95% confidence interval (CI) 54, 81.5) with P+BEV and 54% (95% CI 38.5, 67.2) with ET+BEV (HR 1.2, 95% CI (0.7, 1.9), p=0.56). Given these interim results, the probability to show statistically significant PFS at the end of the study was 7%. Deaths were reported for 11 pts in the P+BEV arm vs 6 pts in the ET+BEV arm (median OS not reached). Grade 3-4 AEs rates were lower with ET+BEV (fatigue: 4% of pts vs 14%); neuropathy: 0% vs 12%; pain: 2% vs 8%; neutropenia: 0% vs 12%), as well as serious AEs related to treatment (13% vs 24%). Based on both safety and efficacy results, the IDMC decided to definitely stop the enrollment and to keep patients under tretment in the protocol.Follow-up data will be updated for the final analysis. **Conclusions:** The efficacy hypothesis was not reached, despite a better safety profile of the ET+BEV maintenance therapy. Exploratory analyses are planned to identify potential subgroups benefiting from it. Clinical trial information: NCT01303679.

**502** **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

**A phase 1b study of trebananib plus paclitaxel (P) and trastuzumab (T) in patients (pts) with HER2+ locally recurrent or metastatic breast cancer (MBC).** *Presenting Author: Peter Andrew Kaufman, Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, NH*

**Background:** Trebananib (AMG 386) suppresses tumor angiogenesis by neutralizing the interaction between the Tie2 receptor and its ligands, angiopoietin-1 and -2. This study evaluated the tolerability and efficacy of trebananib plus P and T as first-line treatment in $HER2^+$ MBC. **Methods:** Pts in cohorts A1 and A3 received open-label trebananib (A1, 10 mg/kg; A3, 30 mg/kg) IV QW plus P 80 mg/m$^2$IV QW and T (loading dose of 8 mg/kg, then 6 mg/kg Q3W). If dose-limiting toxicity (DLT) criteria were not met, each cohort was expanded to 20 pts. A3 enrollment was initiated if DLT criteria were not met for A1. Results describing trebananib plus capecitabine and lapatinib will be reported elsewhere. Endpoints were the incidence of DLTs and treatment-emergent adverse events (AEs; primary); and efficacy and pharmacokinetics (PK). **Results:** Of 40 enrolled pts in A1 (n = 20) and A3 (n = 20), two DLTs occurred across A1 (grade 3 transient ischemic attack, n = 1) and A3 (grade 3 increased gamma-glutamyltransferase, n = 1). The most common (> 50%) AEs in A1/A3 were peripheral edema (n = 13/15), diarrhea (n = 13/14), alopecia (n = 13/13), fatigue (n = 15/9), nausea (n = 11/13), nail disorder (n = 12/7), and rash (n = 12/6). Grade ≥ 3 AEs occurring in > 10% of pts were peripheral neuropathy (n = 4/4), peripheral sensory neuropathy (n = 4/0), and dyspnea (n = 3/1). In evaluable pts (A1/A3, n = 20/17), confirmed objective response rates (ORRs) were 80% (complete responses [CRs], n = 0; partial responses [PRs], n = 16) in A1 and 88.2% (CRs, n = 3; PRs, n = 12) in A3. The median duration of response (DOR; 95% CI) was 12.6 (4.3 – 20.2) months in A1 and 16.8 (8.2 – not evaluable) months in A3. Median (95% CI) progression-free survival (PFS) was 14.5 (6.9 – 20.6) months and 18.7 (10.4 – not evaluable) months in A1 and A3, respectively. No apparent PK drug-drug interaction was observed. Trebananib exposure appeared dose proportional with intersubject variability of 40.5% and 28.6% in A1 and A3, respectively. **Conclusions:** In this phase 1b study, trebananib at 10 mg/kg and 30 mg/kg plus P and T appeared tolerable. The ORR, DOR, and PFS observed in this study suggest that further investigation of trebananib in this setting is warranted. Clinical trial information: NCT00807859.

**503** **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

**Effect of obesity in premenopausal ER+ early breast cancer: EBCTCG data on 80,000 patients in 70 trials.** *Presenting Author: Hongchao Pan, Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom*

**Background:** Obesity (body mass index [BMI] ≥30 kg/m$^2$) is reportedly associated with worse prognosis in early breast cancer. But, this association could depend strongly on estrogen receptor (ER) positivity and ovarian activity (or young age). **Methods:** Through EBCTCG, anonymised information on each individual with early breast cancer in any trial is requested periodically, including BMI (at randomisation), ER status, menopausal status, age, treatment, recurrence and death. The global Steering Committee has requested analyses of the independent effects of BMI on outcome. Results are provided for 80,000 patients (in 70 trials) who had all these data items; most also had data on tumour diameter and nodal status. Mean follow-up was 8 woman-years. Cox regression (stratified for trial and treatment, and adjusted for age) assesses the relevance of BMI to mortality with recurrence (as a surrogate for the relevance of BMI to breast cancer mortality). Few had BMI <20 kg/m$^2$; the standard WHO cut-points define overweight (25-30 kg/m$^2$). **Results:** In 20,000 women with ER-poor disease there was little association of BMI with breast cancer mortality, and none after adjustment for tumour diameter and nodal status. In 60,000 with ER+ disease, BMI was positively associated with breast cancer mortality in pre/peri- and in post-menopausal women (each 2P<0.00001). But, after adjustment for tumour characteristics the association remained clearly significant only in 20,000 pre/peri-menopausal women with ER+ disease (breast cancer mortality rate ratio comparing BMI ≥30 versus BMI 20-25 kg/m$^2$ [RR] = 1.34, 95%CI 1.22-1.47, 2P<0.00001, with a steady trend between BMI <25, 25-30, 30-35 and ≥35 kg/m$^2$); little association remained in 40,000 post-menopausal women with ER+ disease (RR=1.06, 95%CI 0.99-1.14, 2P=0.12; heterogeneity between RRs 2P<0.0001). In analyses of ER+ disease subdivided by age (instead of menopausal status), obesity appeared importantly relevant only to age about 55 years. Findings were not materially altered by excluding the first 5 years of follow-up. **Conclusions:** In women with early breast cancer, obesity appears strongly independently related to breast cancer mortality only in pre/peri-menopausal ER+ disease.

**504** **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

**Prognostic associations of 25OH vitamin D in NCIC CTG MA.21, a phase III adjuvant RCT of three chemotherapy regimens (EC/T, CEF, AC/T) in high-risk breast cancer (BC).** *Presenting Author: Ana Elisa Lohmann, Mount Sinai Hospital / University of Toronto, Toronto, ON, Canada*

**Background:** Low vitamin D (VitD) has been associated with poor outcomes in BC. We examined in MA.21 the association of VitD blood levels with relapse-free-survival (RFS) in all patients, and in BC subtypes. **Methods:** Fasting blood was collected pre-chemotherapy in 935/2,104 ((44.4%) of subjects (blood collection was initiated part-way through the trial); serum was frozen at -80C and shipped on dry ice to Mount Sinai Hospital (Toronto); it was analyzed for Vit D (radioimmunoassay, Diasorin) 25(OH)D (nmol/L). VitD underwent a $\lambda=0.5$ Box-Cox transformation for analysis to reduce asymmetry; data were back-transformed for reporting. VitD was assessed as a transformed continuous factor, and by quartiles and IOM categories (<40, [40-50), [50-125), >125 nmol/L). Univariate and multivariate (mv) assessments were with Cox models, adjusted for treatment, stratification factors, and imbalances in who had VitD assessed. **Results:** Median age was 47.8 years; most patients were white (91.6%), premenopausal (69.4%) with good performance status (PS) 0-1 (99.9%). The majority presented with grade III (52%), HER2 neg (66.6%), HER2 missing (22.9%), ER pos (61.9%), T1-2 (89.4%), N+ (72.7%) BC. 52.1% underwent mastectomy and 74.3% received adjuvant radiotherapy. Compared to the full MA.21 population, those with VitD levels were marginally (but significantly) more likely to be white, PS 1 or 2, to have undergone mastectomy and to have ER+, HER2 neg tumors. Mean Vit D was 69.7 nmol/L [95% CI (68.1-71.3)] nmol/L. The majority (752/935 = 80.5%) had levels > 50nmol/L (20ng/ml), considered adequate by the Institute of Medicine (IOM). In adjusted mv analyses, (continuous) VitD was not associated with RFS (HR 0.98, 95% CI (0.93-1.03); p=0.36) or categorical variable (between quartiles, p=0.20-0.43; between IOM categories, p=0.33-0.78). There were no significant differences in mean VitD levels or association of VitD with RFS in tumor subtypes (ER+, HER2- / any ER, HER2+ / ER-, HER2-; p=0.14-0.50). **Conclusions:** There is no evidence that VitD was associated with RFS in MA.21; the majority of subjects had adequate VitD levels at study entry. Clinical trial information: NCT00014222.

**LBA505** **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

**Phase III trial (Prevention of Early Menopause Study [POEMS]-SWOG S0230) of LHRH analog during chemotherapy (CT) to reduce ovarian failure in early-stage, hormone receptor-negative breast cancer: An international Intergroup trial of SWOG, IBCSG, ECOG, and CALGB (Alliance).** *Presenting Author: Halle C. F. Moore, Cleveland Clinic, Cleveland, OH*

**The full, final text of this abstract will be available at abstracts.asco.org at 2:00 PM (EDT) on Friday, May 30, 2014, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2014, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Saturday edition of *ASCO Daily News*.**

**506** **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

**Gene expression signatures in pre- and post-therapy (Rx) specimens from CALGB 40601 (Alliance), a neoadjuvant phase III trial of weekly paclitaxel and trastuzumab with or without lapatinib for HER2-positive breast cancer (BrCa).** *Presenting Author: Lisa A. Carey, Division of Hematology Oncology, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

**Background:** Response to chemotherapy and HER2-targeting varies by molecular subtype. In C40601, 305 patients (pts) with stage II-III HER2+ BrCa were randomized to receive 16 weeks of preoperative paclitaxel and trastuzumab (TH), T and lapatinib (TL), or THL, and were followed for pCR. Primary data were reported previously. **Methods:** Gene expression by mRNA sequencing (RNAseq) was performed on 271 pre-Rx and 136 matched post-Rx samples. RNAseq was normalized to HER2+ tumors in The Cancer Genome Atlas Project, and genomic signatures applied including intrinsic subtype and immune cell features. **Results:** 60% of pre-Rx specimens were hormone receptor+. Overall, 30% were Luminal A, 31% Luminal B, 31% HER2-Enriched, 5% Basal-like, 2% Normal-like, and 1% Claudin-Low. In-breast pCR was 46%, which varied significantly by subtype: Luminal A 35%, Luminal B 36%, Basal-Like 36%, HER2-Enriched 69% (p<0.0001). Within HER2-Enriched, pCR rates by arm were: 50% TL, 71% TH, 80% THL. pCR also varied by risk of relapse score including proliferation genes (ROR-P): high 56%, medium 44%, low 33% (p=0.01). RNAseq on pre/post-Rx pairs revealed a change in subtype prevalence to: 43% Luminal A, 3% Luminal B, 2% Basal-like, 9% Claudin-Low, 5% HER2-Enriched, and 38% Normal-like. Excluding 49 normal-like tumors, which likely represent little tumor remaining after Rx, the most frequent subtype change among 84 paired non normal-like samples was to the Luminal A subtype, which occurred in 70% of baseline Luminal B, 20% of Basal-like, and 67% of HER2-Enriched tumors. Most (87%) had decreased ROR-P scores (p<0.0001). High expression of immune signatures, especially B-cell related, were significantly associated with pCR (IgG signature high 59%, low 32%, p=0.0002). **Conclusions:** HER2-Enriched had substantially higher pCR rates to chemotherapy + HER2-targeting than other subtypes. Residual disease was enriched for Luminal A and Normal Breast-like profiles. Among HER2-Enriched, taxane plus trastuzumab alone produced pCR rates in excess of 70%, which suggests that dual HER2-targeting or more aggressive chemotherapy may not be needed in this biologic subtype. Clinical trial information: NCT00770809.

**507** **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

**AVATAXHER: An open-label, randomized, multicenter study investigating the addition of bevacizumab (B) to neoadjuvant trastuzumab (T) plus docetaxel (D) in patients with early stage HER2-positive breast cancer (HER2+ BC) stratified according to PET change after one therapy cycle.** *Presenting Author: Bruno P. Coudert, Department of Medical Oncology, Centre Georges-Francois Leclerc, Dijon, France*

**Background:** T-based neoadjuvant chemotherapy achieves pCR rates of ~50% in HER2+ BC, enabling frequent conservative surgery. Pre-clinical and clinical data support the synergistic combination of B and T. The ph II AVATAXHER trial (EUDRACT 2009-013410-26) investigated whether adding B to neoadjuvant T+D improved pCR rates in tumors with a low likelihood of attaining pCR (predicted based on relative change in FDG tumoral uptake [ΔSUV] after one cycle of T+D). **Methods:** Patients were ≥18 yrs old with stage T2/3, N0/1 HER2+ BC. Patients received two 3-weekly cycles of T (8 mg/kg, then 6 mg/kg) and D (100 mg/m$^2$). Those with ≥70% ΔSUV in PET values between cycle 1 and 2 received four more cycles of T+D, one cycle of T, then surgery (standard arm). Those with <70% ΔSUV were randomized 2:1 to four cycles of T+D+B (15 mg/kg; arm a) or T+D (arm b), then one T cycle and surgery. The primary endpoint was pCR rate at surgery. The positive (PPV) and negative predictive value (NPV) of ΔSUV on pCR rate and safety were also investigated. **Results:** 152 patients were recruited at 26 sites (10 were withdrawn pretreatment; ITT=142). 37/69 (53.6%) patients in the standard arm achieved pCR, 21/48 (43.8%) in arm a and 6/25 (24.0%) in arm b. pCR rates in patients with hormone receptor –ve/+ve disease were: 69.0%/42.5% (standard arm), 57.9%/34.5% (arm a), and 40.0%/13.3% (arm b). Surgery (133 pts) was conservative in 84.8% of patients with surgery in the standard arm, 67.4% in arm a, and 62.5% in arm b. In patients without B, ΔSUV after one cycle predicted pCR with a PPV of 52.9% and a NPV of 75%. Toxicity was mild and included asthenia, myalgia, and increased lacrimation (all pts had ≥1 AE). Grade 3/4 AEs (in 31% of pts) included neutropenia (8.6% pts), febrile neutropenia (3.6%), myalgia (3.6%), asthenia (2.9%), and nail toxicity (2.9%). **Conclusions:** Adding B to neoadjuvant T+D, in tumors with a low likelihood of pCR predicted by PET ΔSUV, increased the pCR rate from 24.0% to 42.5%. PET ΔSUV, by selecting low responding HER2+ tumors, may be a useful tool for optimizing neoadjuvant therapy for HER2+ BC. Clinical trial information: 2009-013410-26.

**508 Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

**Efficacy of adjuvant trastuzumab (T) compared with no T for patients (pts) with HER2-positive breast cancer and tumors ≤ 2cm: A meta-analysis of the randomized trastuzumab trials.** *Presenting Author: Ciara Catherine Maria O'Sullivan, National Cancer Institute, Bethesda, MD*

**Background:** Adjuvant T plus chemotherapy improves disease-free survival (DFS) and overall survival (OS) vs. chemotherapy alone for pts with early stage HER2-positive breast cancer. We conducted a meta-analysis to estimate DFS and OS for pts with small tumors (≤2cm) in the T arms from 5 of the 6 randomized adjuvant trastuzumab trials. Pts with tumors ≤2cm, with 0 or 1 positive lymph nodes, and hormone receptor (HR) positive disease had a 5-year DFS of 91% and a 5-year OS of 97% (O'Sullivan, SABCS 2013; abstract:1327). We now plan to conduct an additional meta-analysis to assess the efficacy of T compared with no T for pts with small tumors (≤2cm). **Methods:** Six randomized controlled trials (RCT) were identified by a Medline search from 2004-2013. Trial groups from 5 phase III RCTs provided data (HERA, NCCTG N9831, NSABP B31, PACS 04, and FinHER).In total, 11,200 pts were randomized in these 5 trials;4,220 of whom had ≤2cm tumors, and known number of positive axillary lymph nodes and HR status(2,588 randomized to T and 1,632 to no T). The individual pt meta-analysis will include pts with tumors ≤2 cm (T1a, T1b and T1c) and 0-1, 2-3 and ≥ 4 positive lymph nodes. Separate analyses will be performed for the two HR cohorts. This analysis will complement the published summary data-based Cochrane Review (Moja *et al.* 2012) by allowing a detailed investigation of the effect of disease characteristics, such as HR, on treatment effects. In addition to the standard Yusuf-Peto fixed effects model (Yusuf *et al.* 1985) we will investigate the impact of heterogeneity in study baseline hazards and study treatment effects by fitting random effect models.An intention to treat approach will produce a conservative effect estimate as substantial numbers of control-group pts 'crossed over' to the T arm after positive DFS results were reported. Methods to account for this 'selective crossover' are being developed; we plan to extend these methods to the meta-analysis setting to provide less conservative estimates. **Results:** Pending. **Conclusions:** A meta-analysis of 5 randomized adjuvant T trials focusing on pts with tumors ≤2cm will be performed and results submitted before the meeting.

**509 Clinical Science Symposium, Sat, 1:15 PM-2:45 PM**

**Association of genomic analysis of immune function genes and clinical outcome in the NCCTG (Alliance) N9831 adjuvant trastuzumab trial.** *Presenting Author: Edith A. Perez, Mayo Clinic, Jacksonville, FL*

**Background:** Some 20-25% of patients with HER2+ disease relapse after adjuvant trastuzumab (H). We used a genomic approach to define biological processes that predict benefit from H. **Methods:** Whole genome DASL technology was used to identify genes associated with relapse-free survival (RFS) among 1,282 patients enrolled in the N9831 adjuvant H trial (NCT00005970). Cox proportional hazard ratios (HR), adjusted for significant clinical/pathological risk factors, were used to determine the association of each gene with RFS (median follow-up 6years, 11months) for 433 patients who received chemotherapy alone and 849 patients who received chemotherapy plus H. Functional ontology analysis and network modeling were used to identify key biological processes associated with RFS in patients who received chemotherapy alone or chemotherapy plus trastuzumab. **Results:** Using probes with HR $p<0.01$, 10/13 significantly enriched biological processes associated with increased RFS ($p<0.01$) were linked to immune functions. These 10 processes defined a cohort of 87 immune function genes. Patients defined as immune function positive based on the 87 genes experienced a favorable outcome when treated with H (HR=0.55, p=0.0005). Patients who did not exhibit immune function enrichment and were treated with H did not have better RFS than patients with immune function enrichment who were treated with chemotherapy alone (HR=0.93, p=0.72). Among patients who received chemotherapy alone, enriched immune function was not associated with increased RFS (HR=1.01, p=0.96). **Conclusions:** Improved RFS following treatment with adjuvant H appears to be associated with a heightened state of immunological function. This observation may define a significant biological process that is linked to the efficacy of HER2-targeted therapy, may provide a means of predicting probability of relapse following adjuvant trastuzumab, and suggests possible routes of therapeutic enhancement.

**510 Clinical Science Symposium, Sat, 1:15 PM-2:45 PM**

**Expression of immunologic genes in triple-negative and HER2-positive breast cancer in the neoadjuvant GEPARSIXTO trial: Prediction of response to carboplatin-based chemotherapy.** *Presenting Author: Carsten Denkert, Charité-Universitätsmedizin Berlin, Institute of Pathology, Berlin, Germany*

**Background:** We have recently described tumor-infiltrating lymphocytes (TILs) as predictors of pathological complete response (pCR = ypT0ypN0) to neoadjuvant carboplatin-based chemotherapy in the GeparSixto breast cancer (BC) trial. To further dissect the immunological status in tumor tissue we have evaluated a total of 12 immunologically relevant genes, including T-cell markers, B-cell markers, chemokines and immunoregulatory factors, in 481 pretherapeutic FFPE samples. **Methods:** GeparSixto investigated the addition of carboplatin to a doxorubicin/taxane combination in HER2-positive (HER2+) or triple-negative (TN) primary BC. Trastuzumab and lapatinib were added for HER2+ disease and bevacizumab for TN disease. Expression of 12 immunologically relevant genes (CXCL9, CCL5, CD8A, CD80, CXCL13, IGKC, CD21, IDO1, PD-1, PDL1, CTLA4, FOXP3) was evaluated by quantitative RT-PCR in 481 core biopsies. **Results:** All immune mRNA markers showed a strong positive correlation with each other and with the stromal lymphocyte infiltrate. Hierarchical clustering revealed three different immune-subtypes of tumors with different expression of immunological genes and different amounts of tumor infiltrating lymphocytes. In the GeparSixto cohort all 12 immune markers were significantly linked to increased pCR rates in univariate analysis. 11 of the markers were also significant in multivariate analysis including clinical parameters. Some markers, such as CCL5, IDO1 and PDL1 provided predictive information even if controlled for TILs. CCL5, CD8A, CTLA4, IDO1 and PD1 showed a significant interaction with treatment (carboplatin vs. control) in the complete cohort. In TN disease CCL5 and CD8A provided predictive information for carboplatin response even after adjustment for TILs. **Conclusions:** Expression of immune marker mRNAs in BC is predictive for response to neoadjuvant chemotherapy. In GeparSixto, these immunological parameters can be used in addition to TILs to identify patients with increased response rates to carboplatin. The results should be validated in other breast cancer trials evaluating carboplatin therapy.

**511 Clinical Science Symposium, Sat, 1:15 PM-2:45 PM**

**Tracking tumor-specific mutations in circulating-free DNA to predict early relapse after treatment of primary breast cancer.** *Presenting Author: Nicholas C. Turner, The Royal Marsden NHS Foundation Trust, London, United Kingdom*

**Background:** Despite progress in the management of early breast cancer, a substantial number of patients relapse with metastatic breast cancer. Tumour-derived mutations can be detected in circulating free DNA (cfDNA) of patients with metastatic breast cancer. We assessed whether analysis of cfDNA can used to predict which patients will relapse following treatment of primary breast cancer. **Methods:** A cohort of 20 patients with primary breast cancer, all of whom received neoadjuvant chemotherapy (NAC) prior to surgery, had plasma samples for cfDNA extraction taken at baseline pre-NAC, post-surgery, and every 6 months in follow-up. Targeted next generation sequencing (NGS) was performed on the baseline tumour biopsy, and personalized tumour specific digital PCR assays were developed to track the identified mutations in cfDNA. **Results:** NGS identified at least one mutation in 60% (12/20) tumours. Mutation specific digital PCR assays were accurate and reproducible, with high correlation in tissue with NGS ($r^2=0.95$), and between mutation assays in cfDNA ($r^2=0.95$). Five patients relapsed at a median of 8.1 (5-16.6) months post-surgery, with the remaining patients disease free at a median of 11.5 months post-surgery. Tumour specific mutation was detected in 75% (9/12) of cfDNA samples at baseline, with no difference between patients who did, and did not, relapse early. In contrast, four patients had tumour specific DNA detectable in cfDNA in the first six months post-surgery, and all patients with detectable mutations in cfDNA relapsed. None of the patients who have not relapsed had a detectable mutation in cfDNA post-surgery (p=0.01), indicating clearance by the primary treatment. A patient with isolated relapse in the brain on trastuzumab, after a pathological complete response in the primary, did not have detectable mutations in cfDNA at relapse. **Conclusions:** We provide proof of principle that tracking tumour specific mutations in cfDNA can predict early relapse following treatment of primary breast cancer. Patients with detectable mutations in cfDNA post-primary treatment are at high risk of relapse, and may be suitable for therapeutic trials of novel agents.

**512 Poster Highlights Session (Board #1), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Obesity and menopausal status as determinants of procarcinogenic breast inflammation.** *Presenting Author: Neil M. Iyengar, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Chronic inflammation predisposes to several malignancies. We previously demonstrated an obesity → inflammation → aromatase axis in breast tissue. As obesity is a risk factor for postmenopausal (PoM) but not premenopausal (PreM) breast cancer (BC), we examined whether menopause and body mass index (BMI) independently impact breast white adipose tissue (WAT) inflammation. **Methods:** WAT was prospectively collected from patients (pts) from 04/10 – 08/13. WAT inflammation, detected by CD68 immunohistochemistry, was defined by the presence of dead/dying adipocytes surrounded by an envelope of macrophages known as crown-like structures of the breast (CLS-B). WAT area was measured with NIH Image J. Adipocyte diameter was measured with Canvas 11 Software. Endpoints: 1) CLS-B (+/-) and 2) CLS-B/cm$^2$. Clinicopathologic associations with CLS-B were analyzed by logistic regression and Fisher's exact test. **Results:** WAT (237 mastectomies, 13 abdominal reconstructions) was obtained from 238 women; median age 48 (range 22 – 90). CLS-B occurrence and number of CLS-B/cm$^2$ were greater in overweight/obese (BMI ≥25) and PoM pts compared to lean (BMI <25) and PreM pts (Table). In multivariable analyses, BMI and PoM state were independently associated with CLS-B presence (P<.01 and P=.04) and greater CLS-B/cm$^2$(P<.01 and P=.01). PoM pts had larger mean adipocyte diameter (105.2 +/- 14.0 $\mu$) than PreM pts (95.7 +/- 15.6 $\mu$; P<.01). In pts with bilateral breast WAT and abdominal WAT, concordant CLS status (+/-) was found in 49/63 (78%) and 10/13 (77%) pts, respectively. **Conclusions:** Breast WAT inflammation (both presence and severity), which we have previously linked to increased aromatase activity, is associated with both increased BMI and menopause. These findings can explain the increased risk of estrogen receptor-positive BC with obesity and PoM status and may also provide targets for rational therapies.

| Feature | CLS-B – N, (%) | CLS-B + N, (%) | P | CLS-B/cm$^2$Median, (range) | P |
|---|---|---|---|---|---|
| Lean (N=116) | 76 (66%) | 40 (34%) | | .27 (.06 – 4.37) | |
| Overweight (N=73) | 34 (47%) | 39 (53%) | | .26 (.05 – 51.85) | |
| Obese (N=48) | 5 (10%) | 43 (90%) | <.01 | .47 (.09 – 2.35) | .01 |
| Premenopausal (N=144) | 80 (56%) | 64 (44%) | | .26 (.05 – 5.49) | |
| Postmenopausal (N=93) | 35 (38%) | 58 (62%) | <.01 | .49 (.09 – 51.85) | <.01 |

**513 Poster Highlights Session (Board #2), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Association between visceral adiposity, BMI, and clinical outcomes in postmenopausal women with operable breast cancer.** *Presenting Author: Shalini Dalal, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** High body mass index (BMI), an indicator of excess body fat, has been shown to negatively impact clinical outcomes in breast cancer. Metabolic dysfunction associated with high visceral fat may be contributory. Since BMI provides no information on the anatomical distribution of stored fat, we conducted this retrospective study to examine the association between visceral adiposity parameters and clinical outcomes. **Methods:** 1,237 postmenopausal women with stage I-III invasive breast cancer, diagnosed between 1997 to 2012, and who received neoadjuvant chemotherapy (NC) were included. Computed tomography images were used to quantify visceral fat (VFA) and subcutaneous fat area (SFA). The VFA/SFA Ratio was used as a metric of regional fat distribution. We conducted univariate and multivariate analyses to examine the association between body composition parameters (VFA, SFA, VFA/SFA Ratio, BMI) and key outcomes (pathologic complete response [pCR], relapse-free [RFS], disease-specific [DSS] and overall survival [OS]), adjusting for demographics and known prognostic factors, including stage, tumor grade, receptor status and type of NC. **Results:** Median age was 58 years; 63% white. A majority were overweight (32%) or obese (44%). Median VFA was 110 cm$^2$, SFA 239 cm$^2$and VFA/SFA Ratio 0.41. In multivariate analysis, higher VFA (odds ratio [OR]=0.52; 95% CI, 0.36-0.75; p< 0.001) and lower SFA (OR=0.56; 95% CI, 0.39-0.81; p=0.002) were independently associated with lower likelihood of achieving pCR. Higher VFA/SFA Ratio was an independent predictor of lower RFS (hazard ratio [HR]=1.41; 95% CI 1.05-1.89; p=0.02), DSS (HR=1.71; 95% CI, 1.20-2.44; p=.003) and OS (HR=2.18; 95% CI, 1.52-3.13; p<0.001). **Conclusions:** Our study suggests fat-depot specific differences in breast cancer outcomes. Higher visceral fat and lower subcutaneous fat were independently associated with lower likelihood of pCR. Higher visceral to subcutaneous fat ratio predicted worse RFS, DSS and OS. The predisposition to accumulate fat viscerally versus subcutaneously may be a novel prognostic factor independent of BMI, absolute fat stores and tumor characteristics.

**514 Poster Highlights Session (Board #3), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Impact of insulin resistance (IR) on the prognosis of metastatic breast cancer (MBC) patients treated with first-line chemotherapy (CT).** *Presenting Author: Alessandra Gennari, E.O. Ospedali Galliera, Genoa, Italy*

**Background:** Higher insulin levels have been associated with a worse prognosis in early BC patients. However, the effect of higher insulin levels on MBC prognosis has not been explored so far. The aim of this study was to evaluate the influence of IR on the prognosis of HER2 negative, non-diabetic, MBC patients receiving first line CT. **Methods:** The relationship between IR, identified by HOMA index > 2.5 (fasting glucose [mmol/L] × insulin [mU/L]/22.5), and progression free (PFS) or overall survival (OS) was assessed in 87 MBC patients enrolled in a clinical trial of first line CT with non-pegylated liposomal doxorubicin 60 mg/sqm plus cyclophosphamide 600 mg/sqm Q21 days. PFS and OS were calculated by Kaplan-Meier estimation; multivariate Cox analysis was performed adjusting for age, PS, endocrine status, metastatic site and BMI. **Results:** Information on patient's IR status at baseline was available on 79 women. Median follow up was 15 months (IQR 9-21). Overall,48.4% patients wereclassified as insulin resistant (HOMA > 2.5), 41.0% were overweight (BMI 25-30) and 19.2% were obese (BMI > 30). Median age was 61 years (range 36-77); PS was 0 in 76.6% of the patients. Endocrine status was positive in 87.5% and visceral disease was present in 63.6%. Overall, median PFS was 9 months (IQR 5-18): median PFS was 14 months (IQR 8-18) in patients with HOMA index ≤2.5 and 8 months (IQR 2-17), in patients with HOMA index >2.5; HR=1.79 (95%CI: 1.01–3.18, p 0.04). By multivariate analysis, after adjustment for age, PS, endocrine status, visceral disease and BMI, a statistically significant higher risk of disease progression was detected in patients with HOMA Index > 2.5 (HR 2.28; 95%CI: 1.06 – 4.89, p = 0.035). **Conclusions:** In this study IR, indicated by an HOMA Index >2.5, was associated with a significantly worse prognosis; after adjusting for other acknowledged prognostic factors, the IR status was the only one to maintain its adverse prognostic effect. These data suggest that host metabolic status might influence the prognosis of MBC treated with CT and therefore additional alternative strategies, targeting host metabolism, should be considered in this unfavorable subset of patients.

**515 Poster Highlights Session (Board #4), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Inhibition of polo-like kinase 1 (PLK1) in endocrine-resistant ER+ breast cancer.** *Presenting Author: Valerie Malyvanh Jansen, Vanderbilt University, Nashville, TN*

**Background:** Estrogen receptor (ER)-positive breast cancers initially respond to antiestrogens but eventually become hormone-independent and recur. ER+ breast cancer cells resistant to long-term estrogen deprivation (LTED) exhibit estrogen-independent ER transcriptional activity and growth. Mechanisms of endocrine resistance remain to be fully characterized. **Methods:** A siRNA screen was used to identify kinases required for growth of MCF7/LTED cells. PLK1 RNAi oligonucleotides and the small molecule inhibitor volasertib were tested against ER+ LTED cells. Estrogen independent transcription and target genes were assessed with ER reporter assays and qRT-PCR, respectively. Volasertib and fulvestrant were used in ovariectomized athymic mice bearing MCF7 xenografts. Preclinical findings were correlated with RPPA and RNA-seq data from tumor biopsies of patients with ER+/HER2– breast cancer who received letrozole prior to surgery (NCT00651976). **Results:** A siRNA kinome screen identified Polo-like kinase 1 (PLK1) as one of the top RNAs required for MCF7/LTED cell growth. RNAi-mediated knockdown of PLK1 inhibited LTED cell growth and ligand-independent transcription of the ER-regulated genes PR, TFF1 and GREB1. Treatment with volasertib reduced ER expression, ER transcriptional activity and LTED cell proliferation. Volasertib in combination with fulvestrant reduced ER expression and inhibited growth of MCF7 xenografts more potently than either drug alone. A PCR array of ER regulated genes in MCF7/LTED cells showed that volasertib decreased expression of JUNB, FOS and BCL2L mRNAs. JUNB knockdown decreased ER transcriptional activity and ER expression suggesting that PLK1 affects ER via JUNB. Finally, in ER+/HER2– tumors from newly diagnosed postmenopausal patients, PLK1 protein and transcript levels positively correlated with resistance to letrozole as measured by high Ki67 levels in post-treatment biopsies (p=0.007; p<0.001). **Conclusions:** These data support a critical role of PLK1 in growth of antiestrogen resistant breast cancer cells. Targeting of PLK1 may abrogate resistance to endocrine therapy in ER+ breast cancer and is worthy of clinical investigation.

**516^ Poster Highlights Session (Board #5), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**SU2C phase Ib study of the PI3K$\alpha$ inhibitor BYL719 with letrozole in ER+/HER2– metastatic breast cancer (MBC).** *Presenting Author: Ingrid A. Mayer, Vanderbilt-Ingram Cancer Center, Vanderbilt University, School of Medicine, Nashville, TN*

**Background:** Mutations in *PIK3CA*, the gene encoding the p110$\alpha$ subunit of PI3K, have been associated with antiestrogen resistance in ER+ BC. In general, antiestrogen-resistant cancers retain ER and responsiveness to estradiol. This suggests that treatment of ER+ BC should include PI3K inhibitors plus antiestrogens. **Methods:** We conducted a phase Ib 3+3 dose escalation trial of letrozole (2.5 mg/day) with the PI3K$\alpha$ inhibitor BYL719 in post-menopausal patients (pts) with ER+/HER2- MBC refractory to previous endocrine therapies. BYL719 doses ranged from 300-400 mg/daily. Treatment continued until unacceptable toxicity or disease progression. Disease was assessed every 2 months. *PIK3CA* mutation status in archival tumor was obtained in all patients. **Results:** Twenty-one pts were accrued; 18 had progressed on an aromatase inhibitor (AI). Median age was 53 years (31-72); 76% of pts had bone and 61% had visceral metastases. Toxicities are summarized in Table 1. Rash was the dose limiting toxicity* at 350 mg/day dose. No pts had a complete response; 3 pts had a partial response; 6 patients had stable disease; 6 pts had disease progression; 6 pts have not yet had their first tumor assessment and 13 pts are still on treatment. Ten of 18 (56%) pts had a *PIK3CA* mutation; of these, two had a partial response, and two have been on treatment for >6 months. **Conclusions:** The combination of letrozole/ BYL719 is safe and tolerable in pts with AI-refractory ER+/HER2 MBC. The MTD and recommended dose for phase II trials of BYL719 in combination with letrozole was 300 mg/day. Grade 2-3 rash and hyperglycemia observed at this dose suggest inhibition of PI3K by BYL719. Clinical activity was not restricted to pts with *PIK3CA* mutant tumors. A correlation of *PIK3CA* mutations with clinical benefit cannot yet be fully established. Clinical responses and therapy duration will be updated at the meeting. Clinical trial information: NCT01791478.

| | 300 mg (N=15) | | | 350 mg (N=6) | | |
|---|---|---|---|---|---|---|
| | Grade (%) | | Total | Grade (%) | | Total |
| Toxicity | 2 | | 3 | 2 | | 3 |
| Hyperglycemia | 18 | 9 | 45 | 20 | 20 | 70 |
| Diarrhea | 0 | 9 | 100 | 10 | 0 | 50 |
| Fatigue | 0 | 0 | 45 | 30 | 0 | 80 |
| Rash | 9 | 0 | 27 | 10 | 20* | 40 |
| Nausea | 0 | 0 | 90 | 10 | 10 | 60 |
| Vomiting | 0 | 0 | 18 | 0 | 0 | 30 |
| Anorexia | 9 | 0 | 18 | 10 | 0 | 40 |
| Dysgeusia | 0 | 0 | 0 | 0 | 0 | 50 |

**517 Poster Highlights Session (Board #6), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Monitoring *PIK3CA* mutant allele fraction (AF) in cell-free DNA (cfDNA) in metastatic breast cancer (MBC) patients treated with PI3K$\alpha$–inhibitor plus letrozole (L) or exemestane (E).** *Presenting Author: Mary Ellen Moynahan, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** In tumors that harbor activating mutations, tumor-derived cfDNA extracted from patient plasma can be serially quantified by droplet digital PCR (ddPCR). Mutant AF may be predictive of target-directed therapy for initial response and evolving resistance. We report results of a correlative aim assessing serial mutant AF in a phase I study of a PI3K$\alpha$-inhibitor, BYL719, with L or E in MBC. **Methods:** *PIK3CA* status was mutant/wild-type/unknown in 8/5/1 pts as determined by molecular analysis of tumor. Plasma samples were collected at baseline and on day 1 of each 28 day cycle while on protocol. cfDNA was extracted using QIAamp Circulating NA kit and quantified by KAPA hgDNA qPCR. Allele specific assays for *PIK3CA* E542K, E545K, H1047R and H1047L mutations were designed for quantification on BioRad QX200 Droplet Digital PCR System. Mutant AF is determined from the counts for mutant as compared to wild-type. The detection limit for each assay is calculated from the number of events detected. All sample runs are replicated. **Results:** 5/8 pts with *PIK3CA* mutation were evaluable by ddPCR having received treatment for at least 2 cycles with the PI3K$\alpha$-inhibitor. In the plasma of 4 pts, we identified a brisk decrease in *PIK3CA* mutant AF at cycle 2, day 1(C2D1) ranging from 91.8 - 99.6% decrease from baseline. All 4 pts had stable or responding disease as best response. In 1 patient, later determined to have disease progression there was a small change (19% decrease) in *PIK3CA* mutant AF at C2D1 with a 16X increase in mutant AF at C3. Ongoing responses result in a persistent low (>98% decrease) or undetectable mutant allele. In 1 patient, with a transient response, the marked decrease in mutant AF at C2D1 was followed by an increase at C3 predicting her clinical progression. **Conclusions:** Targeted therapies directed towards specific oncogene mutations may be assessed serially by ddPCR to confirm mutant target sensitivity. Assessment for early tumor resistance may allow a more rapid treatment change with real-time monitoring of target mutant alleles. Serial assessment may be helpful in the exploration of best and better tolerated dosing schedules. Clinical trial information: NCT01870505.

**518 Poster Highlights Session (Board #7), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**SAKK 24/09: Safety and tolerability of bevacizumab plus paclitaxel versus bevacizumab plus metronomic cyclophosphamide and capecitabine as first-line therapy in patients with HER2-negative advanced stage breast cancer—A multicenter, randomized phase III trial.** *Presenting Author: Christoph Rochlitz, University Hospital, Basel, Switzerland*

**Background:** Bevacizumab combined with chemotherapy has been shown to improve response rate and PFS in metastatic breast cancer. The aim of our study was to demonstrate decreased toxicity of metronomic chemotherapy/ bevacizumab when compared to paclitaxel/bevacizumab. **Methods:** In this multicenter, randomized phase III trial, we compared bevacizumab (10 mg/kg i.v. q 2 weeks) with either paclitaxel (90 mg/m2) i.v. on days 1, 8, and 15 of a 4 week cycle (arm A) or daily oral capecitabine (3x500 mg) and cyclophosphamide (50 mg) (arm B) as first-line treatment in patients with HER2-negative advanced breast cancer. Primary endpoint was the incidence of grade 3–5 adverse events (AE): febrile neutropenia, infection, sensory and motor neuropathy, mucositis and hand-foot-syndrome. Secondary endpoints included: objective response (OR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), other adverse events (AEs), and quality of life (QoL). **Results:** Between September 2010 and December 2012, 147 patients were included at 22 centers in Switzerland, 73 in arm A and 74 in arm B. The incidence rates of primary endpoint events were 25% (18/71; 95% CI 15–35%) for arm A and 24% (16/68; 95% CI 13–34%) for arm B (p=0.96). Objective response rates were 58% (42/73; 95% CI 0.46–0.69) and 50% (37/74; 95% CI 0.39–0.61) in arms A and B, respectively (p=0.45). Median PFS was 10.3 months (95% CI 8.7–11.3) in arm A and 8.5 months (95% CI 6.5–11.9) in arm B, p=0.90; other secondary efficacy endpoints (DCR, OS) were not significantly different between the two arms. Less hair loss in arm B was the only clinically and statistically significant difference in QOL. **Conclusions:** This trial failed to meet its primary endpoint of a reduced rate of prespecified grade 3–5 AEs of metronomic bevacizumab, cyclophosphamide and capecitabine but the combination could be an active, convenient treatment in HER-2-negative metastatic breast cancer. Clinical trial information: NCT01131195.

**519 Poster Highlights Session (Board #8), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Randomized phase 2 study of abiraterone acetate (AA) with or without exemestane (E) in postmenopausal patients (pts) with estrogen receptor–positive (ER+) metastatic breast cancer (MBC).** *Presenting Author: Joyce O'Shaughnessy, Texas Oncology-Baylor Charles A. Sammons Cancer Center and US Oncology, Dallas, TX*

**Background:** Androgen receptor (AR) signaling and/or incomplete inhibition of agonistic estrogen synthesis may contribute to MBC resistance to a nonsteroidal aromatase inhibitor (NSAI). Combined inhibition of the AR with AA and the ER with E may be of clinical benefit. We assessed the safety and efficacy of AA + prednisone (P) in postmenopausal pts with NSAI-pretreated ER+ MBC. **Methods:** 297 pts were randomized to receive 1000 mg AA + 5 mg P (AA + P) vs AA + P with 25 mg E (AA + P + E) vs 25 mg E alone (E); 293 pts were treated. The primary end point was progression-free survival (PFS). Secondary end points included overall survival (OS) and clinical benefit rate (CBR). **Results:** The median age was 63 (37-87); 64% (AA + P + E), 64% (AA + P), and 65% (E) of pts had prior NSAI for MBC while 70% (AA + P + E), 66% (AA + P), and 65% (E) had prior chemotherapy. AA + P enrollment was discontinued (n = 89) after the planned interim analysis. 181 pts had measurable disease at baseline by RECIST. There was no significant difference in PFS or CBR with AA + P or AA + P + E compared with E (Table). Median OS was not reached. Increased serum progesterone concentrations were observed in both AA arms but not with E. The grade 3 or 4 toxicities associated with AA included (AA + P + E vs E) hypokalemia (5.8% vs 2.0%), hypertension (5.8% vs 2.9%), AST increase (4.8% vs 3.9%), and ALT increase (2.9% vs 2.9%). Treatment discontinuation for treatment-emergent adverse events was uncommon and only included 6 (5.9%) in E and 10 (9.6%) pts in AA + P + E. **Conclusions:** Adding AA to E in NSAI-pretreated MBC pts did not improve PFS or CBR. Administration of 5 mg of P adequately suppressed AA-associated mineralocorticoid excess effects. AA-induced CYP17 inhibition may not suppress steroid hormone receptor signaling in ER+ MBC potentially due to AA-induced increased progesterone synthesis. Clinical trial information: NCT01381874.

| Outcome | E | AA + P | AA + P + E |
|---|---|---|---|
| | n = 102 | n = 89 | n = 106 |
| PFS, median (months) | 3.7 | 3.7 | 4.5 |
| HR (95% CI) | | 1.1 (0.82-1.60) | 0.96 (0.70-1.32) |
| p value | | 0.437 | 0.794 |
| | n = 63 | n = 52 | n = 66 |
| CBR, n (%) | 8 (13) | 5 (10) | 15 (23) |
| RR (95% CI) | | 0.76 (0.26-2.18) | 1.79 (0.82-3.93) |
| p value | | 0.603 | 0.137 |

Abbreviations: HR, hazard ratio; HR < 1 favors AA + P or AA + P + E. RR, relative risk; RR > 1 favors AA + P or AA + P + E.

**520 Poster Highlights Session (Board #9), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Evaluation of biomarker association with efficacy for abiraterone acetate (AA) plus prednisone (P) with or without exemestane (E) in postmenopausal patients (pts) with estrogen receptor-positive (ER+) metastatic breast cancer (mBCa) progressing after a nonsteroidal aromatase inhibitor (NSAI).** *Presenting Author: Weimin Li, Janssen Research and Development, Spring House, PA*

**Background:** AA treatment may suppress androgens and estrogens that stimulate BCa growth. We conducted a biomarker analysis of circulating tumor cells (CTCs) and formalin-fixed paraffin-embedded tissues (FFPETs) from a phase 2 study of the efficacy and safety of AA in postmenopausal ER+ BCa pts to analyze serum steroid concentrations and identify subgroups with AA sensitivity. **Methods:** Treatments: AA (1 g/d) + P (5 mg/d) vs AA + P + E (25 mg/d) vs E alone. FFPETs from diagnosis and blood samples collected at baseline, during treatment, and at the end of treatment were used for molecular characterization and serum endocrine marker analysis. Expression of androgen receptor (AR), estrogen receptor (ER), Ki-67, CYP17, CYP19, and other biomarkers was evaluated in CTCs and/or FFPETs. Cox regression analysis stratified by number of prior therapies and type of therapy was used to evaluate biomarker associations with progression-free survival (PFS). Statistical comparisons were performed for treatment effect in biomarker-positive and -negative subgroups using Cox regression to identify those with better PFS. **Results:** Serum testosterone, estradiol, and estrone were decreased by AA treatment. An increase in progesterone was observed in most pts (AA + P and AA + P + E) but was not associated with PFS. 104 pts had $\geq$ 3 CTCs (median age 62; prior NSAI in metastatic setting 66%). Individually, baseline expression of AR or ER in CTCs or FFPETs was not associated with PFS. However, there was a positive association for the combination of AR and ER expression in CTCs with PFS in favor of AA + P + E vs E (HR 0.41 [0.16-1.07], p = 0.070). In recent FFPETs obtained $<$ 1 yr prior to first dose (67 pts), AR expression suggested positive association with PFS (HR 0.56 [0.24-1.33], p = 0.191) for AA + P + E vs E. **Conclusions:** A positive pharmacodynamic effect of AA was shown by the decrease in serum estrogen and androgen and potentially by the increase in progesterone in most pts. Baseline AR and ER expression in CTCs and AR expression in recent FFPETs may predict improved PFS. Clinical trial information: NCT01381874.

**521 Poster Highlights Session (Board #10), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Comparison of breast cancer recurrence and outcome patterns between patients treated in 1986-1992 and 2004-2008.** *Presenting Author: Rachel Jorge Dino Cossetti, BC Cancer Agency, Vancouver, BC, Canada*

**Background:** Different patterns of breast cancer (BC) recurrence overtime have been reported according to estrogen receptor (ER) status. We report a change in BC recurrence patterns. **Methods:** Females with biopsy proven BC, stages I-III, treated at the BCCA 1986-1992 (cohort 1 – C1) and mid 2004-2008 (cohort 2 – C2), with known ER and HER2 status were eligible. Data was prospectively collected. C2 cases were matched to C1 by random case selection for grade and stage to adjust for imbalances. Endpoints were annual hazard rates of recurrence (HRR) and annual hazard rates of death (HRD). **Results:** After random sampling, 10,283 pts were included: 3672 in C1 and 6611 in C2. BC subtypes in C1 and C2 were, respectively, ER+/HER2-: 71.2 vs 64.8%; ER+/HER2+: 6.7 vs 11.7%; ER-/HER2+: 6.5 vs 8.2%; ER-/HER2-: 15.5 vs 15.3%. The HRR per yearly interval (up to year 9) for all subtypes have halved in C2. For ER+/HER2- BC, HRR in C2 was half of the HRR in C1. Differences in HRR between C1 and 2 were greater in the initial 5 intervals for HER2+ and triple-negative (TN) BC. The HRD have also decreased, but to a lesser extent. **Conclusions:** Outcomes have improved for all BC subtypes, but particularly for HER2+ and TN BC. The early spike in disease recurrence has markedly decreased. These contemporary hazard rates are important for treatment decisions and patient discussions, but also for planning of early BC trials.

| HRR (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Yearly interval | | 0-1 | 1-2 | 2-3 | 3-4 | 4-5 | 5-6 | 6-7 | 7-8 | 8-9 |
| Cohort 1 | | 4.7±0.4 | 8.8±0.5 | 6.8±0.5 | 5.0±0.4 | 4.2±0.4 | 3.7±0.4 | 3.0±0.4 | 3.1±0.4 | 1.8±0.3 |
| Cohort 2 | | 2.7±0.2 | 4.0±0.3 | 3.6±0.2 | 2.6±0.2 | 2.0±0.2 | 1.3±0.2 | 1.2±0.2 | 1.2±0.3 | 0.3±0.3 |
| ER+/HER2- | C1 | 2.7±0.3 | 6.2±0.5 | 5.0±0.5 | 4.3±0.5 | 4.1±0.5 | 4.1±0.5 | 3.3±0.4 | 3.4±0.5 | 1.9±0.4 |
| | C2 | **1.5±0.2** | 2.5±0.2 | 3.0±0.3 | 2.2±0.2 | 1.9±0.2 | 1.4±0.2 | 1.7±0.3 | 1.3±0.4 | 0.4±0.4 |
| ER+/HER2+ | C1 | 6.7±1.7 | 13.7±2.5 | 12.1±2.6 | 21.6±2.6 | 6.9±2.2 | 3.7±1.7 | 3.2±1.6 | 4.3±1.9 | 2.8±1.6 |
| | C2 | **2.5±0.6** | 3.1±0.7 | 3.9±0.7 | 3.0±0.7 | 2.7±0.7 | 1.8±0.6 | 0.3±0.3 | 0.7±0.7 | 0 |
| ER-/HER2+ | C1 | 13.9±2.5 | 23.6±3.6 | 17.0±3.4 | 7.8±2.5 | 6.8±2.4 | 2.7±1.6 | 1.8±1.3 | 1.9±1.3 | 2.0±1.4 |
| | C2 | **4.0±0.9** | 8.3±1.3 | 5.5±1.1 | 3.0±0.8 | 1.3±0.6 | 0.3±0.3 | 0 | 1.7±1.2 | 0 |
| TNBC | C1 | 9.4±1.3 | 14.6±1.7 | 11.0±1.6 | 5.3±1.2 | 2.5±0.8 | 1.5±0.7 | 1.8±0.7 | 1.6±0.7 | 1.3±0.6 |
| | C2 | **7.3±0.9** | 9.1±1.0 | 5.5±0.8 | 3.8±0.7 | 2.0±0.5 | 0.7±0.4 | 0.5±0.3 | 0.9±0.6 | 0 |

**522 Poster Highlights Session (Board #11), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Emerging trends in type of chemotherapy (CT) received among patients (pts) with stage I breast cancer (BC).** *Presenting Author: Ines Maria Vaz Duarte Luis, Dana-Farber Cancer Institute, Boston, MA*

**Background:** We examined time trends of CT used and associations with pts characteristics in Stage I BC. **Methods**: Prospective cohort studyincluding pts with Stage I BC treated at a National Comprehensive Cancer Network center from 2000-09. We examined the proportion of pts receiving intensive vs. non-intensive CT over time.We defined an intensive regimen as: a combination of anthracyclines and taxanes (e.g. ACT ± H) or a combination of carboplatin and docetaxel (e.g. TCH), and non-intensive as: anthracycline-based (e.g. AC), taxane-based (e.g. TC) or similar. We evaluated factors associated with type of CT using multivariable logistic regression. Analyses were stratified by HER2 receptor status**. Results:** Of 8,907 pts, 33% received adjuvant CT. There was a dramatic increase of intensive CT: among HER2+ pts from 31% in 2000-05 to 63% in 2008-09 (including an increase in the use of TCH) and among HER2- from 15% in 2000-05 to 41% in 2008-09. Among non-intensive regimens there was an increase in the use of regimens such as TC with a parallel decrease in the use of regimens such as AC, in both HER2+ and HER2- groups. Characteristics which factored into CT decisions differed by tumor subtype, with significant center variations. **Conclusions:** Over time, there was an increase in use of intensive regimens among Stage I BC. CT use differed by HER2 status with striking center and temporal variations.

| | HER2+ | | | | HER2- | | | |
|---|---|---|---|---|---|---|---|---|
| | CT type | | | | | | | |
| Year | N | % Intensive | % TCH* | AC-TH* | N | % Intensive | % TC# | AC# |
| 2000-05 | 357 | 31 | 5 | 95 | 1,311 | 15 | 0.3 | 99.7 |
| 2006-07 | 193 | 65 | 27 | 73 | 463 | 33 | 21 | 79 |
| 2008-09 | 172 | 63 | 56 | 44 | 427 | 41 | 66 | 34 |

| | Associations with CT type (diagnosis 2006-2009) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Intensive vs. nonintensive | | TCH vs. ACTH | | Intensive vs. nonintensive | | TC vs. AC | |
| | OR | P | OR | P | OR | P | OR | P |
| Age (decade) | 1.0 | 0.11 | 1.0 | 0.20 | 0.95 | <0.01 | 1.03 | 0.01 |
| HR + (v -) | 0.7 | 0.25 | 1.0 | 0.97 | 0.3 | <0.01 | 0.8 | 0.48 |
| Tumor size (cm) | 2.0 | 0.04 | 0.3 | <0.01 | 2.6 | <0.01 | 1.1 | 0.71 |
| Race/ethnicity (other vs. white) | 0.5 | 0.11 | 1.3 | 0.59 | 1.3 | 0.21 | 1.6 | 0.22 |
| Comorbidity score (1+ v 0) | 0.7 | 0.26 | 1.9 | 0.12 | 1.1 | 0.71 | 1.3 | 0.52 |
| Year | 1.4 | 0.02 | 1.8 | <0.01 | 1.3 | <0.01 | 3.5 | <0.01 |
| High grade | 1.2 | 0.57 | 2.9 | <0.01 | 1.9 | <0.01 | 0.8 | 0.35 |
| Lymphovascular invasion | 1.5 | 0.37 | 0.9 | 0.85 | 2.1 | <0.01 | 1.0 | 0.95 |
| Center | | <0.01 | | 0.02 | | <0.01 | | <0.01 |

Among pts receiving *TCH/ACTH (represents 53% of pts with HER2+disease ). # TC/AC ( 68% of pts with HER2- disease).

**523 Poster Highlights Session (Board #12), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Changing pattern for HER2 positivity due to updated ASCO/CAP guidelines for HER2 testing and its impact.** *Presenting Author: Mithun Vinod Shah, Mayo Clinic, Rochester, MN*

**Background:** ASCO/CAP guidelines for HER2 testing in breast cancer were published in 2007 and updated in 2013. HER2-directed therapies (HDT) should be recommended in patients who are deemed HER2 positive, while they are not recommended in HER2 negative patients. If HER2 testing is equivocal, the guideline suggests that HDT be considered. It is not known how implementation of updated guidelines will change clinical practice. **Methods:** After the implementation of the 2013 guidelines, 321 breast tumor samples were received by the Mayo Clinic Cytogenetics laboratory for FISH analysis of HER2 status. The prevalence of HER2 alterations in this cohort was analyzed using both 2007 and 2013 guidelines. We also retrospectively analyzed HER2 data from N9831 (Alliance), a prospective multicenter randomized trial that evaluated the use of trastuzumab in the adjuvant setting. The trial included 3,505 women with histologically confirmed node-positive/high-risk node-negative HER2 positive invasive breast cancer. US FDA criteria were used to define HER2 positivity in N9831. **Results:** Using 2007 guidelines, 44 (14%) of the Mayo clinical practice cases were HER2 positive, 262 (82%) negative, and 11 (3.5%) equivocal. Using 2013 guidelines, 80 (25%) were positive, 225 (70%) negative, and 12 (4%) equivocal. The interpretation changed in 48 (15%) cases (p$<$ 0.0001). In N9831 using 2007 guidelines, 2,878 cases were HER2 positive (80.7%), 607 negative (17%), and 80 (2.2%) equivocal. Using 2013 guidelines, 2,937 (82.4%) were positive, 538 (15.1%) negative, and 90 (2.5%) equivocal. The increase in the prevalence of positive cases was significant (p$<$0.0001). Preliminary analysis suggests no disease-free survival benefit in women who had change in classification when stratified by whether they received HDT or not. **Conclusions:** There is a significant increase in the proportion of HER2 positive cases when breast cancer specimens are assessed using the 2013 ASCO/CAP guidelines. The updated guidelines also result in more equivocal cases requiring reflex testing. Interpreting HER2 status using updated guidelines will result in an increase in the number of breast cancer patients eligible for HDT. Clinical trial information: NCT00005970.

**524^ Poster Highlights Session (Board #14), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Oncotype DX and proliferation response to short-term preoperative endocrine therapy for chemotherapy decision in early breast cancer: Biomarker data from the prospective multicenter phase II/III WSG-ADAPT trial.** *Presenting Author: Oleg Gluz, West German Study Group; Evangelic Hospital Bethesda, Moenchengladbach, Germany*

**Background:** WSG-ADAPT aims to optimize early breast cancer therapy within a genomically classified (by OncotypeDX) intermediate-risk group using individual endocrine sensitivity. **Methods:** WSG-ADAPT HR+/HER2- analyzes biomarker changes after 3 weeks of preoperative ET [aromatase inhibitors (AI) in postmenopausal, tamoxifen (Tam) in premenopausal women]. Overall, n=1760 patients (HR+/HER2-, pN0-1) with Recurrence Score (RS) 0-11 or RS 12-25 and post-Tx Ki-67<10% are treated by ET alone. Other RS 12-25 and all RS ≥26 patients are included in phase III CTx design (n=2200). **Results:** 1118 patients from 61 centers have been enrolled (01/2014); run-in phase analysis included 383 patients (median age 54 years, 175 Tam, 208 AI). RS distribution (≤11/12-25/≥26) was 23%/57%/20%; median relative Ki-67 decreases were 0.67/0.60/0.40 by RS groups (p=0.017). Median relative Ki-67 decrease was more pronounced in post- vs. premenopausal patients (75% vs. 38%; p<0.001). Mean PR (not ER) expression changes were also more pronounced in postmenopausal patients (-39.5 %- vs. -10.4%-units; p<0.001). Pre- and post-endocrine RS (n=187) are moderately correlated ($r_S$ =.70, p<.001); no significant RS change was seen (95% CI: -1.7 to 0.3). Absolute change in Ki-67 by IHC was correlated with change in RS proliferation ($r_S$= .62, 95% CI: 0.52 to 0.7). Median ER expression by RT-PCR was higher in post- than premenopausal patients (10.25 vs. 9.3, p<0.001); median PR expression by RT-PCR trended oppositely (7.7 vs. 8.1, p=0.01). Baseline ER expression by RT-PCR (not IHC) was associated with relative Ki-67 decrease ($r_S$=.29, p<0.001). Baseline Ki-67, menopausal status/endocrine agent, and RS were independent predictors for post-treatment Ki-67. **Conclusions:** Postmenopausal patients (mostly AI) and those with lower baseline RS showed stronger proliferation response to short preoperative endocrine therapy. The difference in outcome between early proliferation responders (>70%) treated with ET alone among pN0/N1 patients with RS 12-25 and those with RS<11 will be tested in the WSG-ADAPT HR+/HER2- main phase. Clinical trial information: NCT01779206.

**525 Poster Highlights Session (Board #15), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Prognostic score for Luminal A-like breast cancer patients.** *Presenting Author: Caterina Fontanella, German Breast Group, Neu-Isenburg, Germany*

**Background:** Luminal A breast cancer (BC) is considered a subtype with a good prognosis, but some poor prognostic factors can be identified, i.e. advanced stage and/or young age at presentation seem to be associated with higher risk of recurrence after neoadjuvant treatment (NAT). The importance of the progesterone receptor (PR) in Lum A BC prognosis has also been explored. **Methods:** We evaluated 2,248 patients with Lum A like BC (HER2-/estrogen receptor +/grade1-2) from 6 anthracycline-taxane based NAT trials (plus adjuvant endocrine therapy (ET) and radiotherapy if indicated). Combining tumor stage (AJCC Cancer Staging seventh), PR status, and age at baseline, we generated a score to divide Lum A like BC into 5 groups (Table). We used Kaplan Meier and uni/multivariate Cox regression analyses to explore the effect of the score on disease free (DFS) and overall survival (OS) and to evaluate its interaction with CPS+EG score (Mittendorf EA, JCO 2011), body mass index (BMI≤30/>30kg/m²), pCR (ypT0 ypN0), NAT density (conventional/dose-dense), and duration (24/18/≤12 weeks). **Results:** Mean DFS and OS decreased from score A to E (DFS: A 106.9 months, B 98.9, C 90.7, D 80.5, E 46.5; *p*< .001; OS: A 109.9 months, B 107.2, C 100.6, D 91.0, E 57.8; *p*< .001). Univar. analysis hazard ratios (HR) are displayed below. In multivar. analysis, our score independently predicted DFS (*p*< .001) and OS (*p*= .049). No interactions were observed (DFS: score*CPS+EG *p*= .440, s*BMI *p*= .347, s*pCR *p*= .462, s*density *p*= .350, s*duration *p*= .590; OS: s*CPS+EG= .734, s*BMI *p*= .784, s*pCR *p*= .999, s*density *p*= .870, s*duration *p*= .999). **Conclusions:** Using characteristics available in daily practice before treatment, we developed a score to identify Lum A like BC patients with poorer prognosis, despite NAT and ET, who are candidates for more aggressive NAT or additional postNAT in future studies.

| | | DFS | | | OS | | |
|---|---|---|---|---|---|---|---|
| **SCORE (patients)** | | **HR** | **95%CI** | **p** | **HR** | **95%CI** | **p** |
| **A (686)** | I-IIA/PR+/age≥40 | 1.0 | | | 1.0 | | |
| **B (592)** | IIB/PR+/age≥40 | 2.1 | 1.4-3.1 | < .001 | 1.8 | 1.1-3.0 | < .001 |
| **C (709)** | I-IIA/PR-/age≥40<br>I-IIA/PR+/age<40<br>IIB/PR+/age<40<br>IIIA-B/PR+/age≥40 | 3.4 | 2.4-4.9 | < .001 | 3.0 | 1.8-4.8 | < .001 |
| **D (230)** | I-IIA/PR-/age<40<br>IIB/PR-/any age<br>IIIA-B/PR+/age<40<br>IIIA-B/PR-/any age | 5.4 | 3.6-8.1 | < .001 | 4.8 | 2.8-8.4 | < .001 |
| **E (31)** | IIIC | 11.7 | 6.3-21.6 | < .001 | 10.9 | 4.8-24.6 | < .001 |

**526 Poster Highlights Session (Board #16), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Phase II study of 3'-deoxy-3'-18F fluorothymidine PET/CT (FLT-PET) in the assessment of early response in locally advanced breast cancer (LABC): Preliminary results of ACRIN 6688.** *Presenting Author: Lale Kostakoglu, Department of Radiology, Mount Sinai Medical Center, New York, NY*

**Background:** FLT-PET imaging can be exploited as a marker of cellular proliferation and tumor (tm) therapy response. Our primary objective was to determine if early change in tm FLT uptake predicts pathologic complete response (pCR) to neoadjuvant chemotherapy (NAC) in primary tms in LABC pts. The secondary objective was to correlate standardized uptake values (SUVmax) with Ki-67 at baseline and after NAC. **Methods:** In this phase II study, 51 LABC pts [stage IIA-IIIC] were evaluable for primary objective analysis. NAC was according to standard of care; imaging was not used to change management. All 51 pts underwent FLT-PET imaging at baseline (FLT-1), and after one cycle (FLT-2);43 pts were imaged post-NAC (FLT-3). SUVmax's were averaged for multiple primary tms. The percent change in SUVmax (ΔSUVmax) between FLT-1 and FLT-2 was calculated. Pathologic response, Ki-67 assay and PET/CT were assessed at core labs. The predictive value of ΔSUVmax for pCR was determined by ROC; by area under the curve (AUC). Correlation between SUVmax and Ki-67 was assessed by the Spearman coefficient (R). **Results:** A pCR was achieved in 9 of 51 pts. At FLT-1, primary tm SUVmax range:0.9-11.8. FLT-1 uptake was not different between pts with pCR and non-pCR (p=0.59). NAC led to a significant ΔSUVmax (mean,36%;95%CI 28%-45%). AUC for ΔSUVmax in the prediction of pCR=0.68 [95%CI 48%-86%]. The best ΔSUVmax cut-off for predicting pCR was 51% (sensitivity 56%;specificity 79%). The difference in ΔSUVmax between pts with and without pCR was significant (20%;one-sided p=0.045). The correlation between FLT-1 SUVmax and Ki-67 was weak (R,0.29, p=0.04) but stronger at FLT-3 (R, 0.67%, p<0.0001). **Conclusions:** There was a significant difference in FLT ΔSUVmax in responders vs. non-responders after one NAC cycle, and FLT-PET was marginally predictive of pCR despite variable therapy. Post-NAC FLT uptake correlated with Ki-67. These data suggest that further work is warranted to define the clinical utility of FLT-PET in early evaluation of LABC therapy response. This project was funded in part with funds from the Department of Health & Human Services (DHHS); Grant#CA80098. Clinical trial information: NCT00572728.

**527 Poster Highlights Session (Board #17), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**A phase I trial of palbociclib and paclitaxel in metastatic breast cancer.** *Presenting Author: Amy Sanders Clark, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA*

**Background:** Palbociclib (Palb) is an oral CDK 4/6 inhibitor that is under development in breast cancer as a single agent and in combination with endocrine therapy. Preclinical studies suggest that Palb synergizes with paclitaxel (Pac) when given on an alternating schedule. We conducted a Phase I trial investigating the combination of weekly Pac and alternating Palb to synchronize the cell cycle in the tumors of patients (pts) with metastatic breast cancer. **Methods:** Pts with tumors expressing Rb protein, adequate organ function, and ≤3 prior cytotoxic metastatic regimens were eligible. Prior taxane was allowed. Palb was dose-escalated in a standard 3+3 design and taken on days 2-6, 9-14, 16-20 of each 28 day cycle. Pts received Pac 80mg/m2 weekly for 3 cycles; thereafter, Pac was administered on days 1, 8 and 15. After 6 cycles of therapy, pts had the option to drop the Pac and continue on Palb alone. Toxicity was assessed weekly and response was assessed every 2 cycles using RECIST 1.0. **Results:** The table below shows Palb dose level, enrollment, dose limiting toxicities (DLT), number of patients with Grade 3/4 neutropenia (NTP) and response (partial response (PR), stable disease (SD) or progressive disease (PD)). 8 patients had previously received a taxane. The only DLT was grade 3 AST and ALT (LFT). Among 11 pts with PR or SD, 8 pts continued on therapy >6 months and 4 >12 months. 11 pts are off study; 10 for PD, and one for toxicity (NTP in cycle 17) and 3 remain on study. Median time on treatment is 8 cycles. **Conclusions:** Combination Pac and Palb is safe and well tolerated. Prolonged tumor responses were seen. However, because uncomplicated grade 3/4 NTP was common and frequently led to dose reduction or dose interruption with 5-day Palb dosing, an additional Phase 1 expansion to examine Palb 100mg on a 3-day schedule (days 2-4, 9-11 and 16-18) is underway. Clinical trial information: NCT01320592.

| Starting dose level Palb | Number (total 15) | DLT | Grade 3/4 NTP (n) | Final dose Palb mg (n) | Dose interruption (n) | Best response (n) |
|---|---|---|---|---|---|---|
| **50 mg** | 3 | 0 | 0 | 50 (1)<br>50 (1)<br>50 (1) | No (2)<br>Yes (1) | PR (1)<br>SD (1)<br>PD (1) |
| **75 mg** | 3 | 0 | 2 | 75 (1)<br>50 (1)<br>25 (1) | No (1)<br>Yes (2) | PR (2)<br>SD (1) |
| **100 mg** | 6 | 0 | 5 | 100 (2)<br>75 (3)<br>25 (1) | No (1)<br>Yes (5) | PR (2)<br>SD (1)<br>PD (3) |
| **125 mg** | 3 | 1-LFT | 3 | 75 (1)<br>50 (2) | No (0)<br>Yes (3) | PR (1)<br>SD (2) |

**528 Poster Highlights Session (Board #18), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**TBCRC 022: Phase II trial of neratinib for patients (Pts) with human epidermal growth factor receptor 2 (HER2+) breast cancer and brain metastases (BCBM).** *Presenting Author: Rachel A. Freedman, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Evidence-based treatments for metastatic, HER2+ breast cancer to the central nervous system (CNS) are limited. Neratinib is an irreversible inhibitor of erbB1, HER2, and erbB4 with promising activity in HER2+ disease. Preclinical evidence suggests it may cross the blood brain barrier. We evaluated neratinib in pts with HER2+ BCBM in a multicenter, phase II open label trial. We report the results of cohort 1 here. **Methods**: Pts with measurable BCMC (>/= 1 cm in longest dimension) who progressed after receipt of local CNS therapy were eligible. Pts received neratinib 240 mg orally once daily over 28 day cycles. Brain MRI and non-CNS imaging were obtained at baseline and every two cycles. Circulating tumor cell collections and neurocognitive evaluations were performed serially. The primary endpoint was composite CNS objective response rate (ORR). CNS ORR required all of the following: >/=50% reduction in volumetric sum of target CNS lesions, no progression of non-target lesions, no new lesions, no escalating steroids, no progressive neurologic signs/symptoms, and no non-CNS progression by RECIST 1.1. If patients progressed outside the CNS, the addition of trastuzumab was offered. We used a two-stage design to distinguish between ORR 6% vs 20% (responses in >/=1/18 pts to enter 2$^{nd}$stage; responses in >/=5/40 pts to be promising). **Results:** 40 pts were enrolled between 2/12-6/13; median age was 51. Most pts (80%) had received 2+ lines of therapy for metastatic disease, 85% had prior lapatinib, and 75% had prior WBRT. As of 1/10/14, 0 patients remain on protocol therapy and 22 patients have died. Three women experienced a response (CNS ORR=7.5%; 95% CI 2-27%). The median number of cycles received was 2 (range 1-15+); 6 women (15%) received 6+ cycles of therapy. The most common grade 3+ event was diarrhea (25%); this event decreased after an amendment mandated 2 mg loperamide prophylaxis once daily during cycle 1 (33% grade 3+ diarrhea pre-prophylaxis vs. 21% post-prophylaxis). **Conclusions:** Neratinib is associated with a low CNS ORR in pts with BCBM but provided durable disease control in some pts. Updated results will be presented at the meeting. Clinical trial information: NCT01494662.

**529 Poster Highlights Session (Board #19), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Patient-level meta-analysis of randomized trials of aromatase inhibitors (AI) versus tamoxifen (Tam).** *Presenting Author: John F. Forbes, University of Newcastle, ANZBCTG, Calvary Mater Newcastle Hospital, Newcastle, Australia*

**Background:** The optimal way to schedule AIs and/or Tam in the adjuvant treatment of early breast cancer remains uncertain. **Methods:** ITT meta-analysis of individual patient data on 36 889 post-menopausal women with ER-positive invasive breast cancers in randomised trials of [A] Continuous AI (5yrs) vs Tam (5yrs); [B] Sequential Tam then AI (2-3yrs of Tam then 2-3 yrs AI) vs Tam (5yrs); [C] Continuous AI (5yrs) vs Sequential Tam then AI (5yrs). **Results:** [A] Fewer women had breast cancer recurrence with Continuous AI than Tam (827/4,970 vs 964/4,915, p<0.0001) and fewer died of breast cancer: 504 vs 562; rate ratio (RR) 0.86 [0.76-0.97], p=0.014. Recurrence RRs were: 0.66 during yrs 0-1 [95%CI 0.54-0.80], 0.75 during yrs 2-4 [0.64-0.88] and 0.90 in yrs 5+ [0.79-1.04]. [B] Recurrence was also lower with Sequential Tam then AI than with Tam alone (753/5,909 vs 863/5,889, p=0.0001) as was breast cancer mortality (361 vs 428 deaths; RR 0.84 [0.73-0.97], p=0.015). Recurrence RRs were 0.56 during yrs 2-4 [0.46-0.67] and 0.97 in yrs 5+ [0.86-1.09]. [C] In trials comparing Continuous AI versus Sequential Tam then AI, recurrence was lower with AI than Tam during yrs 0-1; RR 0.75 [0.62-0.89], but similar during yrs 2-4 (0.99 [0.85-1.15]), when both groups received AI, and in yrs 5+ (0.96 [0.76-1.21]) after treatment completion; overall, there were fewer recurrences with Continuous AI than Sequential Tam then AI (705/6,422 vs 764/6,377, RR 0.90 [0.81-1.00]; 5yr recurrence 9.6% vs 10.7%, p=0.042) and fewer breast cancer deaths (395 vs 432; 0.89 [0.77-1.02], p=0.097). In the 3 comparisons, proportional recurrence reductions did not differ much by age, nodal status, tumour grade, or PR status and, overall, fewer endometrial cancers (0.2% vs 0.6%, RR=0.37 [0.27-0.51]) but more fractures (8.1% vs 5.9%, RR=1.40 [1.27-1.53]) were seen with AIs than Tam; non-breast deaths were similar. **Conclusions:** AIs, in either Continuous or Sequential regimens, are even more effective than Tam monotherapy in preventing recurrence and breast cancer death, despite substantial cross-over from Tam to AI in some studies. Recurrence reductions are seen mainly while treatments differ, hence somewhat fewer recurrences with Continuous AI than Sequential Tam then AI.

**530 Poster Highlights Session (Board #20), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**An immune-related signature for prediction of risk of late recurrences beyond proliferation and ER-related genes in ER-positive breast cancer.** *Presenting Author: Giampaolo Bianchini, San Raffaele Hospital, Milan, Italy*

**Background:** In ER+ tumors, a dentritic metagene (DM) predicts for lower risk of relapse (Bianchini G JCO 2010; Bianchini G ASCO 2012). We investigated if other immune metagenes provided additional prognostic information and their involvement in early and late (after 5 years) relapses. **Methods:** We evaluated public available Affymetrix-based gene expression profiles from ER+ untreated (n=599) and adjuvant tamoxifen (TAM)-treated pts (n=683). Four previously defined immune metagenes were evaluated: CD8, MHC1, STAT1 and interferon inducible (IF.I) (Gianni L SABCS 2012). Multivariate analyses were adjusted by estrogen-related genes, proliferation (Bianchini G Breast Cancer Res 2013) and HER2 status. Median cut-off points were used to define low and high expression groups. Outcome was assessed according to distant relapse. **Results:** In untreated breast cancer, adjusting for other markers only IF.I metagene retained independent prognostic value [HR 1.19 (1.00-1.41), p=0.043], with higher risk for higher expression value. This effect was driven by its prognostic value in the late period [HR 1.50 (0.99-2.28), p=0.057]. Low and high expression groups of DM and IF.I were combined. The lowDM/highIF.I group had a higher risk of recurrences in the overall period [HR 3.68 (1.96-6.91), p<0.0001], with a similar trend in the late period [HR 2.98 (0.85-10.5), p=0.08]. In tamoxifen treated patients, adjusting for other markers, IF.I was confirmed as prognostic in the overall period [HR 1.25 (1.05-1.49), p=0.01] with an even stronger time varying effect [late period: HR 1.51 (1.14-2.01), p=0.004 and early period: HR 1.12 (0.90-1.39), p=0.29]. From 5 to 10 years, the lowDM/highIF.I group had the highest risk [HR 7.26 (1.78-33.9), p=0.006] with a corresponding relapse rate of 22.8% compared to 3% in the highDM/lowIF group. **Conclusions:** In ER+ breast cancer, high expression of interferon inducible-related genes predicts for higher risk of late recurrences in untreated and tamoxifen-treated patients. Immune related-functions contribute to tumor dormancy and late relapses. Assessment of immune markers might contribute in tailoring extended adjuvant endocrine treatment.

**531 Poster Highlights Session (Board #21), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Phase I/II study of letrozole and sorafenib as first-line therapy of hormone-receptor positive (HR+) metastatic breast cancer (MBC).** *Presenting Author: Antoinette R. Tan, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

**Background:** Preclinical studies show that addition of an antiangiogenesis agent improves efficacy of aromatase inhibition in hormone-sensitive breast cancer. Sorafenib is a multitargeted kinase inhibitor of VEGFRs, PDGFRs, FLT3, c-kit, and RAF. In this phase I/II multicenter study, the addition of sorafenib to letrozole as first-line therapy of HR+ MBC was evaluated. We previously reported the phase II dose to be letrozole 2.5 mg daily with sorafenib 400 mg BID. **Methods:** Eligible patients (pts) were postmenopausal, had measurable or evaluable HR+ MBC, and no prior therapy for metastases. Prior adjuvant tamoxifen (TAM) or aromatase inhibitor (AI) was allowed. The primary endpoint was clinical benefit rate (CBR= PR + SD $\geq$ 6 mo). The trial planned to enroll 58 pts to detect a CBR of $\geq$ 67% in a single-stage phase II design (80% power, $\alpha$ = .05). Secondary endpoints were progression-free survival (PFS) and overall survival (OS). **Results:** 54 pts (median age 54 yrs, range 21-84; median ECOG PS 0, range 0-2) were treated (13 pts in phase I) between 8/2008 – 12/2012 at which time the study closed due to slow accrual. 44% had de novo MBC, 39% pts had prior adjuvant TAM, 11% had prior adjuvant AI, and 2% had both prior TAM and AI. Median no. of cycles was 9 (range 1-62). The median daily dose of sorafenib was 400 mg. Most common gr 1-3 toxicities (%) were hand-foot skin (HFS) reaction (35%), hypertension (33%), rash (26%), diarrhea (19%), joint pains (15%), fatigue (13%), and alopecia (13%). 3 pts had HFS reaction that led to discontinuation of therapy. 5 pts had grade 2-3 rash that led to dose interruption. Of 41 pts evaluable for response, 39% (16 pts) had PRs and 41% (17 pts) had SD $\geq$ 6 mo. The CBR was 80.5% (95% CI: 65.1 - 90.9%). Median PFS was 20.2 mo (95% CI: 12.4 - 54.5 mo) and median OS was 51.5 mo (lower 95% CI: 44.7 mo). 11 pts continue on study with a median duration of 26 mo (range 14 – 60) and the median daily dose of sorafenib for these pts is also 400 mg. **Conclusions:** Letrozole combined with sorafenib was active in the treatment of HR+ MBC, and produced durable clinical benefit in a subset of pts as first-line therapy. Treatment benefit was still observed in pts who received lower than the recommended daily dose of sorafenib. Clinical trial information: NCT00634634.

**532 Poster Highlights Session (Board #22), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Clinical impact of differential risk stratification by breast cancer index (BCI) versus recurrence score (RS) in HR+ early-stage breast cancer: A TransATAC study.** *Presenting Author: Ivana Sestak, Queen Mary, University of London, London, United Kingdom*

**Background:** BCI is a genomic signature that significantly predicts risk of both early (0-5y) and late (5-10y) distant recurrence (DR) in HR+, LN- breast cancer. Previous results from the TransATAC study showed that both BCI and Oncotype Dx RS added significant prognostic information for 10y DR risk. Here, pre-defined risk stratification with BCI vs RS and its potential clinical impact were comparatively evaluated. **Methods:** 665 HR+, LN- patients were examined. BCI and RS risk groups were determined using pre-defined clinical cut-points. Kaplan-Meier estimates of 10y risk of DR and log-rank tests were used to examine cross-stratification between BCI and RS. Likelihood Ratio (LR) tests were used to quantitate relative prognostic information beyond CTS. **Results:** BCI re-stratification of the RS-Intermediate (RS-I) and RS-Low (RS-L) groups significantly impacted risk of 10y DR ($P=0.003$ and $P<0.001$), whereas RS did not significantly re-stratify BCI risk prediction (Table). BCI identified a small subset (20 pts in RS-L) with a high risk of DR (23.3%). Furthermore, BCI identified a large (95 pts in RS-I) and smaller (34 pts in RS-I) subset with 7.1% and 27.8% 10y DR risk, respectively. BCI added significant prognostic information beyond CTS+ RS ($p=0.0009$), whereas RS did not provide additional prognostic information beyond CTS+ BCI ($p=0.1$). **Conclusions:** In this retrospective analysis evaluating individualized risk stratification, BCI identified subsets of RS-L and RS-I LN- patients with significant and clinically distinct rates of DR. BCI identified a small subset of RS-L and RS-I LN- patients that would potentially benefit from additional therapy.

**Risk stratification and 10-year distant recurrence rates (%).**

| No. of patients | | BCI risk groups | | | | |
|---|---|---|---|---|---|---|
| | | Low | Inter | High | Total | P value |
| RS risk groups | Low | 283 (3.9%) | 85 (12.2%) | 20 (23.3%) | 388 (6.6%) | <0.001 |
| | Inter | 95 (7.1%) | 49 (24.3%) | 34 (27.8%) | 178 (15.8%) | 0.003 |
| | High | 12 (10%) | 32 (25.4%) | 55 (31.5%) | 99 (26.9%) | 0.2 |
| | **Total** | 390 (4.8%) | 166 (18.3%) | 109 (29.0%) | 665 | |
| | **P value** | 0.4 | 0.07 | 0.6 | | |

**533 Poster Highlights Session (Board #23), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Phase Ib study of LEE011 and BYL719 in combination with letrozole in estrogen receptor-positive, HER2-negative breast cancer (ER+, HER2− BC).** *Presenting Author: Pamela N. Munster, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

**Background:** Postmenopausal women with advanced ER+ BC are usually treated with aromatase inhibitors (AIs) as first-line therapy but resistance eventually develops. Dysregulation of the PI3K pathway and cyclin D kinases 4 and 6 (CDK4/6) has been implicated in resistance to endocrine therapy. LEE011 (a selective CDK4/6 inhibitor) and BYL719 (an $\alpha$-selective PI3K inhibitor) demonstrate clinical activity in ER+ BC as single agents. In ER+ BC xenograft models, LEE011 has demonstrated enhanced antitumor activity when combined with BYL719 and letrozole versus each agent alone, suggesting this combination may optimize treatment in ER+ BC. In the ongoing Phase Ib part of this study (NCT01872260), two doublet combinations, LEE011 + letrozole (Arm 1) and BYL719 + letrozole (Arm 2), and the triplet combination of LEE011 + BYL719 + letrozole (Arm 3), are explored in patients with ER+ BC. **Methods:** Postmenopausal women with locally advanced/metastatic ER+, HER2− BC not amenable to curative treatment by surgery/radiotherapy receive escalating doses of oral LEE011 QD (3-wks on/1-wk off) or BYL719 QD (continuous) and a fixed dose of letrozole QD (2.5 mg, continuous) in 28-day cycles. The primary objective is to estimate the MTD and/or RP2D of each combination by assessing DLTs in Cycle 1 using an adaptive Bayesian Logistic Regression Model (BLRM) guided by the escalation with overdose control (EWOC) principle. Secondary objectives include safety, PK and preliminary efficacy assessments. **Results:** As of Jan 31, 2014, 6 patients have been treated in Arm 1 (LEE011 600 mg + letrozole), and 1 DLT (G4 neutropenia) has been reported. Five patients have started treatment in Arm 2 (BYL719 300 mg + letrozole). Preliminary PK data are consistent with that for the respective single agents, with no evidence of drug–drug interactions. **Conclusions:** AIs are recommended as first-line endocrine therapy in postmenopausal patients with advanced ER+, HER2− BC, but most patients develop resistance. This is the first trial evaluating an AI in combination with a PI3K and CDK4/6 inhibitor in ER+, HER2− BC. Phase II will compare the preliminary antitumor activity of the doublets vs. triplet combinations. Clinical trial information: NCT01872260.

**534 Poster Highlights Session (Board #24), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**LY2835219, a novel cell cycle inhibitor selective for CDK4/6, in combination with fulvestrant for patients with hormone receptor positive (HR+) metastatic breast cancer.** *Presenting Author: Amita Patnaik, South Texas Accelerated Research Therapeutics (START) Center for Cancer Care, San Antonio, TX*

**Background:** Cyclin-dependent kinases 4 and 6 (CDK4/6) act with D-type cyclins to enable cell proliferation. LY2835219, a small molecule inhibitor of CDK4/6, has shown antitumor activity in xenograft models of multiple cancers. In a cohort of 47 patients (pts) with metastatic breast cancer (MBC) treated with LY2835219, there were 8 confirmed and 3 unconfirmed partial responses (PRs) among 36 pts with HR+ MBC. Fulvestrant is an anti-estrogen used to treat HR+ MBC. Thus, we expanded the Phase I study to evaluate LY2835219 plus fulvestrant for pts with HR+ MBC. **Methods:** We conducted a Phase I study to evaluate the safety, pharmacokinetics, and antitumor activity of LY2835219 in 5 different tumor types. For breast cancer, there were cohorts for both LY2835219 in MBC (n=47) and the combination of LY2835219 plus fulvestrant in HR+ MBC (n=13). Patients in the HR+ MBC combination cohort received LY2835219 at 200mg orally every 12 hours on Days 1-28 of a 28-day cycle plus fulvestrant at 500mg IM once monthly. CTCAE v4.02 was used to grade adverse events (AEs). RECIST v1.1 was used to assess tumor response. **Results:** In the HR+ MBC combination cohort, 13 pts with a median of 4 prior systemic therapies (range 2-8) received LY2835219 plus fulvestrant. Among these pts, the most common possibly related treatment-emergent AEs across all grades were diarrhea (including 8% G3), fatigue (8% G3), neutropenia (31% G3), nausea (no G3), vomiting (no G3), and leukopenia (23% G3); there were no Grade 4 events. LY2835219 dose reductions from 200mg to 150mg occurred in 8 pts, including 2 pts for diarrhea and 1 pt each for fatigue and neutropenia. Importantly, febrile neutropenia was not observed and there were no discontinuations due to toxicity. No serious AEs or deaths were reported. In HR+ MBC, LY2835219 demonstrated clinical activity (8 confirmed and 3 unconfirmed PRs) and also acceptable safety in combination with fulvestrant. **Conclusions:** LY2835219 demonstrates single-agent activity in MBC. For patients with HR+ MBC, the combination of LY2835219 plus fulvestrant shows acceptable safety and merits further clinical investigation for efficacy. Clinical trial information: NCT01394016.

**535 Poster Highlights Session (Board #25), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Phase Ib/II study of LEE011, everolimus, and exemestane in postmenopausal women with ER+/HER2-metastatic breast cancer.** *Presenting Author: Aditya Bardia, Massachusetts General Hospital, Harvard Medical School, Boston, MA*

**Background:** Aromatase inhibitors (AIs) are the recommended first-line endocrine therapy for postmenopausal (PM) patients (pts) with ER+/HER2– advanced/metastatic breast cancer (aBC). However, resistance develops over time. Activation of the PI3K/AKT/mTOR pathway and downstream cyclin D–cyclin-dependent kinase (CDK4/6) has been implicated in endocrine-therapy resistance. Combination of the mTOR inhibitor everolimus (EVE) with exemestane (EXE) significantly improved PFS of pts with ER+/HER2– aBC (BOLERO-2), and preclinical data suggest that combination of EXE, EVE, and the CDK4/6 inhibitor LEE011 may be even more effective in endocrine-resistant ER+/HER2– BC. **Methods:** During Phase (Ph) Ib, PM pts with ER+/HER2– aBC are being treated with escalating doses of LEE011 (3 wks on/1 wk off), EVE (continuous), and a fixed daily dose of EXE (25 mg/d; continuous; arm 1); or with a safety run-in of LEE011 (600 mg/d; 3 wks on/1 wk off) and EXE (25 mg/d; continuous; arm 2) to confirm the recommended Ph II dose (RP2D). The primary objective of the Ph Ib part of the study is to determine the maximum tolerated dose and/or RP2D in arm 1. Safety, tolerability, and PK will also be assessed. Dose escalation is guided by a Bayesian Logistic Regression Model (BLRM) with overdose control principle. **Results:** As of Dec 12, 2013, 6 pts have been treated in arm 1 with 200 mg/d LEE011, 2.5 mg/d EVE, and EXE, and among the 5 pts evaluable for dose determination, no DLTs were observed. AEs observed to date have been mainly hematologic (as expected with a CDK 4/6 inhibitor) and mild to moderate.Preliminary PK suggest that LEE011 exposure in the presence of EVE is similar to that of single agent, while for EVE there was a 2-fold increase in exposure at steady state.Pts are currently being treated in arm 1 cohort 2 (300 mg/d LEE011, 2.5 mg/d EVE, and EXE) and in arm 2. **Conclusions:** To the best of our knowledge, this is the first trial evaluating an AI in combination with an mTOR and a CDK4/6 inhibitor. Preliminary data suggest that the triple combination of LEE011 + EVE + EXE is feasible. The exposure of EVE is slightly increased. In Ph II of the study, pts will be randomized to receive LEE011 + EVE + EXE, LEE011 + EXE, or EVE + EXE, and safety and efficacy compared. Clinical trial information: NCT01857193.

**536 Poster Highlights Session (Board #26), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Whole-exome sequencing (WES) of HER2+ metastatic breast cancer (MBC) from patients (pts) treated with prior trastuzumab (T): A correlative analysis of TBCRC003.** *Presenting Author: Nikhil Wagle, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Although several large sequencing studies have elucidated the spectrum of genomic alterations in primary, treatment-naïve HER2+ cancers, the genomic landscape in metastatic tumors after progression on anti-HER2 therapy remains largely unknown. **Methods:** We performed WES on baseline metastatic tumor biopsies from 57 pts enrolled on TBCRC003 (NCT00470704), a phase II study evaluating combined lapatinib (L) and T that included pts with varying degrees of prior T exposure. Tumors were analyzed for point mutations, insertions/deletions, and copy number alterations. **Results:** Across 57 tumors, the median depth of coverage was 99-fold (range 37-160). The median number of coding mutations per sample was 55 (Range: 1-716). Significant recurrently mutated genes were *TP53* (n=30; 53%) and *PIK3CA* (n=19; 33%). The incidence of mutant *TP53* and *PIK3CA* was not significantly different from 104 primary, treatment-naïve HER2+ tumors sequenced in the TCGA study (53% and 28%, respectively). Comparing the 40 pts who received prior T with the 17 pts who did not, there was no significant difference in the incidence of mutant *PIK3CA* (35% vs 29%, p=0.8) and *TP53* (53% vs 53%, p=1.0). Significant recurrent copy number alterations included amplifications in *FGFR1, MYC, CCND1,* and *MDM2* and deletions in *NF1,* also similar to TCGA data. In 3/40 pts who had received prior T (8%), we identified a HER2 L755S kinase domain mutation. HER2 mutations have been seen in ~2% of HER2-negative cancers and <1% of primary HER2+ cancers. HER2 L755S has been shown to be resistant to L and sensitive to irreversible HER2 inhibitors. 5 additional pts, 2 of whom received prior T, had uncharacterized HER2 mutations at low allelic fractions, including a novel kinase domain mutation in a pt who had received prior T. No HER2 kinase domain mutations were seen in T-naïve pts. **Conclusions:** We present the first genomic landscape of HER2+ MBC using WES data. WES of matched primary tumor tissue is underway. The presence of HER2 mutations in pts with HER2+ MBC treated with prior T suggests that these mutations may be involved in the development of resistance to T. Novel therapeutic approaches may be required for these pts.

**537 General Poster Session (Board #1), Mon, 8:00 AM-11:45 AM**

**Total estrogen blockade and chemotherapy in high-risk premenopausal early breast cancer (BC): Long-term follow-up of a phase II study.** *Presenting Author: Francesco Recchia, Medical Oncology, Civilian Hospital, Avezzano, Italy*

**Background:** Estradiol ($E_2$) mediates two important functions of premenopausal patients with BC: the induction of vascular endothelial growth factor (VEGF) and the expansion of T-Regulatory cells (T-Regs). Both these functions are fundamental for breast cancer development. We hypothesized that, decreasing plasma $E_2$, we could reduce VEGF and T-regs, and therefore, we could decrease the recurrence rate in premenopausal patients with high risk early breast cancer. Primary endpoint of this study was the evaluation of VEGF and T-Regs; secondary end points were the 5 and 15-year disease-free survival (DFS) and overall survival (OS) rates. **Methods:** Between June 1997 and June 2007, 200 premenopausal high risk early BC patients were entered into the study. After surgery and before starting the chemotherapy, an LH-RH analogue was administered to all patients. Chemotherapy was tailored to the biological characteristics of each patient, followed by radiation therapy, and by an aromatase inhibitor in ER+ patients. **Results:** Median patient's age was 43 years (range 26-45). Mean number of positive axillary nodes was 3.2 (range 1-25). Seventy-one percent of patients were ER+, 29% were ER -, and median KI-67 was 30% (range 15% -100%). After a median follow-up of 104 months (range 63-180), $E_2$ was suppressed to values < 40 ng/ml. A statistically significant decrease of VEGF ($P<0.0001$) and T-Regs ($P<0.0001$) were observed. Five-year DFS and OS rate were 89% and 96%, respectively, while the 15-year DFS and OS rate were 62%, and 73%, respectively. ER+ patients had a better DFS ($P<0.05$) with respect to ER- patients, while no difference was observed in OS. No recurrence after 5 years was observed in ER- patients who had late new primaries. ER+ patients had recurrences even after 15 years. The standard pattern of toxicity of chemotherapy was observed, while hot flashes and G1 osteopenia occurred after LH-RH analogue administration. **Conclusions:** $E_2$ deprivation with an LH-RH analogue is able to decrease T-Regs and VEGF and to improve the expected DFS and OS rate in premenopausal high risk ER+ and ER- BC patients, at the price of a moderate toxicity.

**538 General Poster Session (Board #2), Mon, 8:00 AM-11:45 AM**

**Phase 1b study of orteronel in postmenopausal women with hormone-receptor positive (HR+) metastatic breast cancer.** *Presenting Author: Murtuza M. Rampurwala, University of Wisconsin Carbone Cancer Center, Madison, WI*

**Background:** Endocrine therapies are the treatment of choice for HR+ metastatic breast cancer; novel drugs are needed due to resistance. Reducing both androgens and estrogens may circumvent resistance by reducing androgen receptor stimulation. Orteronel is a selective, reversible, nonsteroidal inhibitor of the 17, 20-lyase enzyme (which generates androgens and estrogens). We conducted a phase 1b study of orteronel in HR+ metastatic breast cancer; the primary objective was the recommended phase 2 dose (RP2D) of orteronel in women. **Methods:** Key inclusion criteria were postmenopausal status and evaluable or measurable HR+ metastatic breast cancer. Doses escalated via standard 3+3 design. Initial dose was 300 mg BID and escalated to 400 mg BID (the RP2D in men). Cycle length was 28 days. Patients were evaluated every 8 weeks for progression. Correlative studies assessing hormone levels via liquid chromatography-mass spectrometry were performed. **Results:** Seven patients enrolled (median 56 yo, range 47-71). Patients were heavily pre-treated: 6 had prior endocrine therapy for metastatic cancer (median 4 lines, range 0-5) and 5 had prior chemotherapy regimens for metastatic cancer (median 2, range 0-5). Four received 300 mg BID at dose level 1 (1 was not evaluable per protocol); 3 received 400 mg BID at dose level 2. Orteronel was well tolerated: no dose limiting toxicities were observed. Common adverse events at least possibly related to therapy were: grade 1 hot flashes (28%), grade 1-2 nausea (28%), grade 1 hypokalemia (28%), and grade 1 elevated AST (28%). 6 patients received 14 cycles of treatment. 2 patients remain on therapy with evidence of clinical benefit: 1 with stable disease for > 6 months (best response) and 1 with stable disease for 3 months. **Conclusions:** Orteronel 400 mg BID is well tolerated in post-menopausal women, and significantly suppresses serum estrogens and testosterone. Clinical benefit was seen among heavily pretreated patients. Clinical trial information: NCT01808040.

**Mean levels ± standard deviation prior to and after orteronel.**

| | Cycle 1, day 1 (n=7) | Cycle 2, day 1 (n=6) | Cycle 3, day 1 (n=4) |
|---|---|---|---|
| **Estradiol (pg/ml)** | 6.2 ± 5.6 | 4.9 ± 4.4 | 0.5 ± 1 |
| **Estrone (pg/ml)** | 24.4 ± 12.8 | 2.7 ± 3.6 | 5.2 ± 6.4 |
| **Testosterone (pg/ml)** | 131.7 ± 102.9 | 7.3 ± 9 | 13.4 ± 25.5 |

**539 General Poster Session (Board #3), Mon, 8:00 AM-11:45 AM**

**Identification of patients with hormone receptor–positive breast cancer who need adjuvant tamoxifen therapy for more than 5 years.** *Presenting Author: Chiao-En Wu, Division of Hematology-Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou, Taoyuan County, Taiwan*

**Background:** Extended hormonal therapy with tamoxifen for more than 5 years has improved disease-free survival (DFS) and overall survival (OS) in hormone receptor (HR)-positive breast cancer patients. However, this strategy in patients with a low risk of recurrence is controversial, since the benefits should outweigh the risk of endometrial cancer or thromboembolic disease. Therefore, we attempt to identify risk factors for late recurrence after 5 years of adjuvant tamoxifen therapy. **Methods:** Between 1990 and 2004, 1,104 HR-positive breast cancer patients who had received tamoxifen treatment at our institution at some point and had been disease free for at least 6 years were included in this analysis. Univariate and multivariate analyses of prognostic factors for late recurrence were performed using the binary logistic regression model. **Results:** During a median follow-up period of 10.9 years after surgery, 70 patients died and 99 showed recurrence. Patients aged <40 years, those aged >65 years, those with stage T2–4 tumors, those with positive lymph nodes, and those with positive estrogen receptor (ER) status had significantly higher rates of recurrence. In multivariate analysis, age < 40 years (odds ratio [OR] = 4.21, $P < 0.001$) and lymph node metastasis (OR = 2.67, 3.77, 6.10 for N1, N2, N3 *vs.* N0, $P < 0.001$) were associated with higher rates of recurrence. We stratified patients into high-risk (age < 40 years or positive lymph node status, 536 patients) and low-risk (age > 40 years and negative lymph node status, 566 patients) groups. The recurrence rates were 14.6% and 3.5% in the high-risk and low-risk groups, respectively. Patients in the high-risk group had poorer DFS (estimated 15-year DFS rate: 78% vs. 92.3%, $P < 0.01$) and OS (estimated 15-year OS rate: 83.1% vs. 92.6%, $P = 0.01$) than those in the low-risk group. **Conclusions:** Our findings suggest that HR-positive breast cancer patients either aged <40 years or with positive lymph node status were justified in continuing with tamoxifen therapy for more than 5 years.

**540 General Poster Session (Board #4), Mon, 8:00 AM-11:45 AM**

**A simple, validated model for identifying cases that are unlikely to benefit from the 21-gene recurrence score (RS) assay.** *Presenting Author: Michele Maiko Gage, Walter Reed National Military Medical Center, Bethesda, MD*

**Background:** Predicting recurrence risk and chemotherapy benefit in breast cancer can be challenging, and Onco*type*Dx (ODX) is often used to gain insight. Using readily available clinical information, a simple model was created to identify high and low risk patients, saving the expense of ODX testing. **Methods:** Clinical-pathologic data from 221 hormone positive, HER2-negative invasive breast cancer patients was used to create a model with two simple rules: Low Grade and Positive PR tumors (LG+PR) are low risk, and High Grade or Low ER (ER<20%) tumors (HG/LER) are high risk. The TAILORx trial thresholds of RS≤10, where chemotherapy is of limited benefit, (TXNC) and RS≥26 supportive of chemotherapy (TXC) were used to judge model performance. The model was then validated on an independent second institution's set of 319 patients. **Results:** Most HG/LER were RS≥26, (84% on development set, 51% on #2 set), and most LG+PR were RS≤18 (83%, 74%, respectively). Refer to Table for distribution. Impressively, the 2-Step Errors for HG/LER (RS ≤10) were 0% and 2%, and for LG+PR (RS≥26) were 0% and 2.6%, showing it is very unlikely for HG/LER to have a low risk test result or for LG+PR to have a high risk test result.In the validation set, 28% of the indeterminate group result as high or low risk; this group may clinically benefit from ODX. **Conclusions:** In HG/LER and LG+PR, ODX is not clinically valuable because it consistently results in a RS in which benefit of chemotherapy is accepted or unknown for HG/LER, and benefit of chemotherapy is rejected or unknown for LG+PR. The equal hazard ratios of RS and high grade, as evaluated by a multivariate Cox model (using age, pathologic variables, and RS) (Paik et al. NEJM '04), further support the importance of grade when predicting risk. By identifying patients who are unlikely to benefit from ODX testing, expense will be spared.

| | | ODX low risk | ODX intermediate | | ODX high risk | | |
|---|---|---|---|---|---|---|---|
| | | TXNC | TXI | | TXC | | |
| Data Set | | RS ≤10 | 11-17 | 18-25 | 26-30 | 31+ | Total |
| Institution #1 Development Group | HG/LER | 0 | 2 | 4 | 6 | 25 | 37 |
| | Indeterminate | 19 | 41 | 35 | 8 | 8 | 111 |
| | LG+PR | 27 | 33 | 13 | 0 | 0 | 73 |
| | Total | 46 | 76 | 52 | 14 | 33 | 221 |
| Institution #2 | HG/LER | 1 | 10 | 13 | 7 | 18 | 49 |
| | Indeterminate | 39 | 88 | 78 | 16 | 11 | 232 |
| | LG+PR | 11 | 17 | 9 | 0 | 1 | 38 |
| | Total | 51 | 115 | 100 | 23 | 30 | 319 |

Abbreviation: TXI, TAILORx Indeterminate.

**541 General Poster Session (Board #5), Mon, 8:00 AM-11:45 AM**

**Changes in androgen receptor (AR) expression and its phosphorylated isoforms, in breast cancer (BC) patients treated with neoadjuvant letrozole.** *Presenting Author: Angel Guerrero, Medical Oncology. Instituto Valenciano de Oncología, Valencia, Spain*

**Background:** Most of BC express the AR, and this is considered to be a good prognostic factor. However, AR signalling has also been implicated as a possible mechanism to aromatase inhibitors (AIs) resistance. Cell line models suggest a switch from estrogen to androgen-dependent growth as they become resistant to estrogen deprivation therapies. The goal of this study is to examine, in vivo, changes in AR and its phosphorylated sepecies during AI therapy, and to assess its potential role in outcome. **Methods:** Eighty four, consecutive, postmenopausal women, stage II-III primary estrogen receptor positive BC, were treated, in the same institution, with preoperatory letrozole between 2005 and 2012. Pre- and post-treatment BC tissues were examined by inmunohistochemestry for total AR and the phosphorylation of AR at serine 213 (pAR-S213) and serine 650 (pAR-S650). **Results:** Letrozole decreased the expression of pAR-S213, that was positive (H-score≥10) in 65% of pre-treatment samples vs 30% of post-treatment samples (p=0.001). No changes were observed for total AR (90% pre- vs 88% post-) and pAR-S650 (39% pre- vs 41% post-). Only pAR-S213 positivity after treatment was associated with a decreased rate of relapse free survival at 55 months (post-pAR-S213 negative: 90% vs post-pAR-S213 positive: 60%, p=0.0004), and remained significantly associated in a multivariate analysis including classic prognostic factors (PEPI score, Ki-67, ypTNM, ER). **Conclusions:** High expression of pAR-S213 after treatment with letrozole is associated with poor outcome, which suggest the possibility of therapeutic intervention with antagonist of AR activation.

**542 General Poster Session (Board #6), Mon, 8:00 AM-11:45 AM**

**Vitamin B12 (Vit B12) biochemical (BCH) deficiency (DEF) in non-diabetic breast cancer (BC) patients on NCIC CTG MA.32: A phase III randomized adjuvant BC trial comparing metformin (Met) to placebo (Pl).** *Presenting Author: Mira F. Liebman, University Health Network, University of Toronto, Toronto, ON, Canada*

**Background:** Met, a drug used to treat type 2 diabetes, is being evaluated as an anti-cancer agent. Long-term use is associated with BCH Vit B12 DEF in up to 30%; a subset may develop symptomatic DEF. It is unknown if Vit B12 DEF is due to diabetes or Met use. We examined Vit B12 DEF in NCIC CTG MA.32, an RCT of adjuvant Met vs Pl in non-diabetic BC patients (pts). **Methods:** This was a DSMC approved central lab analysis in the first 492 (of 3649) high risk N0/N1-3 BC pts receiving standard therapy randomized onto MA.32 (Met 850 mg bid vs Pl bid for 5 years). VitB12 was analysed in baseline and 6 month (mo) fasting plasma; levels <181 pmol/L were DEF, 181 to 221 pmol/L borderline. Methylmalonic acid (MMA) and homocysteine (HC) (elevated in clinical Vit B12 DEF) were assayed in those with Vit B12 levels <222 pmol/L at either time. Hgb was measured locally. Analysis used Spearman's rank correlation coefficients and Wilcoxon signed rank test for continuous variables and Chi-square test for 2 by 2 tables. **Results:** Mean age was 52.4±9.7 yrs. 237 received Met and 255 Pl; arms were balanced for hormone receptors (73% +ve), BMI (mean 28.3 kg/m$^2$), adjuvant chemo (88%), stage, type of surgery/radiation. Median (Inter Quartile Range) baseline Vit B12 was 390 (281 to 556) and 370 (290 to 552) pmol/L in the Met and Pl arms respectively (p=0.97). 6 mo median levels were MET 320 (244 to 419) and Pl 380 (286 to 546) pmol/L (p=0.0001). 15 pts (11 Met and 4 Pl) had BCH Vit B12 DEF (<181 pmol/L) at diagnosis; 15 Met and 3 Pl at 6 mo (p=0.004). Mean Hgb was similar at baseline 130.1±9.1 (MET) and 131.0±9.9 g/L (Pl), p=0.38 and 6 mo 131.3±9.5 (MET) and 132.7±9.6 g/L (Pl), p=0.11); and in those +/- BCH Vit B12 DEF. Of the 74 with Vit B12 <222 pmol/L (45 Met, 29 Pl), MMA was normal in all pts at baseline; 2 had elevated HC (>15 umol/L). At 6 mo 1 Met pt had MMA >0.4 umol/L and 3 (2 Met, 1 Pl) had HC >15 umol/L. **Conclusions:** There was an increased rate of BCH, but not clinical, Vit B12 DEF after 6 mo of Met. This suggests that Met (not diabetes) lowers VitB12 and supports recommendations to monitor Vit B12 with Met use. Longer follow-up will evaluate clinical VitB12 DEF. Clinical trial information: NCT01101438.

**543 General Poster Session (Board #7), Mon, 8:00 AM-11:45 AM**

**Predictive factors for late (>5 years) distant recurrences in estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer patients: >20-year follow-up.** *Presenting Author: Jaskirat Singh Randhawa, Cleveland Clinic/Fairview, Cleveland, OH*

**Background:** ER+ breast cancer (BC) by virtue of tumor dormancy can present with delayed recurrences, frequently years after initial diagnosis. **Methods:** Over 2,500 charts of ER+/HER2 negative BC patients were reviewed. Patients with follow up < 5 years, recurrence within 5 years and all local recurrences < or > 5 years were excluded. 35 late distant recurrences with minimum follow up of 5 years were identified. Data was analyzed with 50 patients without recurrences during same period. Following factors were used for analysis: age at diagnosis, tumor diameter, smoking history, T- and clinical stage at diagnosis, lymph node involvement (LNI), tumor-grade, histology, progesterone receptor(PR) status, duration of adjuvant therapy and treatment modalities. Recurrence and time to recurrence were assessed. Wilcoxon rank sum, Kruskal-Wallis tests and Chi-square tests were used for univariate analyses. Multivariate analysis was conducted using logistic regression and proportional hazards models. **Results:** The median/mean age at diagnosis was 58/58.5 years and median/mean age at relapse was 63/65.5 years respectively. Tumor size, T-stage at diagnosis, and duration of adjuvant therapy were associated with late relapse (p≤0.025, p≤0.012, p≤0.037 respectively). T-stage at diagnosis was only independent predictor identified; with an estimated odds ratio of 2.62 (95% CI: 1.22, 5.64) and an estimated hazard ratio of 2.22 (95% CI: 1.32, 3.72). No other significant association was detected (age at diagnosis; p≥0.21, tumor-grade; p≥0.27, histology; p≥0.17, smoking history; p≥0.79, LNI; p≥0.08, PR status; p≥0.58). Of patients with recurrent disease, 40% showed identical receptor profile and 11.4% had receptors changed/different from their initial diagnosis. **Conclusions:** In univariate analysis, the tumor diameter, T-stage at diagnosis and duration of adjuvant therapy are associated with both recurrences and time to relapse. Patients who received adjuvant therapy ≥ 5 years had decreased rate of late recurrences. In multivariate analysis, T-stage at diagnosis is the only independent predictor.

**544 General Poster Session (Board #8), Mon, 8:00 AM-11:45 AM**

**IGF-1 receptor activation and intrinsic tamoxifen resistance in postmenopausal breast cancer patients.** *Presenting Author: Karin J. Beelen, Netherlands Cancer Institute, Amsterdam, Netherlands*

**Background**: Elevated insuline-like growth factor 1 receptor (IGF-1R) signaling activates the phosphatidylinositol-3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways and results in hormone indepedent cell growth in vitro, rendering cells resistant to anti-estrogens. The clinical validity of IGF-1R signaling to predict resistance to adjuvant anti-estrogen therapy has not been well established.We tested the predictive value of IGF-1R activation to predict adjuvant tamoxifen resistance in postmenopausal breast cancer patients. **Methods**: We collected primary tumor blocks from 563 ER$\alpha$ positive (stage I-III) postmenopausal patients who had been randomized between tamoxifen (1 to 3 years) vs. no adjuvant therapy (IKA trial). The median follow-up of patients without a recurrence event was 7.8 years. Immunohistochemistry was performed on a tissue microarray using monoclonal antibodies for IGF-1R and phosphorylated(p)-IGF-1R. Cytoplasmic p-IGF-1R and membranous IGF-1R intensity were scored (0-3). To assess IGF-1R activation the ratio p-IGF-1R/ IGF-1R was calculated. Multivariate Cox models including standard prognostic factors were used to assess hazard ratios (HRs) for recurrence free interval and the interaction between tamoxifen treatment and IGF-1R activation, using the median ratio as cutoff. In addition we tested the association between the ratio p-IGF-1R/ IGF-1R and downstream-activated proteins in the PI3K and MAPK pathways. **Results**: Patients with a tumor with a low p-IGF-1R/ IGF-1R ratio ($\leq$ 0.5) derived significant benefit from tamoxifen (HR 0.41, p=0.001), while patients whose tumor did express a high ratio did not (HR=1.47, p=0.53), p for interaction 0.05. Significant positive associations were observed between the p-IGF-1R/ IGF-1R ratio and p-AKT, p-ERK1/2, p-mTOR and p-p70S6K. **Conclusions**: In postmenopausal primary breast cancer patients, IGF-1R activation is associated with downstream PI3K and MAPK pathway activation and intrinsic tamoxifen resistance. A potential benefit from IGF-1R inhibitors in these tamoxifen resistant patients would be interesting to explore.

**545 General Poster Session (Board #9), Mon, 8:00 AM-11:45 AM**

**Enzalutamide plus exemestane: A pilot study to assess safety, pharmacokinetics, and effects on circulating estrogens in women with advanced hormone-positive breast cancer.** *Presenting Author: Lee Steven Schwartzberg, The University of Tennessee Health Science Center, Memphis, TN*

**Background:** Exemestane (EXE) is a commonly used aromatase inhibitor (AI) in patients (pts) with advanced ER/PgR+ breast cancer (BC). The androgen receptor (AR), expressed in the majority of ER/PgR+ BC, is believed to play a role in resistance to AI therapy. Enzalutamide (ENZA), a potent inhibitor of AR signaling, induces CYP3A4, an enzyme involved in the metabolism of EXE. We previously reported that the addition of ENZA (160 mg/day) to EXE 25 mg/day resulted in ~40% reduction in EXE exposure. The US product label recommends doubling the dose of EXE when administered in combination with a potent CYP3A4 inducer. This trial investigates daily ENZA 160 mg + EXE 50 mg. **Methods:** Postmenopausal pts with ER/PgR+ advanced BC received $\geq$14 days of EXE 50 mg/day prior to initiating ENZA 160 mg/day on Day 1 (NCT01597193). Prior EXE and non-measurable disease was allowed. Blood sampling occurred on Day -1 (no ENZA) and on Day 29 (+ ENZA) to assess PK interactions and effects on circulating estrogens (estradiol and estrone). Available tumor tissue was analyzed centrally for AR expression although AR+ disease was not required. Response assessments (RECIST 1.1) were performed approximately every 3 months. **Results:** As of 11 Dec 2013, data were available for 18 of the 24 pts enrolled. Median age/ECOG was 66/0; median number of prior hormonal therapies was 2.5. Common (>10%) treatment-related adverse events (AEs) included nausea, vomiting and fatigue. No treatment-related serious AEs or AEs $\geq$ Grade 3 have been reported. Preliminary data indicate that ENZA + EXE 50 mg achieves similar EXE exposure to EXE 25 mg alone (AUC=127$\pm$70 vs. 131$\pm$64 ng.h/mL) and maintains estrogen suppression for the majority of pts. Full data on PK, tolerability, estrogen levels and anti-tumor activity will be presented. **Conclusions:** To date, the combination of daily ENZA 160 mg + EXE 50 mg has been well tolerated. Doubling the dose of EXE appears to restore EXE exposure thereby maintaining the suppression of estrogens. An ongoing randomized double-blind, placebo-controlled phase 2 trial in ER/PgR+ advanced BC will determine if the combination of daily ENZA 160 mg + EXE 50 mg is more active than EXE 25 mg alone. Clinical trial information: NCT01597193.

**546 General Poster Session (Board #10), Mon, 8:00 AM-11:45 AM**

**Effect of multifocality and multicentricity on outcome in early breast cancer: A systematic review and meta-analysis.** *Presenting Author: Francisco Emilio Vera-Badillo, Princess Margaret Cancer Centre - University Health Network, Department of Medicine, University of Toronto, Toronto, ON, Canada*

**Background:** Women with multifocal or multicentric breast tumors (multifocality henceforth) have been reported to have greater probability of nodal metastasis and relapse and worse survival than women with unifocal tumors. However, these associations have been inconsistent and multifocality is not taken into account by staging guidelines and prognostic models. **Methods:** A systematic review of Medline and EMBASE (host: Ovid) from 1946 to July 2013 identified publications exploring the association between multifocality and overall survival (OS), disease-free survival (DFS), disease-specific survival (DSS) and loco-regional relapse (LRR). The hazard ratios (HR) for OS and DFS for multifocal compared to unifocal tumors were extracted from multivariable analyses and included in a meta-analysis. For studies not reporting multivariable analyses, odds ratios (OR) were estimated from Kaplan-Meier curves for all endpoints at 5 and 10 years. **Results:** Twenty-two studies comprising 67,557 women were included. Multifocality was reported in 9.5% of patients. Classical prognostic factors were well balanced between unifocal and multifocal populations. In multivariable analyses, multifocality was associated with significantly worse OS (HR=1.65, p=0.02), and a non-significant association with worse DFS (HR=1.96, p=0.07). Inter-study heterogeneity was significant (Cochran Q p<0.001 in both analyses). Similar results were observed for the odds of death or disease recurrence by 5 years (OR=1.39, p=0.02; OR=1.52, p=0.02, respectively). Additionally, multifocality was associated with worse DSS and a higher odds of LRR (OR=1.56, p=0.03; and OR=3.23, p=0.02, respectively). Similar estimates were observed at 10 years but statistical significance was only reached for DSS and LRR (OS: OR=1.40, p=0.07; DFS: OR=1.49, p=0.06; DSS: OR=1.69, p<0.001; LRR: OR=2.94, p=0.03). **Conclusions:** Multifocality appears to be associated with a worse prognosis. Substantial inter-study heterogeneity limits the precise determination of increased risk; however, the inclusion of multifocality as an independent prognostic factor appears warranted.

**547 General Poster Session (Board #11), Mon, 8:00 AM-11:45 AM**

**Association between androgen receptor (AR) expression, Ki-67, and the 21-gene recurrence score in early breast cancer.** *Presenting Author: Francisco Emilio Vera-Badillo, Princess Margaret Cancer Centre - University Health Network, Department of Medicine, University of Toronto, Toronto, ON, Canada*

**Background:** AR expression is a favorable prognostic factor in estrogen receptor (ER) positive and ER negative breast cancer. Here we explore the association between AR, Ki67, and the 21-gene recurrence score (RS). We hypothesized that ER-positive breast cancers with high AR expression will be associated with a low Ki67 and RS. **Methods:** Sequential patients with lymph node negative, ER positive and HER2 negative breast cancer who had surgery at Mount Sinai Hospital, Toronto between January 2010 and October 2013 and in whom the RS was requested were identified. Archival tissue was sectioned and stained for AR (AR441 clone, Dako) and Ki67 (MIB-1 clone, Dako) and then visualized by protein polymer (MACH4, Biocare) and DAB chromogen. AR was scored using the Allred system and Ki67 by manual count (using the Ki67 working group recommendations) by a single pathologist. Associations between RS and AR, age, grade, mitotic score, Ki67, and the extent of ER and progesterone receptor (PgR) expression were assessed using linear regression. Ki67 was assessed as a continuous and dichotomous variable (using a cut off of 14%). Statistical significance of this exploratory study was defined as p<0.10. **Results:** Seventy cases satisfied criteria for analysis. Median age was 59.5 years, mean tumor size was 1.8 cm (range 0.6-3.9 cm), 24% were grade 1, 66% grade 2 and 10% grade 3. Most tumors had high AR expression (median Allred score = 8, 97% had score $\geq$4). Median RS was 15 (range 1-53). AR expression showed a modest positive correlation with ER (R=0.37), but no correlation with PgR (R=0.09) or Ki67 (R=-0.18). In univariable analysis, AR (p=0.01), ER (p<0.001) and PgR (p<0.001) had significant negative associations with the RS. Ki67 had a non-significant positive association with RS (p=0.11 and p=0.16 for continuous and cut off analyses, respectively). Age (p=0.93), grade (p=0.40) and mitotic count (p=0.23) showed no association with RS. Multivariable analysis showed similar associations with RS (AR [p=0.07], ER [p=0.05], PgR [p=0.001]). **Conclusions:** AR is not associated with proliferative index (Ki67) but is associated with lower probability of disease recurrence (Low RS).

**548^ General Poster Session (Board #12), Mon, 8:00 AM-11:45 AM**

**First-line pertuzumab (P), trastuzumab (H), and taxane therapy for HER2-positive locally recurrent/metastatic breast cancer (LR/mBC): Interim safety results (N=704) from PERUSE.** *Presenting Author: Thomas Denis Bachelot, Département d'Oncologie Médicale, Centre Léon Berard, Lyon, France*

**Background:** Combining P with 1st-line H + docetaxel (DOC) in pts with HER2-positive mBC significantly improved progression-free survival (PFS) and overall survival (OS) in the randomized phase III CLEOPATRA trial. PERUSE is assessing the safety of 1st-line P + H + investigator's chosen taxane in routine oncology practice. **Methods:** In the ongoing multicenter single-arm phase IIIb PERUSE study, pts with HER2-positive LR/mBC, ECOG PS ≤2 and no prior systemic therapy for LR/mBC (except endocrine therapy) receive P (840→420 mg q3w), H (8→6 mg/kg q3w) and a taxane (DOC, paclitaxel [PAC] or nab-PAC) until disease progression (PD) or unacceptable toxicity. Pts will be followed until 45 mo after last pt enrollment. The primary endpoint is safety, including grade (G) ≥3 AEs. Secondary endpoints include PFS, OS, objective response rate and QoL. We report a prespecified interim analysis reviewed by the Independent Data Monitoring Committee. **Results:** As of 13 Sep 2013, 704 of the planned 1500 pts had completed ≥6 weeks' follow-up. Baseline characteristics: median age 55 y (range 26–87); 26% ≥65 y; 76% Caucasian; 61% ECOG PS 0; 32% stage IV at 1st diagnosis; 73% visceral metastases; 67% ER and/or PgR positive; 29% prior (neo)adjuvant H; 43% prior (neo)adjuvant chemotherapy. The initial taxane was DOC in 320 pts (45%), PAC in 331 (47%) and nab-PAC in 45 (6%). The median number of cycles was 9 (range 1–23) for P, 8 (1–23) for H and 6 (1–21) for each taxane; 81% of pts are still receiving ≥1 study therapy. Therapy was discontinued most often for PD (P 7%, H 7%, taxane 4%) and for AEs in 4% (each agent). **Conclusions:** The safety profile of P + H + investigator's choice of taxane in this interim safety analysis is consistent with previous clinical experience of P + H + DOC. No unexpected safety signals were seen. Safety data by taxane will be reported. Clinical trial information: NCT01572038.

**AEs in >15% (any G) or >1% (G ≥3)**

| AE, % of pts | All G | G ≥3 |
|---|---|---|
| Diarrhea | 65.1 | 7.5 |
| Alopecia | 41.8 | 0 |
| Nausea | 28.0 | 0.4 |
| Fatigue | 27.6 | 2.1 |
| Asthenia | 25.0 | 1.8 |
| Peripheral neuropathy | 19.5 | 1.1 |
| Mucosal inflammation | 18.6 | 1.4 |
| Rash | 18.0 | 0.4 |
| Epistaxis | 16.8 | 0 |
| Vomiting | 15.2 | 0.6 |
| Dysgeusia | 15.2 | 0.1 |
| Anemia | 13.9 | 1.6 |
| Neutropenia | 13.1 | 8.7 |
| Dyspnea | 11.1 | 1.1 |
| Febrile neutropenia | 4.4 | 4.4 |

**549 General Poster Session (Board #13), Mon, 8:00 AM-11:45 AM**

**Combined IHC4 score and local recurrence in breast cancer.** *Presenting Author: Roopa Lakhanpal, Department of Radiation Oncology, The Canberra Hospital, Canberra, Australia*

**Background:** The immunohistochemical 4 (IHC4) score is a pathological prognostic score that is a quantative measurement of estrogen and progesterone receptor status, the her2 status and the Ki-67 score. Cuzick et al. created a prognostic model that integrates IHC4 with clinical parameters of nodal status, tumour size, grade and age that may be as useful prognostically as multiple gene expression profiling assays (Cuzick et al J Clin Oncol. 2011 Nov 10;29(32):4273-8.). The role of the IHC4 score in predicting local recurrence is evolving. This study explores the role of the combined IHC4 score and loco-regional recurrence in women who have had breast conservation surgery without radiotherapy. **Methods:** Women with invasive breast cancer treated with breast conservation surgery and no radiotherapy were selected from a prospective cohort of breast cancer patients enrolled in the Australian Capital Territory and South East New South Wales Breast Cancer Treatment Group (ACT&SE NSW BCTG) Quality Assurance Project from 1997-2010.The IHC4 parameters were scored using pathology reports, slide review, and conducting further IHC testing when data was missing. Clinical information was obtained from the database and combined scores were calculated using the formula described by Cuzick. A Cox regression model was used to assess the association between the combined score and the risk of loco-regional recurrence. **Results:** Fifty-nine women in whom all the IHC4 variables were quantified and who had breast conservation surgery, were ER positive and who did not have adjuvant radiotherapy or chemotherapy were used to test the model. Using the same cut-off points and patient selection criteria for the combined IHC4 score described by Cuzick for low, intermediate and high risk groups, the loco-regional recurrence rates were zero for the low risk group(n=34), 23.5% in the intermediate group (n=17), and 37.5% in the high-risk group (n=8). Local recurrence tended to occur within 5 years for the high-risk group and beyond 5 years in the intermediate group. **Conclusions:** The combined IHC4 clinical effectively defined a sub-group of women with breast cancer treated with breast conservation surgery without radiotherapy that had negligible local recurrence rates.

**550 General Poster Session (Board #14), Mon, 8:00 AM-11:45 AM**

**Comparison of test results and clinical outcomes of patients assessed with both MammaPrint and Oncotype DX with pathologic variables: An independent study.** *Presenting Author: David J. Dabbs, Department of Pathology, Magee Women's Hospital, Pittsburgh, PA*

**Background:** There are no comparisons between test results of MammaPrint and Oncotype DX. **Methods:** Oncotype DX (ODX) recurrence score (RS) on 437 patients with pathologically characterized ER+ tumors who had a minimum of 5 years follow-up from diagnosis was compared with MammaPrint (MP), BluePrint (BP) and TargetPrint (TP). **Results:** Of 301 MP low risk cases, 191 were low risk by ODX (63% agreement) and of 136 MP high risk, 63 were high risk by ODX (46%). Of ODX intermediate risk cases (161), 104 of were MP low risk (65%), 57 (35%) were MP high risk. Of BP low risk luminal tumors, 188/287(66%) were ODX low, 95/287 (33%) ODX intermediate, and 4/287 (1%) ODX high risk (Table). Tumor grade was significantly correlated at P<.0001 with risk assessment by both tests. BP class was correlated with ER, PR and HER2 results. Overall agreement between clinical ER, PR, HER2 (IHC+FISH) results with TP results were 92% (401/435), 85% (370/436), 95% (412/435), but percent positive agreement for HER2 was only 50% (20 of 40 unequivocally HER2 positive cases identified correctly by TP). Four percent of ODX low risk, 34% of intermediate and 77% of ODX high risk ODX patients received chemotherapy. There were 7 distant recurrences: 4 were MP high, 3 MP low; For ODX, 5 were intermediate, 1 high,1 low (Table). **Conclusions:** (1) There are real differences in risk assignments between MP and ODX that may affect treatment decisions. (2) There was close correlation between pathologic variables and MP and BP, but HER2 TP -FISH/IHC agreement is low. (3) Further follow-up of this cohort is required, along with prospective trials, to determine clinical utility of these tests compared to pathologic analysis.

**MammaPrint versus Oncotype Dx.**

| | | RS | RS | RS | |
|---|---|---|---|---|---|
| MammaPrint | BluePrint | High *1 | Intermediate *5 | Low *1 | Total |
| High risk MP | Basal-like | 8 | 2 | | 10 |
| | ERBB2 *2 | 28 | 8 | | 36 |
| | Luminal-like *2 | 27 | 47 | 16 | 90 |
| High risk total | | 63 | 57 | 16 | 136 |
| Low risk MP | ERBB2 | 2 | 9 | 3 | 14 |
| | Luminal-like *3 | 4 | 95 | 188 | 287 |
| Low risk total | | 6 | 104 | 191 | 301 |
| Grand total | | 69 | 161 | 207 | 437 |

* Distant recurrences.

**551 General Poster Session (Board #15), Mon, 8:00 AM-11:45 AM**

**Adjuvant denosumab for breast cancer: What efficacy in the D-CARE trial will translate into cost effectiveness?** *Presenting Author: Nathan William Dana Lamond, Department of Medicine, Dalhousie University, Halifax, NS, Canada*

**Background:** Bone targeted agents are important therapies in the treatment of metastatic breast cancer and have a potential role in the adjuvant setting. Several trials and metaanalyses have suggested that adjuvant bisphosphonates may reduce breast cancer recurrence rates by 15% or more in postmenopausal women. Adjuvant denosumab is currently being investigated in D-CARE, an ongoing phase III trial. The aim of the current study was to estimate the absolute disease-free survival (DFS) advantage that would have to be observed in D-CARE for adjuvant denosumab to be considered cost-effective in the Canadian healthcare system. **Methods:** A Markov model was developed to calculate cumulative lifetime costs and quality-adjusted life year (QALY) gains for adjuvant therapy with and without denosumab in a hypothetical cohort of women with early-stage breast cancer. Costs, utilities and probabilities were derived from the literature. A one-way sensitivity analysis (SA) was performed to explore the relationship between a range of DFS hazard ratios (HR) and incremental cost-effectiveness ratios (ICER) with all other parameters held constant. Further one-way and probabilistic sensitivity analyses were performed to explore the effects of changes to other model parameters including menopausal status. The model took a direct payer perspective with all costs and benefits discounted at 3%. **Results:** The one-way SA showed that the ICER for adjuvant denosumab was directly related to the HR for DFS. At an ICER threshold of $100,000/QALY, the corresponding DFS HRs were 0.94 and 0.89 for pre and postmenopausal breast cancer patients, respectively. The ICER also varied with changes to other model parameters, but was stable over reasonable ranges of uncertainty. **Conclusions:** This model suggests that adjuvant denosumab will be considered cost-effective by current North American standards, should it reduce breast cancer recurrence rates by more than approximately 10%. In the event of positive results from D-CARE of at least this magnitude, the current anticipatory analysis may help inform treatment choices, influence drug funding decisions, and provide patients with timely access to disease-modifying therapy.

**552 General Poster Session (Board #16), Mon, 8:00 AM-11:45 AM**

**Cardiology monitoring substudy in the PERSEPHONE trial: 6 versus 12 months of trastuzumab.** *Presenting Author: Louise Hiller, Warwick Clinical Trials Unit, University of Warwick, Coventry, United Kingdom*

**Background:** PERSEPHONE is a randomised trial comparing 6month (6m) to 12month (12m) of trastuzumab in patients (pts) with HER2-positive early breast cancer. The trial has recruited 3,166 of 4,000 pts. We report the results of the cardiology monitoring substudy, which the iDSMC reviewed in June 2013 and recommended we release. **Methods:** Left ventricular ejection fraction (LVEF) was measured prior to trastuzumab, and then 3-monthly for 12 months (x5). Low LVEF was defined as either <50%, or reported as 'low'. **Results:** 11,413 LVEF tests have been reported in 2,484 pts (see Table). Only 10% pts reported low LVEFs, similar across arms (p=0.19). In total, only 483 low LVEFs were reported. There was no difference in time to first low LVEF between treatment arms (log-rank p=0.49). On each treatment arm, there were statistically significant reductions in LVEF % at 6 and 12 months (all p<0.0001). Significantly more 12m pts reported delays (p=0.007) and discontinuations (p<0.0001) due to low LVEFs. **Conclusions:** Both PERSEPHONE arms are considered safe, with only small relative reductions in LVEF. Duration of treatment has no effect on numbers of pts reporting low LVEFs or time to first low LVEF. However the longer treatment suffers from more delays and discontinuation due to low LVEFs. Low LVEF may relate more to pt factors (e.g.pharmacogenetics), than length of treatment. The data support, and the iDSMC now recommend, less intensive cardiology monitoring during treatment. Clinical trial information: 52968807.

| | 6 m trastuzumab | 12 m trastuzumab | |
|---|---|---|---|
| **No. pts** | 1,243 | 1,241 | |
| **No. (%) pts reporting low LVEFs** | 110 (9%) | 130 (10%) | p=0.19 |
| **No. LVEF tests** | 5,462 | 5,951 | |
| **No. (%) low LVEFs** | 213 (4%) | 270 (5%) | |
| **Time to first low LVEF** | | | Log-rank p=0.49 |
| **6 month low LVEF rates** | 7% | 6% | |
| **12 month low LVEF rates** | 10% | 11% | |
| **Relative change from baseline Median (IQR), p** | | | |
| **Baseline to 6 month** | .96 (.90-1.02), p<0.0001 | .97 (.91-1.03), p<0.0001 | p=0.01 |
| **Baseline to 12 month** | .98 (.91-1.03), p<0.0001 | .97 (.90-1.03), p<0.0001 | p=0.07 |
| **Cardiology effect on treatment** | | | |
| **Trastuzumab doses** | 11,171 | 20,383 | |
| **No. pts** | 1,233 | 1,231 | |
| **Pts reporting delays** | 38 (3%) | 66 (5%) | p=0.007 |
| **Pts reporting discontinuations** | 20 (2%) | 62 (5%) | p<0.0001 |

**553 General Poster Session (Board #17), Mon, 8:00 AM-11:45 AM**

**A phase I study of the AKT inhibitor MK-2206 plus hormonal therapy in postmenopausal women with estrogen receptor positive (ER+) metastatic breast cancer (MBC).** *Presenting Author: Cynthia X. Ma, Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO*

**Background:** Inhibition of the PI3K/AKT pathway synergize with hormonal therapy for ER+ BC in preclinical studies. We conducted a phase I trial of MK-2206 plus anastrozole (A) (Phase IA and IB) or fulvestrant (F) (Arm C) or A+F (Arm D) in postmenopausal women with ER+ MBC to obtain the recommended phase II treatment dose (RPTD). **Methods:** phase IA employed a 3+3 design to determine the maximum tolerated dose (MTD) of MK-2206. Pts treated at the MTD were eligible for Phase IB to determine RPTD based on first 3-cycle adverse events (AE). Arms C and D evaluated whether MK-2206 at the RPTD was tolerable when combined with F or A+F. Cycle 1 day 1 (C1D1) MK-2206 began after at least 2 weeks (wks) of A and/or 4 wks of F. FDG PET was performed in Phase IA on C1D1 prior to MK-2206 and C1D2. Tumor was measured every 3 28-day cycles. Baseline blood was assayed for PIK3CA E545K and H1047R mutations. **Results:** Thirty one pts, median age 55 (range 32-79) years, were enrolled (Table 1). MK-2206 was administered PO wkly, with A and/or F. Because grade (G)3 rash occurred in 3 of the first 8 pts, prophylactic prednisone was added subsequently. Treatment was well tolerated. G3 rash was the only dose limiting toxicity (DLT). The most common all-cycle AEs were rash (n=10), hyperglycemia (n=11), and hypophosphatemia (n=5). The MTD and RPTD of MK-2206, plus A and/or F, were 150mg PO wkly with prophylactic prednisone. Median SUV reduction was 14.5% (-58% to 19%) on C1D2 compared to C1D1. Twenty six pts, with a median of 1 (0-7) metastatic therapy, were evaluable for response. Eleven pts, 42% (95% CI 23% - 63%), derived clinical benefit, including 2 PR and 9 SD >= 6 months. Time to progression was significantly associated with prior adjuvant hormonal therapy (p=0.02), but not with circulating PIK3CA mutation or hyperglycemia. Tumor specimen analysis is ongoing. **Conclusions:** MK-2206 plus hormonal therapy was well tolerated with anti-tumor activity observed. Rash was common but incidence reduced with prophylactic prednisone. Clinical trial information: NCT01344031.

| Arm | Dose Level | MK-2206 (mg) | N | N (DLT) |
|---|---|---|---|---|
| **1A** | 1* | 150 | 5 | 2 |
| **1A** | -1 | 100 | 3 | 1 |
| **1A/1B** | 1# | 150 | 6 | 0 |
| **1A** | 2# | 200 | 2 | 2 |
| **Arm C** | 1# | 150 | 8 | 1 |
| **Arm D** | 1# | 150 | 7 | 1 |

* Starting dose #prednisone 20mg PO the day before, the day of, and the day after MK-2206.

**554 General Poster Session (Board #18), Mon, 8:00 AM-11:45 AM**

**Intracellular intermolecular relationships of LKB1 in breast cancer.** *Presenting Author: Binafsha Manzoor Syed, Liaquat University of Medical & Health Sciences Jamshoro, Jamshoro, Pakistan*

**Background:** The role of liver kinase B1 (LKB1), a serine/threonine kinase, has been described in the development of Peutz Jagher's syndrome, where a large proportion (45%) of patients have been reported to develop breast cancer in their life time. Cell line studies have also shown a link of LKB1 with the action of oestrogen, metformin and diabetes. This study aimed to analyse the intracellular molecular relationships of LKB1 in older women with early operable primary breast cancer. **Methods:** Between 1973-2010, a consecutive series of 1,758 older (≥70 years) women with T0-2 N0-1M0 breast carcinoma were managed in a dedicated facility. Of these 813 patients underwent primary surgery and 575 had good quality tumour samples available for tissue microarray construction. LKB1 was assessed by indirect immunohistochemistry using Ley37D/G6-ab15095/Abcam (primary antibody) and Envision method (secondary antibody). Tumours having 30% of cells with cytoplasmic expression were considered positive. **Results:** Positive LKB1 was seen in 318 (78.1%) patients. Such expression was significantly associated with high tumour grade (p=0.01), positive expression of HER2 (p=0.003), Ki67 (p=0.01), VEGF (p=0.002), HER4 (p=0.001), BRCA2 (p=0.01), MDM2 (p<0.001) and negative expression of CD44 (p=0.03). However there was no significant correlation with tumour size, axillary lymph node status, ER, PgR, p53, cytokeratins 5, 5/6, 14, 17, 18 and 19, bcl2, Muc1, EGFR, HER3, MDM4, E-cadherin, and BRCA1. **Conclusions:** LKB1 showed strong correlations with most biomarkers known to be associated with poor prognosis. Given the evidence from cell line studies mentioned, further studies are required to explore its relationship with clinical outcome and its role as a potential therapeutic target.

**555 General Poster Session (Board #19), Mon, 8:00 AM-11:45 AM**

**Estrogen receptor-positive (ER+) metastatic breast cancer (MBC) patients (pts) with extreme responses (ERs) to capecitabine having tumors with genomic alterations in DNA repair and chromatin remodeling genes.** *Presenting Author: Maren K. Levin, Baylor-Sammons Cancer Center, Texas Oncology, US Oncology, Dallas, TX*

**Background:** We sought to understand the genomic alterations in tumors of MBC pts who had extreme durations of response to capecitabine (C). **Methods:** Following IRB-approved informed consent, targeted next generation sequencing (NGS) was performed on pts' FFPE primary breast cancer (n=4) or MBC (n=2) specimens at a CLIA-certified laboratory to characterize genomic alterations across 287 cancer-related genes. Reverse phase protein microarray (RPMA) was also performed. **Results:** Six postmenopausal pts with ER+/HER2- MBC and ERs with C were studied. Metastases comprised bone/lymph node (n=1) or liver (n=5; liver only, liver/bone, liver/bone/chest wall). Four pts had received ≥2 prior chemotherapy regimens for metastatic disease. Four pts received C + paclitaxel (mean 17 mos; range 4–57); three of these then continued C alone (mean 86 mos; range 59–118). Two pts received C monotherapy (54 and 91+ mos). C was discontinued after a mean of 66 mos in four pts (range 54–86); two pts remain on C (91+ and 122+ mos). On NGS, 50% (3/6) of pts' tumors had likely functional alterations in DNA repair and chromatin remodeling genes (Table) – a higher than expected prevalence in ER+ MBC. Three pts had variants of unknown significance (VUS) in these pathways. *PIK3CA* substitutions or amplifications of *AKT2, FGFR1, ZNF703*, as well as phosphorylation of HER family receptors and their downstream proteins on RPMA did not appear to preclude ERs to C. **Conclusions:** Three MBC pts with ERs to C (54–122+ mos) had genomic alterations in DNA repair pathways (double strand break response and homologous recombination) and in histone acetyl- and methyltransferase genes. We are exploring the potential function of the VUS in the other three pts. Preclinical data show that sensitivity to 5-FU is enhanced by deficiencies in chromatin remodeling and homologous recombination genes (Matuo, et al. Genet Mol Res, 2013), suggesting a strategy for pt selection for C.

| | Genomic alterations or *[VUS]* | |
|---|---|---|
| **Patient** | **DNA repair** | **Chromatin remodeling** |
| **1** | *[BRCA2, FANCF]* | *[SETD2]* |
| **2** | *CHEK2, PALB2* | *NCOR1, TET2* |
| **3** | *CHEK2* | *[BCORL1]* |
| **4** | *ATM* | *EP300* |
| **5** | *[PARP1]* | *[NCOR1, CBFβ]* |
| **6** | *[SETD2]* | *[EP300, SETD2]* |

**556 General Poster Session (Board #20), Mon, 8:00 AM-11:45 AM**

**A phase II clinical trial of HDACi (vorinostat) and AI therapy in breast cancer with molecular imaging correlates.** *Presenting Author: Hannah M. Linden, University of Washington, Seattle, WA*

**Background:** Histone deacetylase inhibitors (HDACi) have shown preclinical promise in estrogen receptor-modulation and restoring sensitivity to endocrine manipulation in ER+ breast cancer. Vorinostat is an FDA approved HDACi for CTCL, and could have a beneficial role in restoring ER-signaling in endocrine-resistant tumors. [F-18]fluoroestradiol (FES) PET imaging may be used to monitor regional ER expression in patients with breast cancer. **Methods:** Patients with metastatic breast cancer with prior clinical benefit from endocrine manipulation and who progressed on AI therapy were eligible. In part A patients cycled between vorinostat for 2 wks, and AI for 6 wks. In part B (reflecting results of HDACi trials) patients were given vorinostat 400mg po daily 5/7 days 3/4 wks while AI was given continuously. Paired FES and FDG PET were performed at baseline, wks 2 and 8; clinical/radiologic assessment of disease was also performed at wk 8. Patients with clinical benefit (response or stable disease) continued on treatment until progressive disease or study withdrawal. Lesion-level analysis of the association between baseline FES uptake (logged) and FES/FDG ratio used generalized estimating equations (GEE). **Results:** 16 of 20 planned patients have accrued and treatment is well tolerated; one withdrew for toxicity. The majority of patients have longstanding, bone/soft tissue dominant disease, and were previously treated with multiple endocrine and chemotherapy regimens. Six patients have had clinical benefit (4/8 evaluable on part B), remaining on study treatment for >40, 29, >21, and >8 wks. FES and FDG uptake was analyzed in 101 lesions in 16 patients. FES uptake in general remained stable during treatment and FDG declined in responding patients. Two responding patients showed increase in FES with clinical benefit and two patients with clinical benefit had negligible pre-therapy FES uptake. **Conclusions:** HDACi therapy can be effective in hormone-refractory breast cancer. Molecular imaging in parallel with early studies indicate a heterogeneity of response patterns, suggesting that some patients benefit from AI plus vorinostat, and some may benefit from the HDACi alone. Clinical trial information: NCT01153672.

**557 General Poster Session (Board #21), Mon, 8:00 AM-11:45 AM**

**Patient-reported endocrine symptoms, sexual functioning, and quality of life (QoL) in the IBCSG TEXT and SOFT trials: Adjuvant treatment with exemestane (E) plus ovarian function suppression (OFS) versus tamoxifen (T) plus OFS in premenopausal women with hormone receptor-positive (HR+) early breast cancer (BC).** *Presenting Author: Juerg Bernhard, International Breast Cancer Study Group, Bern, Switzerland*

**Background:** Little is known about endocrine symptoms, QoL and sexual function in premenopausal women with BC receiving adjuvant endocrine therapy. TEXT and SOFT are the first trials providing patient-reported data in this population. **Methods:** From Nov 2003 to Apr 2011, 4096 premenopausal patients (pts) with HR+ BC were enrolled and included in the QoL analysis of the randomized phase III trials, TEXT and SOFT, to receive adjuvant treatment with 5 yrs E+OFS or T+OFS. Chemotherapy (chemo) was optional in both trials; received concurrently with OFS after randomization in TEXT and prior to randomization in SOFT, with women eligible if they remained premenopausal after completing chemo. Pts completed a questionnaire consisting of global and symptom-specific indicators at baseline, every 6 months for the first 24 months, and annually yrs 3 to 6. Differences in change of QoL from baseline between the two treatments were tested at short-, mid-, and long-term (6, 24 and 60 months post-randomization, respectively) for 3 global QoL and 5 symptom indicators using mixed models with repeated measures. **Results:** Pts on T+OFS were significantly more affected by hot flushes than E+OFS, with treatment difference persisting over time (each $p<.05$). The change of hot flushes from baseline improved over time for both treatments. Throughout treatment, pts on E+OFS reported more vaginal dryness and greater loss of sexual interest, while T+OFS reported more vaginal discharge (each $p<.0001$). The difference between treatments in bone/joint pain was most pronounced in the short-term in favor of T+OFS, but a difference persisted (each $p<.0001$). Changes of global QoL indicators (mood, physical wellbeing, and coping effort) from baseline were similar between treatments over the whole treatment period. **Conclusion:** Overall from a QoL perspective, there is no strong indication to favor either E+OFS or T+OFS. The differential effects of the two treatments on endocrine symptoms burden need to be addressed with patients individually. Clinical trial information: NCT00066783/NCT00066690.

**558 General Poster Session (Board #22), Mon, 8:00 AM-11:45 AM**

**SWOG S0307 phase III trial of bisphosphonates as adjuvant therapy in primary breast cancer: Comparison of toxicities and patient-stated preference for oral versus intravenous delivery.** *Presenting Author: Julie Gralow, University of Washington, School of Medicine, Seattle, WA*

**Background:** Bone metastases are a common site of distant recurrence in breast cancer. Evidence from randomized trials, including a recent meta-analysis, suggests that adjuvant bisphosphonates can decrease recurrence and death. SWOG S0307 compares efficacy of 3 bisphosphonates in early stage breast cancer. **Methods:** Patients with stage I-III breast cancer receiving adjuvant systemic therapy were randomized to receive 3 years of clodronate (CLOD) (1600 mg po qd), ibandronate (IBAN) (50 mg po qd) or zoledronic acid (ZA) (4 mg IV q month x 6, then q3 months x 2.5 years). The primary endpoint is disease-free survival. Overall survival, sites of first recurrence, and adverse events are secondary endpoints. **Results:** Between Nov 2005 and Feb 2010 6,097 patients were enrolled. Survival data are maturing with 50% of the expected events occurring to date. Annual interim analyses are being conducted. 5,752 patients are assessable for toxicity. Median age was 53. 78% of tumors were ER positive, 16% HER2 positive, 16% triple negative. 34% were stage I, 45% stage II, and 21% stage III. Planned adjuvant treatment included chemotherapy in 80%, endocrine therapy in 76%, and both in 56%. 25 (0.4%) and 494 (8.6%) patients experienced grade 4 or 3 toxicities, respectively. The most common adverse events were musculoskeletal, pain, gastrointestinal, metabolic/laboratory (creatinine, calcium), and constitutional symptoms (acute phase reactions). There have been 40 reported cases of osteonecrosis of the jaw (ONJ): ZA 24/2094 (1.15%), CLOD 6/2151 (0.28%), and IBAN 10/1507 (0.66%) ($p=0.003$). Fractures have been reported in 4.5% of patients in ZA arm, 4.8% in CLOD arm, and 4.1% in IBAN arm ($p=$ ns). Prior to randomization, 76% preferred oral medication versus 24% for intravenous if drugs proved equal in efficacy. Preferences changed little at completion of therapy, although some switched preference. **Conclusions:** Grade 3 and 4 toxicities were low in S0307. ONJ, a rare but serious complication, was statistically highest for ZA and lowest for CLOD. Fractures were equal across arms. The majority of patients indicated a preference for oral formulation. Clinical trial information: NCT00127205.

**559 General Poster Session (Board #23), Mon, 8:00 AM-11:45 AM**

**An estimation model for Oncotype DX recurrence score using routine histopathologic variables.** *Presenting Author: Hyunseok Kim, The Johns Hopkins University School of Medicine, Baltimore, MD*

**Background:** The gene expression profile assayOncotypeDx (ODX) is frequently used to guide adjuvant chemotherapy decisions for patients with estrogen receptor (ER)-positive, lymph node (LN)-negative breast cancer. We hypothesized that in cases where ODX is being considered, the observed recurrence score (RS) category can be accurately estimated using routinely available, less costly histopathologic variables. **Methods:** We retrospectively reviewed pathology reports between June 2006 and August 2012 from Johns Hopkins (JH) patients ($n=301$) with early stage ER-positive, LN-negative breast cancer, for whom ODX was ordered. We developed a linear regression model using routine histopathologic markers (ER and progesterone receptor [PR] expression, HER2 status, tumor grade, and Ki67) to calculate an Estimated Recurrence Score (ERS), and correlated it with the observed ODX RS assay result. This model was internally cross-validated in the JH cohort, and externally validated in a separate 326-patient cohort from three Maryland community settings. **Results:** In the JH cohort, 244 patients had an observed RS $\leq$ 25 (80%) and 57 patients had an observed RS above 25 (20%). When the ERS was $<21$ ($n=200$), we accurately classified 95% of them (191) who were found to have a low risk(observed RS $\leq$ 25). Similarly, 95% of those (18/19) with an ERS $>30$ fell into a high risk category with observed RS $>25$. An accuracy of 93% was observed in the external validation cohort (Table). **Conclusions:** We developed a clinical estimator of the ODX RS using cases in which the clinician chose to order ODX RS in routine clinical practice. For more than 80% of patients in the external validation cohort, ERS was estimated to be $<21$ or $>30$ and in this group, the Hopkins ERS model correctly predicted the observed RS category ($\leq 25$ or $>25$) in 93% of cases. Although further validation of this model is warranted, preliminary evidence supports use of ERS to reliably identify those patients most likely to benefit from including ODX RS results in therapeutic decision-making.

| JH cohort | ODX RS ≤ 25 | ODX RS > 25 | Total | External cohort | ODX RS ≤ 25 | ODX RS > 25 | Total |
|---|---|---|---|---|---|---|---|
| ERS < 21 | 191 | 9 | 200 | ERS<21 | 227 | 17 | 244 |
| ERS(21-30) | 52 | 30 | 82 | ERS(21-30) | 31 | 22 | 53 |
| ERS(> 30) | 1 | 18 | 19 | ERS(>30) | 2 | 27 | 29 |
| Total | 244 | 57 | 301 | Total | 260 | 66 | 326 |

**560 General Poster Session (Board #24), Mon, 8:00 AM-11:45 AM**

**Preclinical activity of MCLA-128, an ADCC enhanced bispecific IgG1 antibody targeting the HER2:HER3 heterodimer.** *Presenting Author: Cecile Geuijen, Merus, Utrecht, Netherlands*

**Background:** Amplification and dimerization of HER2 promotes growth and survival of malignant cells. Tumor responses to available therapeutic agents targeting HER2 are variable. Re-activation of the potent HER2:HER3 signaling dimer by up-regulation of the HER3 ligand heregulin (HRG) has recently been identified as an important resistance mechanism. Treatment of patients with tumors expressing HER2 could be improved with agents that specifically target and potently inhibit the HER2:HER3 heterodimer. **Methods:** Inhibition of HRG mediated cell growth and invasiveness was assessed by proliferation inhibition and high content imaging. ADCC activity was measured by standard PBMC assays and reporter cell lines. The trastuzumab-resistant, HER2 amplified JIMT-1 xenograft model was used to assess in vivo activity. Activation status of HER dimers was determined by specific phosphorylation readouts. **Results:** MCLA-128 is a human common light chain bispecific antibody targeting HER2 and HER3 selected from > 500 bispecific antibody candidates. MCLA-128 inhibits HER2:HER3 heterodimer phosphorylation. This molecular phenotype correlated with potent inhibition of HRG driven growth and invasiveness in BT474, SKBR3 and N87 cell lines [$IC_{50}$ 100 – 200 pM]. In contrast, HER3 antibodies, trastuzumab alone or combined with either pertuzumab or HER3 antibodies could not inhibit growth under these conditions even at concentrations two orders of magnitude higher. The ADCC activity of MCLA-128, a low fucosylated IgG1, was equivalent to trastuzumab when targeting $HER2^{hi}$ cell lines but significantly superior when targeting $HER2^{lo}$ cell lines and when low affinity FcgRIII effector cells were used. In vivo, weekly dosing of MCLA-128 at 25 mg/kg reduced tumor burden significantly compared to lapatinib or trastuzumab + pertuzumab treatment groups. **Conclusions:** MCLA-128 specifically and potently inhibits ligand dependent HER2:HER3 signaling resulting in suppression of tumor growth in vitro and in vivo. The unique functional profile of this novel full-length bispecific antibody, including its strong ADCC activity, supports further development and clinical evaluation in patients with HER2 positive tumors.

**561 General Poster Session (Board #25), Mon, 8:00 AM-11:45 AM**

**Does increasing the daily tamoxifen dose in patients with diminished CYP2D6 activity increase toxicity?** *Presenting Author: Daniel Louis Hertz, University of Michigan, Ann Arbor, MI*

**Background**: Tamoxifen treated breast cancer patients with diminished CYP2D6 activity have lower endoxifen exposure, which may lead to inferior treatment outcomes. Increasing the daily tamoxifen dose from 20 mg to 40 mg increases endoxifen in CYP2D6 poor (PM) and intermediate (IM) metabolizing patients. We previously reported that endoxifen exposure of an IM pt receiving 40 mg is similar to that of an extensive or ultra-rapid metabolizer (EM/UM) receiving 20 mg, while a PM at 40 mg continues to have lower exposure. Here we investigated whether increasing the dose to 40 mg/day in CYP2D6 PM and IM increases treatment toxicity. **Methods**: Patients receiving 20 mg tamoxifen for ≥ 4 months who were not taking a strong CYP2D6 inhibitor were genotyped for CYP2D6 using the Amplichip CYP450 test (Roche Diagnostics, Indianapolis, IN). PM and IM were increased to 40 mg for 120 days while EM/UM remained on 20 mg. Toxicity data was collected on the ordinal FACT-B Endocrine Subscale (0: "not at all" to 4 "very much") at enrollment and 120 days. The prevalence of patients reporting any toxicity ≥ 3 ("quite a bit") and the rating (0-4) of specific toxicities were compared across CYP2D6 phenotypes. **Results**: Of the 484 evaluable patients, 29 were PM, 293 IM and 162 EM/UM. At enrollment (all receiving 20 mg) there was a non-significant trend toward greater prevalence of toxicity as CYP2D6 activity increased (PM=55.2%, IM=57.0%, EM/UM=62.4%, p=0.25) with a significantly higher rating of vaginal dryness (PM=0.76, IM=0.84, EM/UM=1.06, p=0.03) but not hot flashes (p=0.80). After 120 days of 40 mg treatment there was a significant increase in the prevalence of toxicity in IM (change from baseline= +7.4%, p<0.001), but not PM (change=-11.7%, p=0.71). There was no significant increase in the rating of any toxicity (p>0.05). **Conclusions**: Increasing the daily tamoxifen dose in CYP2D6 IM, but not PM, is associated with a corresponding increase in global toxicity that cannot be attributed to any single toxicity. Analysis as to whether this impacts patients' QOL is ongoing. Given the absence of known impact on outcomes, increasing the tamoxifen dose should be discouraged in patients with diminished CYP2D6 activity. Clinical trial information: NCT00764322.

**562 General Poster Session (Board #26), Mon, 8:00 AM-11:45 AM**

**Competing risks of mortality by PAM50 intrinsic subtype: BC tamoxifen-treated cohort.** *Presenting Author: Judy-Anne W. Chapman, NCIC Clinical Trials Group, Queen's University, Kingston, ON, Canada*

**Background:** We previously showed that baseline patient/tumour characteristics, or prior treatment affected cause of death in NCIC CTG endocrine therapy trials (MA.14, MA.17, MA.27), in particular older age was associated with non-breast cancer death. We now examine whether PAM50 intrinsic subtypes were differentially associated with cause of death in a cohort of British Columbia tamoxifen-treated patients. **Methods:** Patients were 718 post-menopausal women, treated with tamoxifen, without adjuvant chemotherapy who had tumours which were Luminal A, Luminal B, Basal, or HER2 intrinsic subtype and known cause of death [cancer-specific (BrCa); other cause (OC)]. We tested whether intrinsic subtype and other patient and tumour characteristics were associated with 1) all cause mortality, and if so, 2) cause-specific mortality. We also fit step-wise forward cause-specific adjusted models. **Results:** Patients were followed a median of 11.7 years. In women <70 years of age, 138/425 (32% died of breast cancer) and 80/425 (19% died of other causes); 138/218 (63% of deaths were due to breast cancer). In those ≥70, 78/293 (27% died of breast cancer) and 133/293 (45% died of other causes); 78/211 (37% of deaths were due to breast cancer). Two factors were differentially associated with type of death: intrinsic subtype was associated with breast cancer death (p=0.001), while older age was associated with other causes of death (p<0.0001). Additionally, step-wise cause-specific models indicated larger tumour size (p=0.0002), higher number of positive number of lymph nodes (p<0.0001), and less PgR stain (p=0.03) were associated with worse breast cancer survival; higher number of positive lymph nodes (p=0.002) and no lymphovascular invasion (p=0.02) were associated with worse all cause mortality. Survival from breast cancer and other causes is provided by these factors at 5-, 10-, and 15-years, adjusted for the effects of other significant factors. **Conclusions:** Intrinsic subtype was associated with breast cancer death, and did not affect other cause mortality. Again, older age was associated with other cause mortality with the majority of women 70 or older surviving breast cancer.

**563 General Poster Session (Board #27), Mon, 8:00 AM-11:45 AM**

**The impact of intratumoral heterogeneity on the prognosis of ER-positive/HER2-negative breast cancer.** *Presenting Author: Masahiro Oikawa, Department of Breast Oncology, National Kyushu Cancer Center, Fukuoka, Japan*

**Background:** In this study, we assessed the clinical importance of minor HER2-amplified clones in ER-positive, HER2-negative breast cancer to demonstrate the impact of intra-tumoral heterogeneity on clinical outcome. **Methods:** We retrospectively mined clinical data from the National Kyushu Cancer Center (2008–2013) for surgically resected, primary invasive breast cancers, that were ER-positive and HER2 IHC 2+/FISH-negative (HER2:CEP17 signal ratio by FISH < 2.0). Samples were classified as minor clone (MC) (+) or MC (−) if they had minor clones with HER2:CEP17 ratios ≥ 3.0 or not, respectively. The clinicopathological findings including age, menopausal status, tumor size, lymph node metastasis, lymphatic invasion, PgR, Ki67 labeling index and chemotherapy were analyzed between the two groups by Fisher's exact test and the Wilcoxon rank-sum test. Survival curves were estimated using the Kaplan–Meier method and the significance of differences between survival curves was determined using the log-rank test. **Results:** Of the 149 cases, with mean follow-up period of 732 days, 87 cases (58.4 %) and 62 cases (41.6 %) were classified as MC (+) or MC (−), respectively. When comparing the clinicopathological findings between these two groups, the MC (+) group tended to have larger tumor size (mean size 20.6 mm vs. 18.9 mm, P = 0.078), had a significantly higher Ki67 labeling index (with mean of 36.2 % vs. 22.8%, P = 0.036), and a significantly higher ratio of receiving chemotherapy (59.8% vs. 41.9%, P = 0.045). The MC (+) group showed worse overall survival (OS) compared with the MC (−) group (P = 0.026), while the difference in disease-free survival (DFS) was not significant. **Conclusions:** Among ER-positive, HER2-negative invasive breast cancers, the subgroup with HER2-amplified minor clones showed more biologically aggressive features, which may have an impact on prognosis. Intra-tumoral heterogeneity should therefore be considered in breast cancer therapy, and further investigation is required.

**564 General Poster Session (Board #28), Mon, 8:00 AM-11:45 AM**

**Predictive value of angiogenesis-related gene profiling in patients with HER2-negative metastatic breast cancer (MBC) treated with bevacizumab and weekly paclitaxel (Bev-Pac).** *Presenting Author: Andrés Redondo, Hospital Universitario La Paz, Madrid, Spain*

**Background:** The combination of Bev-Pac significantly improved progression-free survival (PFS), compared with Pac alone in first-line treatment of HER2-negative MBC. To date only a few biomarkers relating to bevacizumab efficacy have been published, and none of them have been validated in prospective studies. The aim of this study is to build a profile predicting PFS in patients treated with Bev-Pac. **Methods:** 60 patients with Her2-negative MBC treated with Bev-Pac were included. RNAs were collected from formalin-fixed paraffin-embedded primary breast samples. Expression levels of 170 angiogenesis related genes were measured using quantitative real time PCR. Predictive models, genetic (G) and combined genetic-clinical (GC), were fitted by Lasso-penalized multivariate Cox proportional hazards modeling and validated by Leave One Out Cross Validation (LOOCV). Cross-validated Kaplan-Meier (KM) curves and time-dependent ROC curves were generated to estimate the predictive accuracy of the PFS models, and a log-rank permutation test was used to evaluate the statistical significance. **Results:** 49 patients had estrogen positive, and 11 had triple negative tumors. 60% received Bev-Pac in first line, and 40% in second or subsequent lines. Median PFS was 11.4 months. The multivariate clinical model generated with 5 variables (number of previous lines, disease free interval, estrogen receptor status, previous chemotherapy and metastatic locations) showed the last one ($<3$ vs $>3$ locations or liver metastasis) as the only clinical variable significantly correlated with PFS. An 11-gene profile (G model) was correlated with PFS. The G model and the GC model identified two groups of patients with different PFS, although the GC model was statistically more consistent across different time points (median PFS 17.9 months in favorable group vs. 7.4 months in the other). **Conclusions:** A molecular signature of 11 genes correlated with PFS in a series of patients treated with Bev-Pac. Better predictive accuracy was obtained by a combination of genetic and clinical variables.

**565 General Poster Session (Board #29), Mon, 8:00 AM-11:45 AM**

**Chromosomal copy number alterations (CNAs) for risk assessment of ductal carcinoma in situ (DCIS).** *Presenting Author: Anosheh Afghahi, Stanford University School of Medicine, Stanford, CA*

**Background**: Population-wide screening mammography has contributed to a significant increase in the diagnosis of DCIS, raising questions about over-diagnosis and over-treatment. We aimed to determine whether adding genomic variables to standard clinico-pathologic factors may identify low-risk versus high-risk DCIS, with an ultimate goal of tailoring therapy. **Methods**: Patient-level clinical and pathologic data were extracted from the electronic medical records of Stanford Cancer Institute and linked to demographic data from the population-based California Cancer Registry; results were integrated with data from tissue microarrays of biopsies revealing DCIS only versus concurrent invasive breast cancer (IBC) with DCIS. We used fluorescence in situ hybridization to investigate the predictive values of CNAs of 1q, 8q24 and 11q13 (reported by The Cancer Genome Atlas to be among the most frequent CNAs in IBC) in the DCIS component of the biopsies. Multivariable logistic regression analysis was performed to describe associations with concurrent IBC, adjusting for variables including CNA frequencies, age at diagnosis, race/ethnicity, hormone receptors and grade. **Results**: We studied 271 patients (120 with DCIS and 151 with IBC and DCIS), most of whom were diagnosed from 2000-2003, were of Non-Hispanic White race/ethnicity, and of top statewide quintile of neighborhood socioeconomic status. We observed no differences in standard clinico-pathologic factors, including hormone receptors and grade. Compared to DCIS only, patients with concurrent IBC had higher frequencies of 2 of 3 (34.8% vs. 18%) and all 3 (10.8% vs. 4.1%) CNAs amplified; on multivariable analysis, this was the only variable significantly associated with concurrent IBC, where having 2 of the 3 CNAs was associated with a risk of IBC that was 5.28 times that of having no CNAs, and all 3 CNAs was associated with a more than 7-fold risk ($P=0.0091$). **Conclusions:** This proof-of-concept study demonstrates the potential of CNAs to improve the identification of high-risk DCIS that is accompanied by IBC. Expanding and validating this approach may enable risk-adapted management of DCIS.

**566 General Poster Session (Board #30), Mon, 8:00 AM-11:45 AM**

**Does endocrine therapy in mucinous and tubular breast cancer improve outcome?** *Presenting Author: Nicola Jane Mitchell, Auckland City Hospital, Auckland, New Zealand*

**Background:** Mucinous and tubular breast cancer (ca) have better prognosis than infiltrating ductal carcinoma (IDC). Patients (pts) often receive adjuvant (adj) treatment as if their risk was standard but questions arise about which pts could safely avoid treatment. We aimed to establish the current local practices and assess outcomes. **Methods:** We identified pts with early-stage mucinous and tubular breast ca using prospectively collected data from the Auckland Breast Cancer Registry between June 2000 and June 2012. Pts were case matched with IDC according to size, grade, nodal status and age. Because endocrine therapy (ET) use increased with higher Nottingham Prognostic Index (NPI), survival outcomes were also analysed by NPI group. **Results:** 161 mucinous and 201 tubular ca were identified. Baseline characteristics and treatment received are shown below. ET was used more in IDC than mucinous (54% vs 40%) or tubular ca (23% vs 12%). Median follow up was 4.3 yrs for mucinous and 4.8 yrs for tubular ca. RFS was superior in mucinous cf matched IDC (HR 0.3, p=0.0012) as well as DDFS (HR 0.2, p=0.011). A trend towards improved OS with ET in mucinous ca was seen in the overall group (HR 0.3, p=0.056), despite ET use being more common in higher NPI groups. RFS (HR 0.7, p=0.38) and DDFS (HR 0.1, p=0.083) were similar in tubular cf matched IDC. Of 182 pts with EPG tubular ca, only 10 received ET with no improvement in OS (HR 2.8, p=0.21). **Conclusions :**In this study, mucinous ca has an inherently better survival than IDC but women at higher risk may still benefit from ET. The good prognosis in tubular ca appears to be due to low stage at presentation. No benefit of ET was seen in tubular or EPG mucinous ca, suggesting selected women may be safely spared the side effects and costs of treatment.

| | Mucinous n = 161 | Tubular n = 201 |
|---|---|---|
| Median age in years (quartiles) | 63 (52,75) | 57 (50, 65) |
| Median size, mm (quartiles) | 18 (12, 27) | 9 (6, 13) |
| Grade | | |
| 1 | 107 (66%) | 189 (94%) |
| 2 | 47 (29%) | 8 (4%) |
| 3 | 4 (2.5%) | 1 (0.5%) |
| Unknown | 3 (1.9%) | 3 (1.5%) |
| Nodal status | | |
| 0 | 129 (80%) | 174 (87%) |
| 1 to 3 | 13 (8%) | 9 (4%) |
| 4 + | 4 (2%) | 0 (0%) |
| Unknown | 15 (9%) | 18 (9%) |
| NPI | | |
| Excellent (EPG) | 65 (40%) | 182 (91%) |
| Good (GPG) | 58 (36%) | 12 (6%) |
| Moderate (MPG) | 32 (20%) | 7 (3%) |
| Poor (PPG) | 6 (4%) | 0 (0%) |
| Adj chemotherapy (%) | 15 (9%) | 6 (3%) |
| Adj endocrine therapy (%) | 64 (40%) | 25 (12%) |

**567 General Poster Session (Board #31), Mon, 8:00 AM-11:45 AM**

**Clinical outcomes of estrogen receptor (ER)-negative and progesterone receptor (PgR)-positive invasive breast cancer.** *Presenting Author: Melissa Chan, Princess Margaret Cancer Centre - University Health Network, Department of Medicine, University of Toronto, Toronto, ON, Canada*

**Background:** Hormone receptor (HR) expression has prognostic and predictive significance in breast cancer. Most HR-positive tumors are ER positive (ER+). In contrast, tumors that are ER negative (ER-) and PgR positive (PgR+) are uncommon and may represent an analytic artifact. We have previously shown that ER-/PgR+ tumors have been associated with younger age, higher grade, and Her2/neu over-expression suggesting a distinct biologic entity (Proceedings 103rdUSCAP Meeting). Here we evaluated clinical outcomes of ER-/PgR+ breast cancers. **Methods:** We retrospectively reviewed a well-characterized database comprising 816 sequential patients diagnosed with early stage invasive breast carcinoma in Salamanca, Spain. Outcomes of interest were time to relapse (TTR) and overall survival (OS). Multivariable Cox proportional hazards analysis was conducted to assess the association of ER-/PgR+ with TTR and OS in comparison to ER+ and to ER- and PgR negative (ER-/PgR-) tumors. **Results:** Fifty-six patients (7%) had ER-/PgR+, 624 (77%) had ER+ and 136 (17%) had ER-/PgR- phenotypes. For ER-/PgR+, ER+ and ER-/PgR- tumors, five-year relapse rates were 36%, 20% and 42%, and five-year OS was 92%, 93% and 66%, respectively. ER-/PgR+ showed annual hazards of relapse that were intermediate between ER+ and ER-/PgR- patients. Relapses occurred early in follow-up for ER-/PgR+ and ER-/PgR- tumors with few relapses beyond year 6. ER+ tumors showed a continuous risk of relapse throughout follow-up. Multivariable analysis for TTR is shown in the Table. Only nodal status and receptor group were associated with worse OS. **Conclusions:** ER-/PgR+ tumors are a rare, but defined subgroup. They have a higher risk of relapse than ER+ tumors, but lower than ER-/PgR- tumors. The timing of relapse more closely resembles ER-/PgR- disease, whereas overall survival more closely resembles ER+ disease. Further research on the role of PgR in breast carcinogenesis is warranted.

| Variable | Hazard ratio | 95% CI | p |
|---|---|---|---|
| Age at diagnosis | 0.97 | 0.96-0.98 | <0.001 |
| Tumor size | 1.13 | 1.04-1.23 | 0.006 |
| Nodal metastases | 2.22 | 1.49-3.33 | <0.001 |
| Grade | 1.36 | 1.00-1.85 | 0.048 |
| Receptor group | - | - | - |
| ER+ | Ref | Ref | Ref |
| ER-/PgR+ | 1.57 | 0.79-3.12 | 0.20 |
| ER-/PgR- | 3.64 | 1.69-7.82 | 0.001 |

**568 General Poster Session (Board #32), Mon, 8:00 AM-11:45 AM**

**Enobosarm: A targeted therapy for metastatic, androgen receptor positive, breast cancer.** *Presenting Author: Beth Overmoyer, Dana-Farber Cancer Institute, Boston, MA*

**Background:** The androgen receptor (AR) is the most highly expressed steroid receptor in breast cancer (BC) with 75-95% of estrogen receptor positive (ER+) and 50% of ER negative BCs expressing AR. Prior studies have shown that women with metastatic BC (MBC) who are progressing on tamoxifen subsequently respond to non-tissue-selective, synthetic androgens with overall response rates of 20-60%. Unfortunately steroidal androgens have unwanted virilizing effects which limit clinical use. Enobosarm, a nonsteroidal, tissue-selective, AR modulator (SARM), provides a novel targeted approach to exploit the therapeutic benefits of AR activation without virilization or estrogenic effects. **Methods:** A proof of concept, phase II study is examining efficacy and safety of enobosarm 9mg daily in 22 postmenopausal women with ER+ MBC who previously responded to adjuvant and/or salvage endocrine therapy. Treatment continues until disease progression (PD). Primary endpoint is clinical benefit response (CBR) by 6 months (m) defined as patients (pts) having a complete response (CR), partial response (PR), or stable disease (SD). CBR will be correlated with AR status of metastatic tumor biopsy. Serum prostate specific antigen (PSA) will be evaluated as a biomarker of AR activity. **Results:** Pt demographics: mean age 63.7 years, mean time from diagnosis 11 years, 68% prior chemo, 94% (15/16) AR+. After a median f/u of 85 days (d) (range 84-209d), preliminary results of 16 pts: 8 SD as best response, median duration 4.5m; 9 PD after a median 84d. Among pts who reached 6m, 3 are AR+ with SD and increased PSA. 7 have yet to reach 6m and no CR or PR has been observed. Enobosarm is well-tolerated, with no drug related serious adverse events. **Conclusions:** Enobosarm is well tolerated and demonstrates promise as a novel targeted therapy for AR+ MBC. The primary endpoint has been achieved, with 3/15 AR+ pts meeting statistical threshold for success. Serum PSA appears to be a surrogate marker for AR activity and disease response. Final analysis is due in June 2014. Clinical trial information: NCT01616758.

**569 General Poster Session (Board #33), Mon, 8:00 AM-11:45 AM**

**Phase 2 study investigating the safety, efficacy, and surrogate biomarkers of response to 5-azacitidine (5-AZA) and entinostat in advanced breast cancer.** *Presenting Author: Roisin M. Connolly, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

**Background:** In breast cancer models, combination epigenetic therapy with a DNA methyltransferase inhibitor and a histone deacetylase inhibitor led to re-expression of genes encoding important therapeutic targets including the estrogen receptor. We conducted a multicenter phase II study of 5-AZA and entinostat in women with advanced breast cancer. **Methods:** Women with advanced HER2-negative (triple-negative [TNBC] or hormone-resistant [HR]) breast cancer received 5-AZA 40 mg/m$^2$ (SQ, ds 1-5, 8-10) and entinostat 7 mg (PO, ds 3,10) q28 ds. Primary endpoint: Objective response rate (ORR) in each cohort. Secondary endpoints: PFS, OS, safety. We obtained mandatory baseline and wk 8 tumor biopsies for gene methylation/expression, and blood samples for pharmacokinetics and pharmacogenetics. At progression, patients were offered optional continuation (OC) with the addition of endocrine therapy. We hypothesized that ORR would be >20% against null of 5% using Simon two-stage design. At least 1 response was required in 1$^{st}$ of 13 patients per cohort to continue accrual to 27 per cohort. Type I error 4%, power 90%. **Results:** TNBC data were presented at AACR 2013. From 08/2011-09/2013, 27 women enrolled in the HR cohort. Median age 55 ys (33-70), median prior endocrine and chemotherapies 3 each. Median cycles received 2 (1-16). Twelve women continued in OC phase and received median 2.5 additional cycles (range 1-9). We observed 1 partial response with epigenetic therapy alone (ORR 4%, 95% CI, 0-19%) and 1 in OC. At median follow up 6.3 ms, median PFS was 1.8 ms (95% CI, 1.7-1.9), and median OS 11.5 ms (95% CI, 5.5-16.3). In OC phase, median PFS was 1.9 ms (95% CI, 1.7-3.7) and median OS 15.6 ms (95% CI, 5.5-NA) vs PFS 1.8 ms (95% CI, 0.8-1.9) and OS 9.2 ms (95% CI, 2.3-16.3) for event monitoring. Therapy was well tolerated with few grade 3/4 events. We obtained 95% baseline core biopsies, and 58% matched samples. Correlative analyses will be presented. **Conclusions:** Combination epigenetic therapy was well tolerated but our primary endpoint was not met. OC results suggest that some women benefit from epigenetic therapy and/or reintroduction of endocrine therapy beyond progression. Clinical trial information: NCT01349959.

**570 General Poster Session (Board #34), Mon, 8:00 AM-11:45 AM**

**The impact of the Oncotype DX recurrence score pathology-clinical (RSPC) on the predicted recurrence risk for node negative breast cancer patients: A cancer center experience.** *Presenting Author: Barbara A. Wexelman, Massachusetts General Hospital, Boston, MA*

**Background:** The OncotypeDX 21-gene assay Recurrence Score (RS) is widely used to risk-stratify ER+, node negative breast cancer to determine the 10 year risk of distant recurrence (RR) and the potential benefit of chemotherapy. The OncotypeDX Recurrence Score Pathology-Clinical (RSPC) tool was recently developed to modify an individual's RR by incorporating clinical and pathological features (age, tumor size, grade, and type of endocrine therapy). We evaluated the impact of the RSPC on the predicted RR in a cohort of patients (pts) at our institution. **Methods:** A retrospective chart review of the last 250 consecutive pts (2012-2013) at our institution with OncotypeDX RS was performed. RSPC was calculated and compared to the RR. Patients were excluded from analysis for the following: DCIS only, node positive, or in-breast recurrence. Low, intermediate (int), and high risk cut-offs were based on published data using RS <18 (RR<12%), RS 18-31 (RR 12-20%) and RS >31 (RR>20%). **Results**: Of 250 RS obtained, 166 (66.4%) met inclusion criteria for this analysis. Mean tumor size was 1.6 cm, median grade=2, mean age=55.6, 49.4% started Tamoxifen, and 14.5% received adjuvant chemotherapy. The mean RS was 15.2 (SD 7.7, range 0-48). The mean 10-year RR compared to RSPC was 10.2% vs 8.6% (p<0.001). In addition, 71.1%, 24.1%, and 4.8% of tumors had a low-, intermediate- and high-risk RS, compared to 81.9%, 14.5%, and 3.6% after RSPC adjustment. RR shifted as 29/40 (72.5%) int-RR pts were reclassified as low risk by RSPC, and 12/118 (10.2%) low-RR pts were reclassified to int/high risk, leading to a 40% decrease in the number of int-risk tumors. Small tumors (T1a/b) had the greatest decrease in RR (-3.2%), while 22 (21.4%) of T1c tumors dropped from int to low RR. **Conclusions:** The RSPC tool modified the RR by a small but statistically significant decrease in the predicted 10 year RR for ER+ node negative breast cancer in a single institutional cohort, with most intermediate RR tumors shifting to low RR. Although RSPC does not alter the predicted relative benefit of chemotherapy, adjustment for the absolute RR may alter absolute chemotherapy benefit and impact treatment choice.

**571 General Poster Session (Board #35), Mon, 8:00 AM-11:45 AM**

**Breast cancer subtypes according to body mass index and insulin resistance.** *Presenting Author: Grazia Arpino, Medical Oncology, AOU Federico II, Naples, Italy*

**Background:** High body mass index (BMI) is considered a risk factor for breast cancer (BC) onset and is correlated with bad prognosis and resistance to endocrine therapy in BC patients. Obesity is also cause of insulin resistance (IR), often associated to resistance to anti human epidermal growth factor receptor (HER) inhibitors. The aim of the present study was to assess the association of BMI levels and IR with BC immunohistochemically-defined subtypes. **Methods:** One thousand consecutive post-menopausal patients with early BC were included in our study. Clinical, metabolic and tumor characteristics were prospectively collected at the time of diagnosis. IR was defined by the homeostatic model assessment (HOMA), with a cut off value to define IR ≥ 3,4. BMI was categorized as low: ≤25; intermediate: 26-30; high: >25. Data were analysed by logistic regression model. **Results:** Patients with luminal (A and B) BC were more likely to be overweight (BMI = 26-30) (OR=2.96 95% CI 1.53-5.74; p=0.006) although they had low HOMA scores (< 3.4) (OR=0.57 95% CI 0.35-0.93; p=0.02). In contrast, patients with HER2+ subtype were at increased risk for elevated HOMA score (OR= 2.36 95% CI 1.27-4.4; p=0.007), whereas the association with BMI was not statistically significant. In additional, no significant association was found between triple negative (TN) BC and anthropometric and metabolic variables. **Conclusions:** Our data suggest that high BMI may be associated with endocrine sensitive BC, whereas high HOMA score, may be more frequent in patients with HER2+ subtype. These findings support the hypothesis that high estrogen exposure of breast tissue in women with higher BMI may drive growth of luminal cancers while insulin an resistance environment may increase the risk of growth factor receptor-dependent BC. If further confirmed, our data suggests that body weight reduction and glycemic control, respectively in these two subsets of women may help to prevent cancer development.

**573 General Poster Session (Board #37), Mon, 8:00 AM-11:45 AM**

**Cremophor EL-free formulation of paclitaxel: A randomized, multicenter, safety, and efficacy study of nanosomal paclitaxel lipid suspension (NPLS) versus paclitaxel in women with metastatic breast cancer (MBC).** *Presenting Author: Ateeq Ahmad, Jina Pharmaceuticals, Libertyville, IL*

**Background:** The primary reason for the development of Lipid Based formulation of Paclitaxel is to improve the drug's safety profile by eliminating Cremophor EL (CrEL) and ethanol from Paclitaxel.The use of CrEL, a surfactant, has been associated with severe anaphylactoid hypersensitivity reactions, hyperlipidaemia, abnormal lipoprotein patterns, aggregation of erythrocytes and peripheral neuropathy in patients treated with Taxol. **Methods:** 120 MBC patients were enrolled in the study and the racial make-up was 100% Asian. They were administered NPLS (Arm A) or Paclitaxel (Arm C) at a dose of 175 mg/m$^2$ tri-weekly or NPLS (Arm B) at dose 80 mg/m$^2$weekly as per randomization schedule, by IV infusion at a ratio of 48 patients on Arm A: 45 patients on Arm B: 27 patients on Arm C. No pre-medication was given to the patients in NPLS groups. Safety and efficacy was determined for all treated patients. The efficacy was measured by Objective Response Rate (ORR = CR + PR) and Disease Control Rate ( DCR = CR + PR + SD). **Results:** (A) Efficacy - An independent radiologic review demonstrated clinically superior efficacy in terms of ORR, in MBC patients receiving the NPLS (175mg/m$^2$) or (80mg/m$^2$) versus the standard dose of Paclitaxel(175mg/m$^2$). The ORR was 36.4% (95% CI, 22.1 – 50.6%) for NPLS arm A, 46.5% (95% CI, 31.6 – 61.4%) for NPLS arm B and 20.8% (95% CI, 4.6 – 37.1%) for Paclitaxel arm C. The DCR was 86.4% for NPLS Arm A, 88.4% for NPLS Arm B and 80% for Paclitaxel Arm C. (B) Safety - A total of 450 adverse events (AEs) reported to 97 patients during the course of the trial. 157 AEs occurred to patients under NPLS Arm A, 239 AEs occurred to patients under NPLS Arm B and 54 AEs occurred to patients under Paclitaxel Arm C. **Conclusions:** In both Arm A and B, patients treated with NPLS showed higher ORR and DCR than patients receiving Paclitaxel (Arm C). The NPLS was well tolerated by patients. Majority of the post-dose AEs were resolved without any sequelae. The patients in NPLS treatment arms were not pre-medicated. Taken together, NPLS tri-weekly or weekly demonstrates clinical benefit versus Taxol for MBC patients. Clinical trial information: CTRI/2010/091/001344.

**574 General Poster Session (Board #38), Mon, 8:00 AM-11:45 AM**

**Prognosis of small tumors according to KI67 and IHC subtypes.** *Presenting Author: Antonella Ferro, Santa Chiara Hospital, Trento, Italy*

**Background:** The incidence of small ( ≤1 cm) node-negative breast cancers (BC) is increasing in mammography-screened populations. These tumors generally have good prognosis with low risk of distant and local recurrence. **Methods:** A retrospective review of 665 patients classified as having ≤1 cmN0 BC treated in our Institution from 1995 to 2008 was done. Clinical-pathological features and long term outcomes (EFS and OS) were analyzed according to KI67 LI, HER2 status, PR expression and intrinsic sybtypes (luminal A, B, HER2 luminal, HER2, Triple negative-TN). **Results:** Median age at diagnosis was 60 years (range: 23 to 86 ys).There were 30 T1mic (4.5%), 122 T1a (18.4%) and 513 T1b (77.1%) cancers. A higher proportion of pT1mic+T1a presented poor grading (G3) and had the HER2 and TN subtypes compared with pT1b BC. HER2 was over-expressed or amplificated in 89 (13.4%) of all cases. Chemotherapy with or without hormonal therapy was administered to 18 T1a (12%) and to 82 T1b (16%); hormonal therapy alone in 46 T1a (30%) and 252 T1b (49%). No one received adjuvant trastuzumab. At a 6,5 ys median follow up there were 29 (4.4%) loco-regional (LRR) or distant relapses (DR), 26 (3.9%) controlateral and 21 (31%) other tumors.Similar incidence of LRR, DR and BC related deaths between T1a and T1b was reported. High ki67 (defined as median value = 15%) confirmed its prognostic significance in term of OS, in particular T1b cases (p=0.015), but not in EFS.No difference was found between Luminal B and Luminal A subtypes for any of the outcomes analysed. TN and HER2 subtypes, but not HER2 luminals were correlated with a significantly increased BC related events if compared with the Luminal A subtype (TN 85.7%, HER2 79.4%, Her2 luminal 90.7%, Luminal A 93.7%, Luminal B 89.1%). **Conclusions:** Our experience confirms good prognosis of ≤ 1 cm N0 BC. However, tumors with more aggressive biological features (high Ki67, HER2 or TN subtypes) had higher incidence of relapses. In this "low stage but adverse biology" BC an intensive (aggressive?) adjuvant approach should always be considered.

**575 General Poster Session (Board #39), Mon, 8:00 AM-11:45 AM**

**Relation of genes in estrogen and vitamin D signaling to bone mineral density loss in aromatase inhibitors treatment.** *Presenting Author: Sonia Servitja, Medical Oncology Department. Hospital del Mar, Barcelona, Spain*

**Background:** Bone mineral density (BMD) loss is a consequence of Aromatase Inhibitors (AI) therapy. This study aims to identify variants of genes in the vitamin D and estrogen signaling pathways associated with AI-related BMD loss in the B-ABLE cohort. **Methods:** B-ABLE is a prospective cohort of women recruited at the time they initiate AI therapy in a bone metabolism unit. Bisphosphonate users were excluded for these analyses. Selected single nucleotide polymorphisms (SNPs) were genotyped. Multivariate linear regression was used to test their association with relative lumbar spine (LS) and femoral neck (FN) BMD loss after 1 and 2 years of follow-up. All models were adjusted for age, body mass index, previous tamoxifen and chemotherapy. Further, potential confounding for baseline 25(OH)-VITD concentrationsand AI used was assessed. **Results:** 391 participants were included. For estrogen signaling, two SNPs in CYP11A1 (rs2959008 and rs7174179) for the association with FN BMD loss at both one ($P$=0.003 and $P$=0.012) and two years ($P$=0.004 and $P$=0.002) of follow-up were significant. For LS BMD lossthree SNPs in HSD3B2 (rs2854964), CYP2C19 (rs12248560) and CYP2C9 (rs28371674) were significantly associated at one year of follow-up ($P$=0.026, P=0.019 and $P$=0.011 respectively). Only rs12248560 remained also significant at 2 years of follow-up (P=0.014). Regarding vitamin D signaling genes, rs11907350 in CYP24A1 was associated with FN BMD loss at one year. As for LS BMD loss one SNP in GC (rs11907350) at one year of follow-up and one SNP in VDR (rs2544037) at two years of follow-upreached significant p-values (P =0.020 and P=0.024, respectively). Only the SNP rs7174179 in CYP11A1 for FN BMD loss association at 2 years of follow-up remained significant after Bonferroni correction. **Conclusions:** Several genes in estrogen and vitamin D signaling appeared involved in BMD loss in AI-treated women, suggesting a complex regulation of this outcome.

**576^ General Poster Session (Board #40), Mon, 8:00 AM-11:45 AM**

**Phase 2 trial of trastuzumab and/or everolimus in hormone-resistant HER2-negative metastatic breast cancer.** *Presenting Author: Amelia Bruce, Zelnak, The Winship Cancer Institute of Emory University, Atlanta, GA*

**Background:** Increased signaling through growth factor receptor pathways, including HER2, has been demonstrated to play a role in resistance to endocrine therapy. Efficacy of inhibiting HER2 and mTOR in HER2-negative, hormone-resistant breast cancer has been previously demonstrated. We evaluated the ability of inhibition of HER2 with trastuzumab (TRAST) and/or mTOR with everolimus (EVER) to reverse resistance to endocrine therapy in patients with hormone receptor (HR)-positive HER2-negative metastatic breast cancer (MBC). **Methods:** Eligibility included HR-positive, HER2-negative (IHC 1+ or 2+ and/or FISH negative) MBC on metastatic biopsy and documented progression within 6-months of starting an endocrine agent in the metastatic setting. Patients continued on the endocrine agent they had experienced disease progression on and were randomized to receive TRAST (8mg followed by 6mg every 3-weeks) or EVER 10mg daily. At disease progression the other agent (TRAST or EVER) was added. Biopsies of metastatic lesions were obtained prior to study entry where possible. **Results:** To date 38 patients have been randomized to TRAST (n = 13) or EVER (n = 22), 3 patients not evaluable. All patients continued the endocrine agent on which they had most recently experienced disease progression. The median PFS is 1.5 (95% CI 1.5 to 4) and 6 (95%CI 4 to 15) months (mos.) for patients initially randomized to TRAST and EVER respectively. At disease progression 13 patients in the TRAST arm received EVER and 5 in the EVER arm received TRAST. The overall PFS for this group is 5.5 (95% CI 3 to 8) mos: 7 (95% CI 3 to 13) mos. for patients in the TRAST arm who then received EVER; and 4 (95% CI 1.5 to 7) mos. for patients in the EVER arm who received TRAST. There were no unexpected toxicities though 2 patients were taken off study for decreases in ejection fraction. Metastatic biopsies are available for 57% of patients. **Conclusions:** This trial demonstrates the efficacy of inhibiting mTOR alone or in combination with HER2 in patients with hormone-resistant HER2-negative breast cancer, suggesting that inhibition of this growth factor pathway may restore sensitivity to endocrine therapy. Updated results and correlative studies will be presented. Clinical trial information: NCT00912340.

**577 General Poster Session (Board #41), Mon, 8:00 AM-11:45 AM**

**Follicle stimulating hormone (FSH) as a surrogate parameter for the effectiveness of endocrine therapy with or without zoledronic acid in premenopausal patients with breast cancer: An analysis of the prospective ABCSG-12 trial.** *Presenting Author: Georg Pfeiler, Department of Gynecology and Gynecological Oncology, Medical University of Vienna, Vienna, Austria*

**Background:** Endocrine therapy is an effective, targeted therapy in patients with hormone receptor positive breast cancer (BC). However, in the adjuvant setting no indicator exists visualizing its effectiveness during therapy. In this analysis we test whether FSH serum levels during therapy might be a surrogate parameter for the effectiveness of adjuvant endocrine therapy. **Methods:** ABCSG-12 examined the efficacy of ovarian suppression using goserelin (3.6mgq4wSC) in combination with anastrozole or tamoxifen ± zoledronic acid (ZOL, (4mgIVq6mo) in premenopausal women with endocrine-responsive BC. Prospective collected data on FSH serum levels were used for the analyses. Disease-free survival (DFS), distant metastasis free survival (DMFS) and overall survival (OS) were calculated by Kaplan-Meier method, results were compared by using the log-rank test and Cox proportional hazard modelling. **Results:** Analyses are based on 503 patients with FSH levels at baseline, 562 patients with FSH levels during therapy and 641 patients with FSH levels during follow up. Mean FSH levels were significantly lower during therapy, when compared to baseline and follow up, respectively (4.87mIU/ml vs. 14.16mIU/ml vs. 22.28mIU/ml, $p<0.001$). Patients treated with anastrozole had significantly higher FSH levels during therapy compared to patients treated with tamoxifen (7.05mIU/ml vs. 2.45mIU/ml, $p<0.001$). Patients with FSH levels above the mean during therapy (4.87mIU/ml) had a worse outcome compared to patients with FSH levels below 4.87mIU/ml (DFS HR 1.347, $p=0.18$; DMFS HR 1.939, $p=0.035$; OS HR 2.208, $p=0.096$). This could be confirmed with borderline significance in the subgroup of patients treated with ZOL (DFS HR 1.886, $p=0.075$; DMFS HR 2.537, $p=0.077$; OS HR 1.306, $p=0.726$). BMI had no impact on FSH serum levels in any group during therapy. **Conclusions:** This study suggests that FSH serum levels during therapy might be a good surrogate parameter for the effectiveness of adjuvant endocrine therapy.

**578 General Poster Session (Board #42), Mon, 8:00 AM-11:45 AM**

**Breast cancer treatment with everolimus and exemestane for ER+ women: Results of the first interim analysis of the noninterventional trial BRAWO.** *Presenting Author: Diana Lueftner, Department of Hematology, Oncology, and Tumor Immunology, Charité University Medicine, Campus Benjamin Franklin, Berlin, Germany*

**Background:** BRAWO is a German non-interventional study of 3000 patients with advanced or metastatic, hormone-receptor-positive and HER2-negative breast cancer treated with Everolimus (EVE) and exemestane (EXE). Here we report the results of the first preplanned interim analysis (IA). **Methods:** BRAWO collects data on the routine clinical treatment with EVE 10mg/d and EXE 25mg/d at about 400 sites. Main objectives are to extend the knowledge on a) the impact of physical activity on efficiency and quality of life, b) prophylaxis and management of stomatitis in clinical routine, and c) the sequence of therapy, when EVE is used in usual daily care. This first IA focuses on objectives b) and c). **Results:** 866 patients (pts) at 253 active sites were analyzed, 53.2% of pts were ongoing at data cut-off. Baseline characteristics: Median age: 66 yrs; median BMI: 25.8. ECOC 0-1: 90%; visceral metastasis: 55.0%; bone only metastasis: 25.1%. 28.8% pts received EVE and EXE as first treatment (first line), 30.3% as second line, 18.0% as third line and 23.0% as forth or later line in the advanced setting. Comparing the first 200 with the most recent 200 documented pts the usage as first or second line treatment increased from 53.5% to 70.0%. Patients treated in first or second line were less likely to experience any adverse event (AE) (68.7% in first or second, 81.4% in later lines, $p<0.0005$). 18.1% of pts had received EXE earlier in their treatment history. Of 445 pts with at least 3 months follow-up 45.8% developed stomatitis: 26.6% grade 1, 16.9% grade 2, 2.7% grade 3. 87.2% of pts received recommendations regarding stomatitis prevention from their physician. QoL remained stable over the course of the treatment. No correlation could be seen between grade of stomatitis and QoL. Regarding global health status, pts without AEs reported better values than pts with AEs. Insights into dosing and therapy sequence will also be presented. **Conclusions:** This IA indicates that pts receiving EVE and EXE in earlier lines are less likely to experience AE. The majority of physicians recommend their pts to take prophylactic measures to prevent stomatitis. QoL remains stable over the course of the treatment.

**579 General Poster Session (Board #43), Mon, 8:00 AM-11:45 AM**

**Relative bone loss during aromatase inhibitors therapy: The B-ABLE cohort.** *Presenting Author: Sonia Servitja, Medical Oncology Department. Hospital del Mar, Barcelona, Spain*

**Background:** Estrogen deprivation induced by aromatase inhibitors (AI) leads to a rapid and prolonged bone loss and increased fracture incidence. The current study aims to evaluate AI-associated bone loss throughout the first two years of the treatment. **Methods:** B-ABLE is a prospective cohort of caucasian, postmenopausal women with early breast cancer, in adjuvant treatment with AI (according to the ASCO guidelines). Bone mineral density (BMD) and x-ray were measured at baseline and every year up to and 1 year after treatment completion. Paired t-tests were carried out to detect differences in lumbar spine (LS) and femoral neck (FN) BMD loss of 1 and 2 years of follow-up relative to baseline. Bisphosphonate users were excluded for these analyses. Women over 65 years old were also excluded from the analyses of LS BMD to avoid the underestimation of bone loss due to osteoarthritis. **Results:** Patients had mean rates of LS BMD loss relative to baseline of 1.98% ($n=241$) at 1 year and 3.51% ($n=182$) at 2 years of follow-up, ($P<0.001$). Mean rates BMD loss for FN were 1.24% ($n=381$) at 1 year and 2.07% ($n=257$) at 2 years, ($P<0.001$). Previous tamoxifen treated patients (40.7%) were younger and had a higher baseline BMD but experienced higher LS BMD loss rates at 1 (83%, $P<0.05$) and 2 (92%, $P<0.001$) years. FN BMD loss rates were also higher for those patients previously treated with tamoxifen at 1 (349%, $P<0.001$) and 2 years (177%, $P<0.01$). **Conclusions:** Rapid bone loss occurs in the first 2 years of AI treatment, especially in tamoxifen pre-treated women.

**580 General Poster Session (Board #44), Mon, 8:00 AM-11:45 AM**

**Gene expression profiling for identification of FYN in tamoxifen resistance and as predictor of early recurrence in patients treated with endocrine therapy.** *Presenting Author: Henrik Jorn Ditzel, University of Southern Denmark, Odense, Denmark*

**Background:** Development of resistance to tamoxifen is an important clinical issue in the treatment of breast cancer. **Methods:** To elucidate the molecular mechanisms of tamoxifen resistance in breast cancer, we performed gene array analyses and identified 366 genes with altered expression in 4 unique tamoxifen-resistant (TamR) cell lines vs. the parental tamoxifen-sensitive MCF-7/S0.5 cell line. **Results:** Most of these genes were functionally linked to cell proliferation, death and control of gene expression, and include FYN, PRKCA, ITPR1, DPYD, DACH1, LYN, GBP1 and PRLR. Treatment with *FYN*-specific small interfering RNA or a SRC family kinase inhibitor reduced cell growth of TamR cell lines, while exerting no significant effect on MCF-7/S0.5 cells. Moreover, overexpression of *FYN* in parental tamoxifen-sensitive MCF-7/S0.5 cells resulted in reduced sensitivity to tamoxifen treatment, while knockdown of *FYN* in the *FYN* overexpressing MCF-7/S0.5 cells restored sensitivity to tamoxifen, demonstrating growth- and survival- promoting function of FYN in MCF-7 cells. *FYN*knockdown in TamR cells led to reduced phosphorylation of 14-3-3 and Cdc25A, suggesting that FYN, by activation of important cell cycle-associated proteins, may overcome the anti-proliferative effects of tamoxifen. Evaluation of the subcellular localization of FYN in primary breast tumors from 2 cohorts of endocrine-treated ER+ breast cancer patients, one with advanced disease ($N=47$) and the other with early disease ($N=76$), showed that in the former, plasma membrane-associated FYN expression strongly correlated with longer progression-free survival ($p<0.0002$). Similarly, in early breast cancer patients, membrane-associated expression of FYN in the primary breast tumor was significantly associated with increased metastasis-free ($p<0.04$) and overall survival ($p<0.004$) independent of tumor size, grade or lymph node status. **Conclusions:** Our results indicate that FYN plays an important role in tamoxifen resistance, and its subcellular localization in breast tumor cells may be an important novel biomarker of response to endocrine therapy in breast cancer.

**581 General Poster Session (Board #45), Mon, 8:00 AM-11:45 AM**

**Bone turnover markers at 3 months of aromatase inhibitor therapy for prediction of 1-year bone mineral density loss: The B-ABLE cohort.** *Presenting Author: Ignacio Tusquets, Hospital del Mar, Barcelona, Spain*

**Background:** Most guidelines recommend bone mineral density (BMD) monitoring at 1-2 years of aromatase inhibitor (AI) therapy for women who do not need bisphosphonate therapy according to baseline assessment. Bone turnover markers (BTM) are sensitive to change in bone remodeling, and can be easily measured in clinic, offering an opportunity to anticipate BMD loss. We aimed to establish the association between changes in levels of BTMs at 3 months and 1-year BMD loss. **Methods:** The B-ABLE prospective cohort includes a consecutive sample of women with early breast cancer eligible for AI therapy. BMD is measured per protocol by DEXA at baseline and yearly, and BTMs (NTX and CTX in a subsample, Bone Alkaline Phosphatase (BALP) and Osteocalcin in all) at baseline, 3-months, and at yearly visits thereafter. Change in BTM levels (3-month minus baseline) was the main exposure and relative 1-year Lumbar Spine BMD loss (baseline minus 1-year over baseline) the main outcome of this study. Linear regression was used to establish the association between exposure and outcome. Multivariate models were adjusted for age, weight, and height. Adjusted standardized beta (ASB) coefficients are reported and must be interpreted as the mean increase in % BMD loss per each standard deviation of 3-month BTM change. **Results:** Data was available on 350 women starting on AI not on bisphosphonates according to ASCO guidelines. 138 and 149 had NTX and CTX data respectively. Changes in NTX (ASB 0.19, p=0.002), CTX (ASB 0.41, p<0.001), BALP (ASB 0.13, p=0.004) and Osteocalcin (ASB 0.21, p<0.001) at 3 months were associated with 1-year BMD loss. **Conclusions:** Changes in BTM (particularly CTX, with a strongest association) concentrations at 3 months of AI therapy can be used to target women with high BMD loss at 1 year. This strategy would identify high-risk women for closer monitoring/treatment.

**582 General Poster Session (Board #46), Mon, 8:00 AM-11:45 AM**

**Low cytolytic T-cell CD8 expression in mesenchymal triple negative (TN) breast cancers and overexpression of the adhesion protein CD24 in ER+ breast cancers that recur within 3 years of adjuvant chemotherapy.** *Presenting Author: Joyce O'Shaughnessy, Texas Oncology-Baylor Charles A. Sammons Cancer Center and US Oncology, Dallas, TX*

**Background:** The phase III trial USON 01062 (O'Shaughnessy J, et al Proc SABCS, 2010, abstract S4-2) showed that the addition of capecitabine to docetaxel following doxorubicin/cyclophosphamide adjuvant chemotherapy did not improve 5-year disease-free survival (DFS) (HR 0.84, p=0.125). We evaluated molecular biomarkers to identify genomic predictors of early recurrence in ER+ and TN breast cancers in USON 01062. **Methods:** 817 FFPE primary breast cancers had good quality gene expression data for PCR-based identification of *PIK3CA*somatic mutations (MT), as well as for Nanostring assessment of 800 breast cancer-related genes encompassing published breast cancer signatures and pathways. IHC for Ki67 and PTEN was also performed. **Results:** Intrinsic subtypes of the 817 cancers: 320 luminal A (Lum A); 124 Lum B; 296 basal (82% TN, 9% ER+ and 8% HER2+); and 69 HER2-enriched (60% HER2+, 33% TN, 7% ER+). Nonsignificant improvements in DFS with capecitabine were seen in the basal cancers with central Ki67 < 70%, and in luminal cancers with Ki67 > 25%. In Lum A pts, exons 9 or 20 *PIK3CA* MT predicted for favorable DFS; there was no difference in DFS outcome in Lum B *PIK3CA*MT vs wild type pts. CD24 and CDCA5 (which encodes the sister chromatid cohesion protein, sororin) were significantly overexpressed in ER+ cancers that recurred within 3 yrs of beginning adjuvant therapy (p=0.0086 and 0.045, respectively), and expression of ESR1 and its regulated genes such as RERG were associated with a low risk of recurrence. For the TNBCs, 42% were basal 1/2, 21% were immunomodulatory (IM), 15% were mesenchymal stem-like, 13% were mesenchymal and 9% were luminal AR. The mesenchymal subtype showed the highest rate of recurrence and low CD8 expression, while expression of IM genes including CD8 was associated with more favorable 5-year DFS outcome. **Conclusions:** Mesenchymal TNBC has low CD8 expression and a poor prognosis with adjuvant chemotherapy. Rapidly recurring ER+ breast cancers have low levels of ESR1 and overexpress CD24 which adheres to activated platelets and interacts with c-src/FAK to stimulate motility (Baumann P, Ca Res 65:10783, 2005).

**583 General Poster Session (Board #47), Mon, 8:00 AM-11:45 AM**

**Population-based evaluation of 21-gene assay in treatment decision making for early breast cancer in Ontario.** *Presenting Author: Mark Norman Levine, Ontario Clinical Oncology Group, McMaster University, Hamilton, ON, Canada*

**Background**: The OncotypeDX 21-gene assay (ODX) is used to aid in decision-making for chemotherapy (CT) in patients with breast cancer (BC). The province of Ontario, with a population of approximately 14 million, has a publically funded healthcare system. Funding of the ODX test by the Ontario Ministry of Health was conditional upon participation in a prospective cohort study by the Ontario Clinical Oncology Group to evaluate the test's impact on decision making. **Methods**: Subjects with node– ER+ Her2– BC who were considered for CT in addition to usual endocrine therapy (ET) were eligible. The oncologist's initial treatment recommendation based on the Adjuvant! Online (AO) result and classical factors (tumor size and grade) was recorded. Once the ODX recurrence score (RS) was available, the patient returned to clinic for final decision-making. Outcomes were the change in the oncologist's treatment recommendation, change in patient's treatment preference, and economics. AO relapse risk categories used in analysis were: low ≤ 25%, intermediate 26-36%, high ≥ 37%. **Results**: Between January 2012 and July 2013, 1,000 consecutive patients were recruited. Median age was 59 (26-88); median tumor size was 1.7cm (0.2-9.0); 24% were Grade I, 58% Grade II and 18% Grade III. Relapse risk groups for ODX (AO) in the 977 ODX tested patients were: 58% (55%) classified as low, 33% (15%) intermediate, and 9% (31%) high risk. The oncologist's recommendation was the same in 463 patients (48%), changed from unsure or CT to ET in 360 patients (37%), and from unsure or no CT to CT in 141 (15%). **Conclusions**: To our knowledge, the Ontario study is the largest population-based prospective cohort to assess the impact of ODX on treatment recommended and received. As expected, the ODX had a substantial impact on the CT plan; CT was avoided in up to 37% of patients and recommended in an additional 15%. Clinical trial information: NCT01423890.

| | CT recommendation: pre → post test | | | | | |
|---|---|---|---|---|---|---|
| | No change | | Change | | | |
| RS group | No | Yes | Unsure → No | Yes → No | Unsure → Yes | No → Yes |
| Low (n=562) | 274 (0)† | 17 (11) | 180 (6) | 86 (2) | 3 (3) | 2 (1) |
| Intermediate (n=316) | 92 (1) | 35 (30) | 64 (1) | 30 (0) | 53 (44) | 42 (26) |
| High (n=89) | 3 (0) | 42 (34) | 2 (1) | 0 (0) | 23 (19) | 19 (16) |
| Total (n=967) | 369 (1) | 94 (75) | 246 (8) | 116 (2) | 79 (66) | 63 (43) |

†Actually received CT.

**584 General Poster Session (Board #48), Mon, 8:00 AM-11:45 AM**

***ERP29* genetic polymorphism and breast cancer susceptibility and prognosis.** *Presenting Author: Gustavo Jacob Lourenco, Department of Internal Medicine, Faculty of Medical Sciences, University of Campinas, Campinas, Brazil*

**Background:** *ERP29*, a tumor suppressor gene, was related with the onset of tumors. The influence of *ERP29* c.*293A>G (rs7114) polymorphism in breast cancer (BC) risk and prognosis has never been performed before and was the aim of this study. **Methods:** We analyzed 742 BC patients and 742 healthy women. The BC patients were treated by conventional procedures. *ERP29* c.*293A>G genotypes were obtained from genomic DNA by TaqMan genotyping assays. The expression of *ERP29* mRNA was determined by quantitative PCR using total RNA from blood leukocytes of healthy individuals with distinct genotypes (12 individuals with AA, 15 with AG, and six with GG). Overall survival (OS) was obtained from date of first diagnosis until the date of death or last follow-up. The differences in frequencies of distinct genotypes in patients and controls were analyzed by logistic regression model, serving to obtain age, ethnic origin and adjusted crude odds ratios (ORs), considering a confidence interval (CI) of 95%. OS time was calculated using the Kaplan-Meier estimate probabilities and differences between survival curves were analyzed by the log-rank test. Statistical significance was established at a $P<0.05$. All computations analyses were done using the SPSS 21.0 software (SPSS Incorporation). **Results:** The frequency of *ERP29* AG+GG combined genotypes was higher in BC patients than in controls (36.6% versus 30.7%, P=0.03). Carriers of G allele were under a 1.33 (95% CI: 1.03-1.72)-fold increased risk for the tumor. The mean mRNA expression was lower in carriers of G allele than those with *ERP29* AA genotype (0.82 arbitrary units (AUs) versus 1.41 AUs; P=0.02). The median of observation of BC patients enrolled in the study was 54 months (1-325). OS of BC patients with the *ERP29* AG+GG combined genotypes was higher than that observed in those with the *ERP29* AA wild genotype (67.5% versus 59.0% at 120 months of follow up; $P=0.04$). **Conclusions:** Our data suggest, for the first time, that *ERP29* c.*293A>G polymorphism alters the risk and prognosis of BC possibly due to variation in the protein production.

**585 General Poster Session (Board #49), Mon, 8:00 AM-11:45 AM**

**Estrogen levels in premenopausal (prem) patients (pts) with hormone-receptor positive (HR+) early breast cancer (BC) receiving adjuvant triptorelin (Trip) plus exemestane (E) or tamoxifen (T) in the SOFT trial: SOFT-EST substudy.** *Presenting Author: Meritxell Bellet, Vall d'Hebron University Hospital, Barcelona, Spain*

**Background:** Optimal endocrine therapy for prem pts with early HR+ BC may depend on complete estrogen suppression with GnRH-A, and is crucial for those receiving concurrent aromatase inhibitors (AI). SOFT-EST is a prospective substudy of the phase III SOFT trial. Aims of SOFT-EST are to describe estradiol (E2), estrone (E1) and estrone sulphate (E1S) during monthly Trip + E or T and to assess if there is a group in E+Trip with suboptimal estrogen suppression (SES). **Methods:** All pts enrolled in SOFT from selected centers who consented, selected Trip as ovarian function suppression method and were randomized to E+Trip or T+Trip were enrolled in SOFT-EST until reaching the accrual goal (E=90;T=30 pts). Prem status for SOFT was based on local E2. Blood sampling timepoints (tp) were: 0, 3, 6, 12, 18, 24, 36 & 48 months (m). Serum estrogens were measured by GC/MSMS due to high specificity/sensitivity and no E cross-reactivity. SES for E+Trip for this first pre-planned (12 m) analysis was defined as E2 levels >2.72 pg/mL (10 pmol/L). **Results:** 116 pts (E/T=86/30) who started Trip and had ≥ 1 sample drawn constituted the analytic cohort. In E+Trip, median reductions from baseline in E2, E1 & E1S levels were >95% at all tp, and significantly lower than in T+Trip. 27 of 79 E+Trip pts with ≥1 post-baseline sample had E2 levels >2.72 pg/mL at least once (25%, 24% & 17% at 3, 6 & 12m, respectively); 2 had vaginal bleeding >3 m beyond start of E+Trip, 1 with SES. Baseline factors related to SES in E+Trip were no prior chemo (p=0.06), high BMI (p=0.05), low FSH & LH (p<0.01 for both), but not age (p=0.8). **Conclusions:** Most pts on E+Trip reached E2 below the defined threshold, consistent with postmenopausal pts on an AI, but some may be suboptimally suppressed. The clinical relevance will be further explored with the full 4-yrs of estrogen results and outcome data. Clinical trial information: NCT00066703/NCT00066690.

| Baseline factors all pts: N=116 | |
|---|---|
| **Age (median, range)** | 44 (25, 53) |
| **BMI (median, range)** | 24 (16, 44) |
| **Prior chemo** | 55% |
| **Prior T** | 31% |
| **Amenorrhea** | 36% |
| **Estrogen (pg/mL) (median, range)** | |
| **E2** | 51 (0.6, 766) |
| **E1** | 42 (1.6, 486) |
| **E1S** | 894 (7.2, 8770) |
| **FSH/LH (IU/L)** | |
| **FSH** | 16 (1.7, 123) |
| **LH** | 14 (0.5, 72) |

**586 General Poster Session (Board #50), Mon, 8:00 AM-11:45 AM**

**Impact of 21-gene RT-PCR assay on adjuvant therapy for stage I breast cancer.** *Presenting Author: Fanny Le Du, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** A recurrence score (RS) derived from a 21-gene RT-PCR assay (Oncotype DX) stratifies patients (pts) with early estrogen receptor (ER)-positive, HER2-normal breast cancer (BC) into 3 groups based on risk of 10-year distant metastasis rate: low, intermediate, and high. High RS predicts benefit from chemotherapy follow-by hormonal therapy (CH-T); whether intermediate RS predicts benefit from CH-T is unknown. For Stage I, NCCN Clinical Practice Guidelines recommend use of RS for T1b BC with unfavorable features (angiolymphatic invasion, high histologic or nuclear grade) and T1c BC. However, data are limited on how RS influences treatment of stage I BC. We sought to define the impact of RS on treatment in pts with stage I BC. **Methods:** In 1057 pts with ER-positive, HER2-normal stage I BC with RS available, we assessed the interaction between RS and treatment by tumor category. Kaplan-Meier survival curves and log-rank tests were used to compare outcomes. **Results:** Pts with T1a, T1b, and T1c BC did not differ in the distribution of low, intermediate and high RS (P=0.53) (Table). In the T1b and T1c groups, 57% and 52%, respectively, of pts with intermediate RS did not receive chemotherapy. Median follow-up is 25.7 months. Among T1b pts with intermediate RS, disease-free survival did not differ between pts who received HT and those who received CH-T (P=0.84). Among T1b pts with intermediate RS, pts who received CH-T had higher RS than pts who received HT (median 23 vs 21, P<0.001). **Conclusions:** Less than 10% of patients with stage I had high RS.More than half of pts with stage I BC and intermediate RS received HT alone. Pts with higher RS were more likely to receive CH-T. Among pts with T1b BC and intermediate RS, pts who received HT alone had the similar DFS as those who received CH-T.

| | No. (%) of pts*** | | |
|---|---|---|---|
| **RS category and treatment** | **T1a (n=36)** | **T1b (n=296)** | **T1c (n=725)** |
| **Low** | 22 | 173* | 391* |
| **HT** | 22 (100) | 156 (90) | 345 (88) |
| **CH-T** | 0 | 7 (4) | 31 (8) |
| **Intermediate** | 13* | 98* | 269** |
| **HT** | 11 (85) | 56 (57) | 140 (52) |
| **CH-T** | 1 (8) | 37 (38) | 116 (43) |
| **High** | 1 | 25* | 65** |
| **HT** | 0 | 2 (8) | 10 (15) |
| **CH-T** | 1 (100) | 21 (84) | 52 (80) |

* DFS did not differ between HT and CH-T (P>0.05).
** DFS differed between HT and CH-T (P<0.05).
*** Percentages in some groups total less than 100% because 18 pts received no treatment and 29 pts had missing treatment data.

**587 General Poster Session (Board #51), Mon, 8:00 AM-11:45 AM**

**A randomized, double-blind phase II trial of exemestane plus MM-121 (a monoclonal antibody targeting ErbB3) or placebo in postmenopausal women with locally advanced or metastatic ER+/PR+, HER2-negative breast cancer.** *Presenting Author: Michaela Jane Higgins, Massachusetts General Hospital Cancer Center, Boston, MA*

**Background:** Ligand-driven ErbB3 signaling has been implicated as a mechanism of resistance to conventional therapies across multiple malignancies, including endocrine resistant metastatic breast cancer (mBC). Here we present results of a trial evaluating MM-121 (M) or placebo (P) in combination with exemestane in postmenopausal women with ER/PR+ HER2-negative mBC. **Methods:** This study enrolled women with locally advanced or mBC who had failed adjuvant therapy or progressed in the metastatic setting. The primary endpoint was progression free survival (PFS) and the study was powered to detect a HR of < 0.5. Secondary and exploratory analyses included overall survival (OS), safety, and analyses of a pre-specified set of mechanistically-linked biomarkers ((BM), heregulin, betacellulin, EGFR, ErbB2, and ErbB3) in archived tissues. **Results:** 115 randomized and treated patients (56 (M), 59 (P)) were included in safety and efficacy analyses. Baseline demographics and disease characteristics were balanced. At the time of the analysis, 92 (80%) patients (78.6% (M), 81.4% (P)) had discontinued treatment, mainly due to progressive disease (66.1% (M), 76.3% (P)). PFS was analyzed after 84 events (38 (M), 46 (P)). The median PFS was 15.9 weeks (M) vs. 10.7 weeks (P), with a stratified hazard ratio (HR) of 0.772 (95% CI [0.496- 1.201]), p=0.249). OS data were immature at the time of the primary analysis (29 events: 11 (M), 18 (P)), with a stratified HR of 0.436 (95% CI [0.197 – 0.966]). In patients positive for two of the pre-specified BMs (31%: 17 of the 55 patients with BM data), the HR for PFS was 0.32 (95% CI [0.10-1.00]). Common adverse events (AEs, >20%) of any grade and causality (M vs. P), were diarrhea (50% vs. 23.7%), nausea (28.6% vs. 23.7%), fatigue (23.2 % vs. 23.7%), and arthralgia (17.9% vs. 20.3%). **Conclusions:** The addition of MM-121 to exemestane did not significantly prolong PFS in the unselected population, although the HR appears to favor the MM-121 arm. The biomarker findings were consistent with preclinical hypotheses, as well as an independently conducted Phase 2 study in platinum resistant ovarian cancer. Clinical trial information: NCT01151046.

**588 General Poster Session (Board #52), Mon, 8:00 AM-11:45 AM**

**Residual estrogen receptor availability during fulvestrant 500 mg therapy in patients with metastatic breast cancer.** *Presenting Author: Michel van Kruchten, University Medical Center Groningen, Groningen, Netherlands*

**Background:** Fulvestrant competitively binds the ER and can decrease its expression. However, it is currently unknown whether the standard dose of 500 mg intramuscularly (days 1, 14, 28 and every 4 weeks thereafter) in metastatic breast cancer patients is sufficient for maximal ER downregulation. In a feasibility study we therefore evaluated whether fulvestrant 500 mg completely abolishes ER availability in patients with ER-positive metastatic breast cancer. **Methods:** Sixteen patients received fulvestrant and underwent positron emission tomography/computed tomography (PET/CT) before therapy initiation (scan 1), on day 28 (scan 2) and day 84 (scan 3) to monitor tumor [$^{18}$F]fluoroestradiol (FES) uptake. A relative decrease of <75% in the median (background-corrected) tumor FES uptake and a residual standardized uptake value ($SUV_{max}$) ≥1.5 was predefined as incomplete reduction in ER availability. Plasma fulvestrant levels were determined concurrently with the scans by liquid chromatography tandem mass spectrometry. **Results:** All patients had at least one FES-positive ($SUV_{max}$ ≥1.5) lesion before therapy initiation. A total of 131 FES-positive lesions were identified on FES-PET/CT (median $SUV_{max}$ in patients = 2.9 [range 1.7 - 6.5]). The relative change in tumor FES-uptake in patients during fulvestrant was -85% at scan 2, but varied widely across individuals (-99% to +60%). Median residual tumor $SUV_{max}$ was 1.7 (1.1 - 3.8) at scan 2 and remained stable at scan 3. Fulvestrant reduced tumor FES uptake incompletely at scan 2 in 6 of 16 patients (38%). Eight of nine patients with ≥75% decrease in median FES-uptake at scan 2 subsequently experienced clinical benefit from fulvestrant therapy, compared to only one of six with <75% decrease. Plasma fulvestrant levels were 33 (16 to 53) nmol/L at scan 2 and 27 (13 to 42) nmol/L at scan 3 and did not correlate with changes in tumor FES uptake. **Conclusions:** FES-PET showed significant residual ER availability in tumors during the first 3 months of fulvestrant therapy in 38% of patients, which was related to early progression. FES-PET may be used as an effect sensor for fulvestrant efficacy and may help to identify patients that could potentially benefit from a higher dose. Clinical trial information: NCT01377324.

**589 General Poster Session (Board #53), Mon, 8:00 AM-11:45 AM**

**The value of tamoxifen and trastuzumab in breast cancer treatment: A study based on uptake and use in Sweden.** *Presenting Author: Nils Erik Wilking, Karolinska Institutet, Stockholm, Sweden*

**Background:** Early breast cancer (EBC) and metastatic breast cancer (MBC) represents major health problems. Tamoxifen has since the late 1970s been a backbone in the treatment of hormone receptor positive (HR+) MBC and EBC, and lately also for primary prevention. Trastuzumab has since 2000 in the EU been the drug of choice for HER2+ MBC and from 2005 also in EBC. **Methods:** Sweden had in the end of the 1970s around 4500 and at present around 8000 new cases of EBC. Mortality has been stable over time with about 1500 patients dying annually. Tamoxifen was first introduced in the 1970s in the treatment of MBC. From 1985 and onwards it has been used extensively in EBC with adjuvant treatment times starting with a 1 year treatment period, which in the mid-1990ies was extended to 5 years. Trastuzumab was introduced in MBC in 2000 and became standard in the adjuvant setting in 2005-2006. We have calculated the value of the use of the two drugs from a societal perspective for two periods; 1979-2004 for tamoxifen (time of introduction of aromatase inhibitors as adjuvant treatment for EBC) and 2001-2011 for trastuzumab. We used outcomes from pivotal clinical trials and real world data on use of drugs from the National Pharmacy registry and the National Board of Health and Welfare. The value was estimated as the gains in QALYs and increased production net of costs for drugs and increased consumption in added years of life. **Results:** The gain from tamoxifen in EBC and MBC during 1979-2004 was 39 billion SEK; 32 from gains in QALY and 7 from added production. The cost was 1.1 billion SEK for drugs and 18 billion SEK for added consumption from improved survival. The gain from trastuzumab in EBC and MBC during 2001-2011 was 4.3-6.1 billion SEK from QALY gains and 5.3-7.2 billion SEK from added production. The cost was 2.0 billion SEK for drugs and 1.4 billion SEK for added consumption. (1 USD= 6.60 SEK). **Conclusions:** Tamoxifen and trastuzumab represent major gains in survival, quality of life and productivity of patients with breast cancer. Data showed a major surplus from a societal perspective for each SEK invested: for tamoxifen there was a return of 18 SEK from gains in QALYs and production; for trastuzumab the return was 3.2-5.0 SEK.

**590 General Poster Session (Board #54), Mon, 8:00 AM-11:45 AM**

**Clinical and pathologic correlation of the activated form of the androgen receptor (AR) in breast cancer (BC).** *Presenting Author: Philippe Jamme, Centre Oscar Lambret, Lille, France*

**Background:** The Androgen Receptor is present in BC, and ongoing studies are testing the activity of antiandrogens in BC. AR has been associated with a better prognosis in ER$\alpha$ positive tumors. AR has a nuclear biology dynamics common to the steroid nuclear receptors. In the absence of ligand, it is evenly distributed in nuclei; when exposed to androgens, it migrates to form sub-nuclear aggregates that can be detected by fluorescence microscopy. Thus, two distinct nuclear patterns, diffuse (D) or aggregated (A), correspond to two receptor functional states. Similarly to previous work on ER and PR (ASCO 2013 abstr # 11535 & 593), we have devised an immunohistochemical (IHC) method to characterize the nuclei patterns that may indicate whether AR is transcriptionally active or not in PEFF tissues. The goal of this study is to explore the AR biological or clinical relevance. **Methods:** As of February 4th, 662 archived BC biopsies have been obtained along with associated clinical data. Biopsies were analyzed for standard HES, ER, PR, AR and Ki67. AR positivity was determined with clone AR27 antibody (Novocastra). The A-AR (aggregated AR) and D-AR (diffuse AR) pattern were analyzed at x1000 magnification. **Results:** 490 cases have been analyzed to date. Mean Age: 57 (17-89). Histology: ductal 82%, lobular 15%, and other 3%; $ER\alpha^{pos}$ , 78%, $PR^{pos}$ 78%. Adj Chemotherapy 46% Hormonotherapy 85%. Stage I 44%, II 48%, III 8%. Grade I 25%, II 50%, III 25%. AR was positive ($AR^{pos}$) in 51%. AR status was diffuse (D-AR) in 66% and aggregated (activated, A-AR) in 34% of the $AR^{pos}$ biopsies. $AR^{pos}$ and D-AR were associated with lower Grade ($p < 0.04$, $p = 0.1$), ER$\alpha$ ($p < 0.000$,$= 0.03$), PR ($p < 0.000$, 0.1), but not HER2, Ki67, or Staging. Median follow up was 36 months (mo). Progressive disease (PD), local or distant, was 19%, and PD was not associated with A-AR ($p=0.25$). With DFS defined as time to PD or death (5 year cut-off), $AR^{pos}$was associated with a HR of 0.61 ($p = 0.08$) but not in a Cox model including both AR and ER positivity (HR for ER = 0.41, for AR 0.92, with $p = 0.006$ and 0.8 respectively). When added, grade was an independent predictor (HR= 0.44, $p = 0.004$). **Conclusions:** A-AR is associated with grade and other steroid receptors suggesting biological relevance.

**591 General Poster Session (Board #55), Mon, 8:00 AM-11:45 AM**

**A phase 1 study to assess the food effect on the pharmacokinetics (PK) of entinostat.** *Presenting Author: Denise A. Yardley, SCRI/Tennessee Oncology, PLLC, Nashville, TN*

**Background:** Entinostat (ENT) is an oral, class 1 isoform selective histone deacetylase inhibitor shown to extend progression free and overall survival when combined with exemestane (EXE) in post-menopausal women with estrogen receptor positive (ER+) metastatic breast cancer (MBC) who have progressed on prior non-steroidal aromatase inhibitors (Yardley et al; JCO 31:2128;2013). Based on these results ENT was granted Breakthrough Therapy designation by the FDA for this indication. This Phase 1 study evaluated the effect of food on ENT PK in patients (pts) with MBC and advanced non-small cell lung cancer (NSCLC). **Methods:** A total of 17 pts (14 postmenopausal ER+ MBC and 3 NSCLC) were randomized 1:1 to receive ENT 10 mg administered Day 1 and 15 of a 28 day lead-in cycle, fasting and with food. Pts randomized to ENT with food on Cycle 1 Day 1 (C1D1) received ENT fasted on Cycle 1 Day 15 (C1D15); pts randomized to ENT fasted on C1D1 received ENT with food on C1D15. Blood samples were obtained pre-dose C1D1 and serially during C1 for PK and pharmacodynamic (PD) analysis. Following C1, ENT 10 mg was continued on D1 and 15 of a 28 day cycle in combination with daily EXE 25mg (MBC) or erlotinib 150 mg (NSCLC) until toxicity or disease progression. Tumor assessments (RECIST 1.1) were performed every 2 cycles. **Results:** Co-administration of ENT with food decreased its Cmax by 71% and overall exposure by 15-17%, as estimated by AUClast and AUCinf. The mean t1/2 of ENT was estimated at 140 hrs under fasted conditions and 178 hrs under fed conditions. Additional PK parameters along with protein lysine acetylation PD will be reported. ENT was well tolerated with no unexpected toxicities. 9 MBC pts experienced stable disease (n=8) or partial response (n=1) with 3 pts continuing beyond 10 cycles; one patient continues on study at cycle 19. Progressive disease was the best response in the 3 NSCLC pts. **Conclusions:** ENT $C_{max}$ and exposure as measured by $AUC_{last}$ and $AUC_{inf}$ were significantly reduced when co-administered with food, leading to recommended ENT dosing under fasted conditions. ENT 10 mg was well tolerated and clinical benefit was observed in MBC pts. A randomized, double blind, placebo-controlled phase 3 trial in ER+ advanced breast cancer is planned. Clinical trial information: NCT01594398.

**592 General Poster Session (Board #56), Mon, 8:00 AM-11:45 AM**

**Effect of age and tumor size on prognostic outcome of women with breast cancer.** *Presenting Author: Shaheenah S. Dawood, Dubai Hospital, Dubai, United Arab Emirates*

**Background:** Increasing tumor size is known to be associated with worse prognostic outcome. The objective of this study was to determine the prognostic impact of change in tumor size by age at diagnosis. **Methods:** Using the SEER registry we identified female patients with stage I to III breast cancer diagnosed between 1990 and 2006. Patients (pts) were divided into 4 groups according to age at diagnosis: a) 18 to 35 years, b) 36 to 50 years, c) 51 to 65 years, and d) > 65 years. Breast cancer specific survival (BCSS) was computed using the Kaplan-Meier method. 5-year BCSS were estimated for each tumor size within each age group. Next, the 5-year BCSS was modeled in a linear regression against tumor size as a continuous variable. **Results:** We identified 385,285 patients with following age distribution: 18-35 years =11,737 (3.05%) pts, 36-50 years = 99,442(25.81%) pts, 51-65 years = 130,011(33.74%)pts and >65 years = 144,095(37.40%) pts. The corresponding 5-year BCSS was 83%, 90%, 91% and 87% respectively ($p<0.0001$). 5-year BCSS among pts with T1, T2 and T3 disease was 96%, 84% and 67% respectively ($p<0.0001$). For pts aged 18-35 years, 36-50 years, 51-65 years and >65 years, a 1 cm increase in tumor size was associated with 4%, 4.1%, 4.4% and 5.3% decrease in 5-year BCSS respectively ($p<0.0001$ for difference between youngest and oldest age groups). Among pts with hormone receptor positive disease, a 1 cm increase in tumor size was associated in a significantly lower decrease in 5-year BCSS in the youngest (3.3%) compared to oldest (4.2%, $p <0.0001$) age groups; the corresponding decrease in 5-year BCSS among pts with hormone receptor negative disease was also significantly different ( 4.1% vs. 6.5%, $p<0.0001$). Similar results were obtained when the prognostic impact of tumor size in different age groups was analyzed by nodal status. **Conclusions:** Increasing tumor size has a significantly greater adverse prognostic impact in older compared to younger women and this result is consistent in subgroups defined by hormone receptor and nodal status. This observation could partly account for the greater impact of breast cancer screening in older compared to younger women.

**593 General Poster Session (Board #57), Mon, 8:00 AM-11:45 AM**

**Genes associated with serum estrone, estrone conjugates, and androstenedione concentrations in postmenopausal women with estrogen receptor-positive breast cancer.** *Presenting Author: Tanda M. Dudenkov, Mayo Clinic, Rochester, MN*

**Background:** Estrone (E1), the predominant estrogen in postmenopausal women, is synthesized from androstenedione (A) in the ovaries and adipocytes and can be converted to conjugates (E1Cs). Both circulating E1 and E1Cs are known risk factors for breast cancer; and E1C is present at concentrations up to 10 fold higher in breast cancer tissue than in serum. However, little is known regarding the genes that regulate serum A, E1 or E1Cs concentrations. **Methods:** In a cohort of 776 postmenopausal women with estrogen receptor positive breast cancer, we used a genome-wide association study (GWAS) to identify SNP signals associated with these concentrations. Serum levels of each hormone were measured using GC-MS/MS, and patients were genotyped at ~600,000 SNPs and another 7 million were imputed. Using linear regression models with additive genetic effects, a GWAS was conducted for each hormone level separately as well as the ratio of E1/A, E1Cs/A and E1Cs/E1. SNP effects were adjusted for BMI, population stratification and other relevant variables. **Results:** Multiple SNPs in *SLCO1B1*, a gene that encodes a transporter, were genome-wide significantly associated with E1C levels, E1Cs/E1 and E1Cs/A ratios. The variant allele of the top genotyped SNP rs4149056 (p value = $3.74x10^{-11}$) is a missense mutation that has an established association with statin-induced myopathy and sex hormone binding globulin levels. SNPs in *EMR2* ($p=1.39x10^{-07}$), *ELMO1* ($p=3.19x10^{-07}$), *LDB3* ($p=5.67x10^{-07}$) and *CYP11B1/2* ($p=6.65x10^{-07}$) genes were associated with androstenedione levels. SNPs downstream of *SYNJ2NP2/ARIP2* and upstream of the testis-specific gene *ADAM21* ($p=1.48x10^{-06}$) were associated with E1 levels, with a non-synonymous SNP in *ADAM21* showing suggestive association (rs45480894, $p=2.58x10^{-06}$). The ratio of E1/A was associated with a missense SNP in *ANO7* (rs74804606, $p=5.69x10^{-07}$). **Conclusions:** These results, particularly those for *SLCO1B1* that encodes a liver transporter of E1C, point towards mechanisms that may explain variation in these hormones that are associated with increased risk of breast cancer.

**594 General Poster Session (Board #58), Mon, 8:00 AM-11:45 AM**

**Impact of marital status on prognostic outcome of women with breast cancer.** *Presenting Author: Shaheenah S. Dawood, Dubai Hospital, Dubai, United Arab Emirates*

**Background:** The objective of this study was to examine the impact of marital status among patients with breast cancer. **Methods:** We searched the SEER registry to identify 549589 patients (pts) with stage I to IV breast cancer diagnosed between 1990 and 2010. Patients were divided into two groups depending on the marital status at diagnosis: a) married, b) unmarried (included never married, separated, divorced and widowed). Breast cancer specific survival (BCSS) was computed using the Kaplan Meier product limit method. Multivariable cox models were then fit to look at the association of marital status and BCSS adjusted for various pt and tumor characteristics. **Results:** Married pts accounted for 56.8% of the cohort. Married pts tended to be younger (median age of diagnosis 56 yrs vs. 65 yrs), have lower stage of disease, smaller tumor size, node negative disease and be of white/other race compared to unmarried pts. 5-year BCSS was 89% and 82% among married and unmarried pts respectively ($p<0.0001$). Among patients of either black or white/other race a 7% significant improvement in 5-year BCSS was observed among married compared unmarried pts. Among pts with stage I, II, III and IV disease a significant improvement in 5-year BCSS of 1%, 3%, 9% and 7% respectively was observed among married compared to unmarried pts. In the multivariable cox model unmarried pts had a higher risk of death from breast cancer compared to married pts (HR=1.2; 95%CI: 1.18-1.22; $p<0.0001$). An interaction term between marital status and age at diagnosis was significant, such that as age increases by one year unmarried pts had increasing risk of death compared to unmarried pts (HR 1.004, 95% CI 1.003-1.005, $p<0.0001$). **Conclusions:** Being married at the time of diagnosis of breast cancer improves survival regardless of pt and tumor characteristics. The impact of marital status appears to be greater among older pts compared to younger patients, which may be explained partly by a more aggressive biology generally seen among younger pts and the increasing need for a support system among older patients.

**595 General Poster Session (Board #59), Mon, 8:00 AM-11:45 AM**

**Breast cancer in young women: A single center study.** *Presenting Author: Joanna Rodriguez, Department of Medical Oncology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA*

**Background:** Breast Cancer among young women is on the rise. It is estimated there will be up to 13,000 new cases this year in this age group. There are no screening guidelines in place for women younger than 40 years old. Breast cancer in this age group is associated with higher morbidity and mortality compared to older women, thus the impact of the disease is significant. **Methods:** We performed a retrospective chart review of women younger than 45 years old diagnosed and treated for breast cancer at Thomas Jefferson University from 1998-2012. Patients were stratified by age, stage, disease subtype (triple negative; HR+/Her2-;HR+/Her2 +; HR-/Her2+), race, and BMI. Descriptive analysis was performed. **Results:** Seven hundred and thirty three patients younger than 45 years old were reviewed from 1998-2012.The majority of patients were Caucasian (74%), followed by African American (14%), Asian (1.36%) and Hispanic (.13%). The analysis demonstrated that ER negative disease was found in 20% of patients, with the percentage increasing over the study period. From 1998-2006, 34% of patients were diagnosed with ER negative disease but from 2008-2012, 44.12% of patients were diagnosed with this type of breast cancer. This trend in incidence was not observed in the HER2 positive subtype set which remained stable at 21%. Moreover, the analysis found that there has been an increase in patients presenting with locally advanced disease (clinical stages III/IV). From 2007-2012 stage III/IV disease was documented in 29% of patients as compared to 13.5% of patients from 1998-2006. **Conclusions:** This retrospective study indicates that breast cancer diagnosed in women younger than 45 years is increasingly associated an aggressive clinical and molecular subtype. Delay in diagnosis has been a concern among this age group given the lack of screening guidelines. Furthermore, our data shows an increase in ER negative disease in recent years, suggesting a possible shift in tumor biology as well. More awareness and screening programs to both practitioners and young women should be implemented.

**596 General Poster Session (Board #60), Mon, 8:00 AM-11:45 AM**

**Characteristics of breast cancer in Ghana and prevalence of aggressive disease and high mortality.** *Presenting Author: Evelyn Mawunyo Jiagge, University of Michigan, Ann Arbor, MI*

**Background:** Breast cancer (BC) is now emerging as the most commonly diagnosed cancer among women in sub-Saharan Africa, surpassing cervical cancer. Although its incidence is relatively low in women in western Africa (approximately 28-35/1000,000), it carries 80% mortality, representing a massive public health problem. We hypothesized that the high mortality of BC is due to late diagnosis and to the high prevalence on estrogen receptor (ER) negative BC that is very aggressive and relatively unresponsive to existing therapies. The overarching objective of this work is to help focus research on the most pressing questions regarding the biological determinants contributing to high mortality from BC in sub-Saharan Africa. **Methods:** All the cancer cases that reported to Komfo Anokye Teaching hospital in Kumasi, Ghana diagnosed or treated at the facility between 2004 and 2011 were compiled and classified by age, stage, and receptor status, if available. The proportion of BC cases was further grouped by histologic type. **Results:** BC comprises nearly 25% of all cancers with male breast cancer accounting for 10% of BC cases. Of the female breast cancers, 50% are estrogen receptor negative. More than a third of the patients are younger than 45 years. The age specific incidence appears shifted to younger ages, after accounting for the population pyramid. **Conclusions:** BC in being increasingly diagnosed in Ghana; increased diagnosed burden may be due to increased awareness and/or to slowly increasing true incidence. BC in Ghanaian women exhibits phenotypic characteristics of younger age distribution, high proportion of ER- disease, high proportion of male breast cancer. These characteristics suggest specific early life exposures, hereditary factors, or both. Molecular genetics studies of tumors of differing ancestries may uncover hereditary factors that contribute to this spectrum of characteristics.

**597 General Poster Session (Board #61), Mon, 8:00 AM-11:45 AM**

**Factors influencing recurrence in long-term survivors with early-stage breast cancer of low risk.** *Presenting Author: Xerxes Pundole, The University of Texas Health Science Center at Houston, School of Public Health, Houston, TX*

**Background:** Approximately 60% of women with breast cancer (BC) are diagnosed with early stage disease with 5-year survival rates estimates of 84.4% to 98.6% depending on tumor type and extent of lymph node involvement. Despite high survival rates, many women experience recurrences after 5, 10 and even 15 years. Little is known about the influence of lifestyle and other 'host' factors and disease recurrence in 'long-term' survivors with low-risk disease. **Methods:** A retrospective case-only study of stage I-II BC patients, at The University of Texas M.D. Anderson Cancer Center from January 1, 1985 to December 31, 2000. The cases were disease free 5 years from diagnosis, and for whom baseline and follow-up information were available. We sought to compare epidemiologic and clinical factors among patients that had a late recurrence of their primary BC to those who did not. **Results:** A total of 2,468 patients were included in the original study from 1985 to 2000, of these 2,047 (83%) women were followed for >5 years. We obtained epidemiologic information on 1,057 (52%) women, of which 1,035 (98%) women were disease free and 22 (2%) had a recurrence after 5 years of being disease free. Multivariable analysis revealed that Hispanic women [Reference (Ref) Caucasian, (odds ratio (OR), 3.78, p =0.02] and heavy alcohol drinkers [Ref never drinkers, OR, 11.2, p=0.00] were significantly associated with recurrence in these patients with low risk disease, after adjusting for the year of diagnosis. No other clinical or histopathological characteristics at diagnosis or other epidemiologic factors (BMI, smoking, family history) were associated with recurrence in this sub cohort. **Conclusions:** Though limited by inherent bias of non-inclusion of women lost to follow-up and a small sample size, to our knowledge, this is the first evidence suggesting that alcohol consumption may increase the risk of late recurrence in an otherwise good prognosis group. Our results contrast published findings of no overall main effect of alcohol at baseline as a risk factor for BC recurrence and suggest a need to test the effect of alcohol consumption on late recurrence, where tumor biology is less likely to overwhelm modest but significant effects of lifestyle factors.

**598 General Poster Session (Board #62), Mon, 8:00 AM-11:45 AM**

**Phase I-II study of the histone deacetytase inhibitor vorinostat plus sequential weekly paclitaxel and doxorubicin-cyclophosphamide in locally advanced breast cancer.** *Presenting Author: Yifan Tu, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY*

**Background:** HDACs regulate chromatin remodeling and gene transcription. Vorinostat (V) is a panHDAC inhibitor that sensitizes breast cancer (BC) cells to taxanes and trastuzumab. **Methods:** 55 patients (pts) with clinical stage IIA-IIIC BC received 12 weekly doses of paclitaxel (P)(80 mg/m2) plus V on days 1-3 (200 mg BID [N=4], 300 mg BID [N=51]) of each P dose plus trastuzumab (if HER2-positive), followed by doxorubicin/cyclophosphamide (AC-60/600 mg/m2 every 2 weeks and pegfilgrastim), The trial was powered to detect an improvement in pathologic complete response (pCR) rate from 30% to 55% ($\alpha$=0.10, $\beta$=0.10) in stratum A (HER2+) and stratum B (triple negative), and from 15% to 40% in stratum C (ER+, HER2-). Immunohistochemistry was done on pretreatment core biopsies for HDAC6, p27, p21, Hsp70, and Ki67, and 3 pts had biopsies done before and after the third V dose for Western blot analysis. **Results:** There were no dose limiting toxicities at either V dose level. Breast/nodal pCR occurred in 13/24 evaluable pts in stratum A (54%, 95% confidence intervals [CI] 34%, 74%), 4/15 evaluable pts in stratum B (27%, 95% CI 95% CI 11%, 52%), and none of 12 evaluable patients in stratum C. Residual cancer burden (RCB) scores were 0-1 in 19 (79%, 95% CI 59%, 91%), 7 (47%, 95% CI 21%, 71%), and 1 (8%, 95% CI 0.4%, 35%) pts in stratums A, B, and C, respectively. Mean/median HDAC6 expression did not differ in each stratum or correlate with pCR. Mean P21 expression was higher in stratum A than B (p=0.03), and HSP70 expression was higher in stratum C than A (p=0.02). By Western blot, V suppressed HDAC6, increased acetylation of HSP90 and alpha-tubulin, and reduced levels of HSP90 client proteins (eg. HER2/neu, pAKT) in vivo. **Conclusions:** Combination of V with weekly paclitaxel and trastuzumab followed by AC induces higher than expected pCR rate in locally advanced HER2/neu-positive breast cancer. V induced biological effects in vivo that may enhance the antitumor effects of paclitaxel and trastuzumab and contribute to the efficacy of this combination. Clinical trial information: NCT00574587.

**599 General Poster Session (Board #63), Mon, 8:00 AM-11:45 AM**

**Differential effects of metformin on breast cancer proliferation according to insulin resistance and tumor subtype in a presurgical trial.** *Presenting Author: Andrea De Censi, E.O. Ospedali Galliera, Genoa, Italy*

**Background:** Treatment of diabetics with metformin decreases breast cancer risk in observational studies, but it is unclear if this drug has clinical antineoplastic activity. In a recent pre-surgical trial (Bonanni et al JCO 2012), we found a heterogeneous effect of metformin on Ki-67 depending upon insulin resistance (HOMA index). Here we determined the associations of additional biomarkers of insulin resistance, tumor subtype, and serum drug concentration with Ki-67 response to metformin. **Methods:** 200 non-diabetics were randomly allocated to either metformin (850 mg/bid) or placebo for 4 weeks prior to breast cancer surgery. Response was assessed by comparing baseline biopsy (Ki-67 and tumor subtype) and serum markers (HOMA, C-peptide, IGF-I, IGFBP-1, IGFBP-3, hsC-reactive protein, adiponectin) with the same measurements at surgery. For patients with a blood sample taken <24 hours from last drug intake, metformin level was measured. **Results:** Compared with placebo, metformin decreased Ki-67 in women with HOMA>2.8, bottom IGFBP-1 quintile, top IGFBP-3 quartile, CRP>2.5 mg/L, and HER2+ve tumors (table). When HOMA was>2.8, serum drug levels were positively correlated with Ki-67 decrease, whereas no trend was noted for HOMA<2.8 (p interaction=.07). **Conclusions:** At antidiabetic doses, the effect of metformin on tumor Ki-67 of nondiabetic breast cancer patients is modest and varies with host and tumor characteristics. These findings are relevant to clinical trials of metformin in breast cancer prevention and treatment. Clinical trial information: ISRCTN16493703.

**Median (IQR) Ki-67 changes (post-pre treatment) by arm and biomarker threshold.**

| Risk biomarker threshold | N | Placebo | Metformin | P interaction |
|---|---|---|---|---|
| HOMA index >2.8 | 53 | 0 (-2.0; 5.0) | 0 (-5.0; 2.5) | 0.03 |
| HOMA index ≤2.8 | 142 | 0 (-2.0; 4.0) | +1 (-2.0; 7.0) | |
| hsCRP>1.81mg/L (3rd tertile) | 65 | +2.5 (0;7) | 0 (-3; 4) | 0.02 |
| hsCRP≤1.81 mg/L | 131 | 0 (-3;5) | +0.5 (-2; 8) | |
| IGFBP-3>4.6ug/mL (4thquartile) | 50 | 0 (-5.0; 7.0) | 0 (-4.0; 2.0) | 0.04 |
| IGFBP-3≤4.6ug/mL | 146 | 0 (-1.5; 4.0) | +1 (-3.0; 7.0) | |
| IGFBP-1<2 ng/mL (1thquintile) | 40 | +1 (-5.0; 14.0) | 0 (-4.0; 5.0) | 0.02 |
| IGFBP-1≥2 ng/mL | 156 | 0 (-2.0; 4.0) | +0.5 (-3.0; 7.0) | |
| HER2+ve | 22 | +3.5 (0; 14.0) | +0.5 (-4.0; 8.0) | 0.07 |
| HER2-ve | 174 | 0 (-3.0; 4.0) | 0 (-3.0; 7.0) | |

**600 General Poster Session (Board #64), Mon, 8:00 AM-11:45 AM**

**Trastuzumab duration effects within patient prognostic subgroups in the PHARE trial.** *Presenting Author: Xavier B. Pivot, Institut Regional du Cancer en Franche-Comté - University Hospital, Besançon, France*

**Background:** At 42.5 months of median follow-up, PHARE failed to show that 6 was non-inferior to 12 month of adjuvant trastuzumab. From the results of PHARE questions remain regarding whether the magnitude of benefit derived from 1 year is sufficient to justify its systematic use for different patient subgroups. **Methods:** Treatment effects were evaluated according to various tumour characteristics, and multivariate Cox proportional hazards regression models were performed on metastatic disease free survival (M-DFS) in the 12 month control arm. A prognostic score was defined providing the identification of patient categories with similar risks. The 6 months arm was used as a validation set in order to test for heterogeneity. **Results:** A total of 261 M-DFS events were observed and 4 prognostic groups were defined: very low, low, intermediate and high risks. In the 12 month arm, the corresponding 3-year M-DFS rates were 98.3%, 95.8%, 90.4% and 78.4% in the 4 prognostic groups, respectively. In the 6 month arm, the 3-year M-DFS rates were 98.3%, 94.2%, 85.7%, and 74.8% in the 4 prognostic groups, respectively. **Conclusions:** In the very low risk and low risk groups, the potential absolute benefit of standard duration of trastuzumab was small enough to indicate that optimal standard treatment might be clinically questionable. On the other hand, the 3-year metastasis occurrence rates strongly support the need for a search of a more efficient treatment in the intermediate and high risk groups. Clinical trial information: NCT00381901.

**601 General Poster Session (Board #65), Mon, 8:00 AM-11:45 AM**

**Lapatinib or trastuzumab with taxane therapy as first-line treatment in metastatic breast cancer (MBC): A biomarker analysis in NCIC CTG MA.31.** *Presenting Author: Wendy R. Parulekar, NCIC Clinical Trials Group, Cancer Research Institute, Queen's University, Kingston, ON, Canada*

**Background:** Lapatinib (L) was associated with shorter progression-free survival (PFS) than trastuzumab (T) when combined with a taxane (Tax) as first line therapy for HER2+ MBC. We report the effects of 6 centrally reviewed biomarkers on efficacy. **Methods:** MA.31 accrued 652 patients with locally assessed HER2+ tumors of which 537 (82%) were HER2+ by central review. Protocol-mandated immunohistochemistry was conducted centrally for ER, PR, Ki67, EGFR, and CK5. The primary endpoint was progression free survival (PFS) defined as time from randomization to progression or death in the intention to treat (ITT) population. Stratified step-wise forward Cox models examined the multivariate (mv) effects of baseline characteristics and continuous biomarkers (% positive) on PFS in the ITT and centrally confirmed HER2+ populations. Predictive effects were investigated with cutpoints of >0% of any staining intensity for ER, PR, EGFR, CK5, and >geometric mean for Ki67 for both populations. **Results:** Assessments were completed for > 80% of patients. Median follow-up was 21.5 months. LTax/L demonstrated inferior PFS to TTax/T (ITT, $p<0.001$). Centrally confirmed HER2+ status conferred a positive prognostic effect on PFS ($p=0.005$). Patients whose tumors had higher % positive ER had longer PFS [stratified HR=0.996 (95% CI 0.993-0.999); ITT, $p=0.01$, HER2+, $p=0.003$]. In ITT, lower % positive CK5 had improved PFS [stratified HR=1.008 (95% CI 1.001-1.014); $p=0.03$]. However, treatment interactions with each of HER2, ER, and CK5 were not significant ($p>0.05$). EGFR had a quantitative interaction with treatment favoring TTax/T: ITT, $p=0.05$; HER2+, $p=0.06$. **Conclusions:** LTax/L therapy was associated with shorter PFS compared to TTax/T as first line therapy for HER2+ MBC. Centrally confirmed HER2+ and higher % positive ER were prognostic for longer PFS. Higher EGFR positivity indicated a better response to TTax/T. Clinical trial information: NCT00667251.

**602 General Poster Session (Board #66), Mon, 8:00 AM-11:45 AM**

**Transcriptional expression of Bcl-2 as predictive of response to neoadjuvant chemotherapy with trastuzumab in HER2-positive ER-positive breast cancer patients.** *Presenting Author: Maki Tanioka, Medical Oncology, Hyogo Cancer Center, Akashi, Japan*

**Background:** Several trials have confirmed that pathologic complete response (pCR) rates after neoadjuvant chemotherapy (NAC) are significantly lower in HER2+/ER+ patients (pts) than in HER2+/ER− pts. To elucidate this phenomenon, we investigated the association of anti-apoptotic Bcl-2, which is frequently overexpressed in ER+ tumors, with to NAC resistance. **Methods:** Pretreatment formalin-fixed tumor tissues were collected from 75 HER2+ pts receiving NAC comprising anthracyclines, taxanes, and trastuzumab. mRNA expression was detected by PCR amplificationand quantitative primer extension using MassARRAY (Sequenom, CA). The panel of 15 genes comprised EGFR, HER2, HER3, IGF1R, FGFR, PTEN, INPP4B, SRC-1, DUSP4, ESR1, PgR, FOXA1, PDL1, CTLA-4, and Bcl-2, whose expressions were dichotomized according to median values. PIK3CA mutations were detected using MassARRAY genotyping. ER, PTEN, and Bcl-2 protein expressions were scored from 0 to 3 according to the frequency and intensity by immunohistochemisty (IHC). The relationship between variables was assessed by Spearman's correlation. Logistic regression analysis was performed to detect predictors of pCR, which was defined as no invasive tumor in the breast or axilla. **Results:** Median age was 58 years; 97% were stage II–III, 47% were ER+, and 52% (40%/ 63% in ER+/ ER−) achieved pCR. Bcl-2 mRNA and protein expression were correlated ($r=0.66$, $p=.001$). In univariate analysis, pCR was associated with high mRNA levels of ESR1, PgR, IGF1R, HER2, CTLA4, PDL-1, and Bcl-2 ($p\leq.05$), but not with PIK3A mutations or PTEN loss by IHC. Bcl-2 expression was significantly correlated with ESR1 ($r=0.74$), PgR ($r=0.74$), and IGF1R ($r=0.68$); thus, PDL-1, CTLA4, HER2, and Bcl-2 were tested in the multivariate model. Bcl-2 retained the predictive value for pCR [$p=.022$; odds ratio (OR), 0.28 (0.10−0.84)]. In ER+ pts, median Bcl-2 levels were 2.2 times higher than in ER− pts, and pCR rates were 17% and 65% in pts with high and low Bcl-2 expression, respectively ($p=.006$; OR, 0.11). **Conclusions:** Our data suggests Bcl-2 expression is predictive of pCR and provides a rationale for the evaluation of Bcl-2 inhibitors in HER2+/ER+ BC pts.

**603 General Poster Session (Board #67), Mon, 8:00 AM-11:45 AM**

**Long-term cardiac safety analysis of NCCTG (Alliance) N9831 adjuvant trastuzumab (H) trial.** *Presenting Author: Pooja Prem Advani, Mayo Clinic, Jacksonville, FL*

**Background:** Significant improvement in disease-free and overall survival has been established with the addition of H to adjuvant chemotherapy. However, H may increase risk of cardiac dysfunction (CD) and warrants long-term evaluation. **Methods:** N9831 compared adjuvant doxorubicin and cyclophosphamide (AC) followed by weekly paclitaxel (T) (Arm A) vs. ACàTàH (Arm B) or ACàTHàH (Arm C) in operable HER2+ breast cancer. Cumulative incidence of cardiac events (CE) (symptomatic CHF and definite/probable cardiac death) and left ventricular ejection fraction (LVEF) assessed by MUGA/ECHO were evaluated in women who proceeded to post-AC therapy. Risk factors for H-related CD were identified by Cox regression models. **Results:** 977 women with clinical and LVEF data beyond 5 years (yr) from study enrollment were included (Arm A=304; Arm B=346 and Arm C=327); median follow up: 6.6 yr. Median age: 50 yr (range, 22–82). Median LVEF at 6 yr: 61% (Arm A); 61% (Arm B) and 60% (Arm C). Absolute median LVEF decrease from baseline: 3.0% (Arm A), 2.5% (Arm B) and 3.0% (Arm C). 6-yr cumulative incidence of CE: 0.6%, 2.8% and 3.4% in Arms A, B and C (minimal difference from CE at 3 yr: 0.5%, 2.6% and 3.4%). Suspected cardiac deaths: 4 (Arm A); 1 (Arm B); 1 (Arm C). There was a statistically significant increase in risk of CE in Arms B (HR 2.6; 95% CI: 1.1–6.2) and C (HR 3.4; 95% CI: 1.4–8.0) vs A ($P = 0.019$). Associated with increased risk of CE in Arms B and C were age > 60 yr (HR 3.2; 95%: CI 1.5-6.8, $P = 0.0019$), LVEF (50-55%) at registration (HR 3.3; 95% CI: 1.1-9.6, $P = 0.030$), and use of antihypertensive medications (HR 2.3; 95% CI: 1.2-4.4, $P=0.015$). Race ($P = 0.318$) and BMI 25-29.9 ($P = 0.1038$) and >30 ($P = 0.0735$) were nonsignificant risk factors. **Conclusions:** 6-yr cumulative incidence of CE was higher by 2.8% in the H-containing arms vs control arm. We noted minimal difference in the cumulative incidence of CE beyond 3-yr (Perez, JCO 2008), suggesting that late development of CE with H is infrequent. Hence, H (in context of anthracycline and taxane-based therapy) continues to have a favorable benefit-risk ratio (5-yr absolute OS benefit: 3.5%; DFS benefit: 12.7%). Older age, lower registration LVEF and antihypertensive medication use were predictive of increased risk of CD with H.

**604^ General Poster Session (Board #68), Mon, 8:00 AM-11:45 AM**

**Phase I/II study of neoadjuvant eribulin mesylate, carboplatin, and trastuzumab (ECH) for operable HER2 positive (HER2+) breast cancer.** *Presenting Author: Lee Steven Schwartzberg, The West Clinic and ACORN Research, LLC, Memphis, TN*

**Background:** Docetaxel, carboplatin (C) and trastuzumab (H) yields substantial pathologic complete response (pCR) in operable HER2+ breast cancer (BC). Eribulin mesylate (E) is a tubulin inhibitor shown to improve overall survival in pretreated advanced BC. This Phase I trial was designed to determine the maximum tolerated dose (MTD) of ECH as neoadjuvant therapy in HER2+ BC with a planned follow-on Phase II component with pCR as the primary endpoint. **Methods:** This was a multicenter open-label single arm trial. Eligible patients (pts) had operable stage IIA – IIIB HER2+ BC, ECOG 0-1, normal LVEF, QTc < 480 msec, < grade 1 neuropathy and no history of invasive cancer within 3 years. Phase I planned up to 18 pts to 1 of 3 E dose cohorts, with pts treated at the MTD also evaluable for the Phase II extension. Starting dose of E was 1.1 mg/m$^2$ with escalation to dose level +1 at 1.4 mg/m$^2$. ECH was given IV for six 3-week cycles with E d1 and d8; C AUC 6 d1; and H 8mg/kg loading dose d1c1 and 6mg/kg d1c2-c6. C1 dose limiting toxicities (DLTs) were defined as: grade 4 thrombocytopenia (TP), anemia, or neutropenia (N) lasting > 5 days; any grade 3-4 non-hematologic toxicity attributable to E, C, H, or the combination; or inability to deliver all three agents at assigned dose and schedule during cycle 1. Standard 3+3 dose escalation design was used. **Results:** 5/6 patients at 1.1 mg/m$^2$ and 4/6 at 1.4 mg/m$^2$ completed 6 cycles of ECH. The MTD of ECH was not determined. At 1.1 mg/m$^2$ E, Grade 3/4 hematologic toxicity: anemia 4 pts, TP in 2 pts, and N 4 pts, and at 1.4 mg/m$^2$ E, anemia 1 pt, TP in 2 pts and N in 5 pts. 8 of 12 (67%) pts required PRBC transfusions (range 2-12 units) and 2 pts required platelet transfusions (range, 4-12 units). 11 of 12 (92%) pts required dose reduction of E. At surgery, 10 pts (83.3%) achieved partial response and 2 (16.7%) had pCR. **Conclusions:** In this Phase I study, the ECH regimen was associated with levels of hematologic toxicities and transfusion requirements not observed in other eribulin-carboplatin studies. This combination is not planned to undergo further Phase II development in the HER2+ neoadjuvant setting. Clinical trial information: NCT01388647.

**605 General Poster Session (Board #69), Mon, 8:00 AM-11:45 AM**

**Relationship between tumor biomarkers (BM) and efficacy in TH3RESA, a phase 3 study of trastuzumab emtansine (T-DM1) versus treatment of physician's choice (TPC) in HER2-positive advanced breast cancer (BC) previously treated with trastuzumab and lapatinib.** *Presenting Author: Sung-Bae Kim, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

**Background:** T-DM1, an antibody–drug conjugate comprising trastuzumab, DM1 (microtubule inhibitor), and a stable linker, is approved for patients (pts) with HER2-positive metastatic BC previously treated with trastuzumab and a taxane. In two phase 3 studies, T-DM1 prolonged progression-free survival (PFS; EMILIA, TH3RESA) and overall survival (EMILIA) v control arms. Here we examine the relationship between tissue BM related to the HER2 pathway and PFS in TH3RESA (NCT01419197). **Methods:** Pts had prior taxane therapy and ≥2 HER2-directed regimens, including trastuzumab and lapatinib, and were randomized 2:1 to T-DM1 (3.6 mg/kg q3w) v TPC. qRT-PCR for HER2, HER3, and G6PDH (ref) mRNA was performed with available pt tumor tissue. Analyses of tumor DNA for PIK3CA mutations (exons 1, 4, 7, 9, 20) and cytoplasmic PTEN expression by IHC were performed as optional research. PFS was analyzed for each BM subgroup using the Kaplan-Meier method and a Cox regression model. **Results:** Overall, median HER2 mRNA, HER3 mRNA, and PTEN levels and PIK3CA mutation status were consistent across arms and with previous results. For all BM subgroups, median PFS was longer with T-DM1 v TPC (Table). Relative risk reduction for PFS was numerically greater for T-DM1 v TPC for >median HER2 mRNA levels than ≤median levels but similar within HER3 mRNA, PIK3CA, and PTEN (not shown) subgroups. **Conclusions:** Similar to previous results, T-DM1 prolonged PFS in all BM subgroups analyzed with a greater benefit observed for pts with tumors expressing >median HER2 mRNA levels. Although PIK3CA mutation status was not associated with decreased PFS in the control arm, benefit was seen with T-DM1 regardless of mutation status. Clinical trial information: NCT01419197.

| | T-DM1 | | TPC | | | |
|---|---|---|---|---|---|---|
| | n | Median PFS (mo) | n | Median PFS (mo) | HR | 95% CI |
| **All pts** | 404 | 6.2 | 198 | 3.3 | 0.52 | 0.42–0.65 |
| **HER2 mRNA** | | | | | | |
| ≤Median | 164 | 5.5 | 89 | 3.9 | 0.68 | 0.49–0.92 |
| >Median | 177 | 7.2 | 75 | 3.4 | 0.40 | 0.28–0.59 |
| **HER3 mRNA** | | | | | | |
| ≤Median | 166 | 6.0 | 90 | 3.3 | 0.52 | 0.37–0.71 |
| >Median | 176 | 6.8 | 73 | 4.1 | 0.55 | 0.38–0.79 |
| **PIK3CA mutation status** | | | | | | |
| Mutated | 65 | 6.2 | 37 | 3.1 | 0.44 | 0.26–0.73 |
| Wild-type | 187 | 6.8 | 78 | 3.4 | 0.47 | 0.33–0.67 |
| Unknown | 33 | 5.9 | 10 | 3.6 | 0.56 | 0.22–1.45 |

**606 General Poster Session (Board #70), Mon, 8:00 AM-11:45 AM**

**Trastuzumab emtansine (T-DM1) plus capecitabine (X) in patients with HER2-positive MBC: MO28230 TRAX-HER2 phase 1 results.** *Presenting Author: Karen A. Gelmon, British Columbia Cancer Agency, Vancouver, BC, Canada*

**Background:** T-DM1, an antibody–drug conjugate composed of trastuzumab, the microtubule inhibitor DM1, and a stable linker, is a newly approved therapy for HER2-positive MBC. Two phase 3 studies have shown significant efficacy in patients previously treated with trastuzumab and a taxane. HER2-directed therapies in combination with X have shown improved efficacy in patients with MBC, and preclinical data show enhanced activity with T-DM1 + 5-fluorouracil. Thus, T-DM1 + X may have increased antitumor activity in patients with HER2-positive MBC. **Methods:** TRAX-HER2 (NCT01702558) is a phase 1/2 study of T-DM1 + X in patients with HER2-positive MBC (IHC 3+/ISH+) or metastatic gastric cancer. Key inclusion criteria are progression on ≥1 trastuzumab + chemotherapy regimen, ≥1 measurable lesion (RECIST v1.1), and LVEF ≥50%. The primary phase 1 objective for MBC was to evaluate the maximum tolerated dose (MTD) of X with T-DM1 (3.6 mg/kg q3w) using a 3 + 3 design. Safety, tumor response, and PK were also assessed. **Results:** As of the data cutoff (1/17/14), 7 patients were enrolled in the T-DM1 + X 750 mg/m$^2$ cohort (a 7th patient replaced one that had not met the stable liver enzymes eligibility criterion). Of the 6 DLT-evaluable patients (follow-up: 3.7–13.2 mos), 2 had a DLT (1 grade 3 vomiting, 1 grade 3 elevated ALT and AST, which prohibited start of cycle 2 at 100% dose). After the DLT evaluation period, 2 patients had grade 3 AEs: 1 elevated ALT, 1 keratitis. No grade ≥4 AEs or SAEs were reported. As of the cutoff, 4 of the 6 patients remain on treatment. The best confirmed overall response was a partial response in 4 patients and stable disease in 1 patient; 1 patient was not evaluable (had only 1 assessment). The T-DM1 PK profile was comparable with that observed in single-agent T-DM1 trials; PK of X was similar ± T-DM1. Due to the 2 DLTs, the next cohort was opened with a de-escalated dose of X (700 mg/m$^2$). Three patients have been enrolled (follow-up: 0.5–1.2 mos); no DLTs or grade ≥3 AEs have yet been observed. **Conclusions:** T-DM1 + X 750 mg/m$^2$ showed encouraging activity. However, due to DLTs, a dose de-escalated cohort (T-DM1 + X 700 mg/m$^2$) was opened. Complete results from this cohort (n=6) will be available at the time of presentation. Clinical trial information: NCT01702558.

**607 General Poster Session (Board #71), Mon, 8:00 AM-11:45 AM**

**Survival among elderly breast cancer patients by receipt of human epidermal growth factor receptor 2-targeted therapy: A matched analysis of national registry data.** *Presenting Author: Jaqueline Willemann Rogerio, Novartis Pharmaceuticals Corporation, East Hanover, NJ*

**Background:** Few studies have examined survival among elderly breast cancer (BC) patients by receipt of human epidermal growth factor receptor 2 (HER2)-targeted therapy. **Methods:** Women aged 65+ with an incident diagnosis of BC (index) and no history of other cancer were identified from 2006-2010 linked Surveillance, Epidemiology, and End Results (SEER) and Medicare data. Women with BC were classified by receipt of HER2-targeted therapy (trastuzumab or lapatinib) or not, each matched 1:1 to a non-cancer comparison cohort by demographics. Patients had one year of continuous enrollment prior to index and were followed through the earliest of disenrollment, death, or the end of the data. Mortality and time to death were evaluated for all cohorts, by stage, age and race. One Cox model for each disease stage (I-IV) was constructed, with indicators for BC with HER2-targeted therapy and BC without such therapy, using the pooled non-BC comparison cohorts as the reference group. **Results:** We identified 1,746 BC patients with and 35,114 without HER2-targeted therapy. Patients with and without HER2-targeted therapy had similar mortality (13.0% versus 14.2%; P = 0.18) during follow-up (mean 28 versus 27 months; P = 0.03). Among patients who died, patients with HER2-targeted therapy experienced longer time to death (median 17 versus 13 months; P < 0.01). Among patients with HER2-targeted therapy, increased age (P<0.01) and later stage (P<0.01) were associated with higher mortality. In the Stage IV Cox model, both BC with HER2-targeted therapy and BC without HER2-targeted therapy (vs. no BC) were associated with significantly higher mortality (hazard ratio [HR] = 2.46 and 5.24, respectively; both P < 0.01). BC without HER2-targeted therapy was also a significant predictor of increased mortality in the Stage III model (HR = 1.37; P < 0.01). Significant predictors of increased mortality across the four models included older age (75+) and baseline Charlson comorbidity score >2. **Conclusions:** BC patients with and without HER2-targeted therapy had similar mortality, with longer time to death among the former. Mortality and time to death also varied by stage, age, and race.

**608 General Poster Session (Board #72), Mon, 8:00 AM-11:45 AM**

**Association of basal marker expression with outcome and trastuzumab resistance in HER2-positive breast cancer.** *Presenting Author: Alice P. Chung, Cedars-Sinai Medical Center, Los Angeles, CA*

**Background:** Herceptin resistance is a significant challenge in the treatment of Her2-positive (Her2+) breast cancer. A subset of Her2+ breast cancers are known to express basal genes (basal Her2). We investigated the effect of basal gene expression on cell viability and Herceptin response in Her2+ breast cancer cell lines and on prognosis in patients with Her2+ breast cancer who received Herceptin. **Methods:** We selected 4 cell lines to represent basal Her2 (HCC1569, HCC1954) and non-basal Her2 (BT474, SKBR3) breast cancer based on their basal gene signature in microarray analysis, and treated each with vehicle, Herceptin (H), Paclitaxel (P), and H + P. Cell viability was assessed by MTT assays. Her2 pathway suppression was compared between groups using immunoblotting with anti-Her2, p-AKT, p-ERK antibodies. Expression of CK5/6, CK14, and EGFR was evaluated after immunohistochemical staining in paraffin-embedded tissue of 88 patients with Stage 1-3 Her2+ breast cancer treated with chemotherapy and Herceptin. Groups with and without basal gene expression were compared with respect to clinicopathologic parameters and survival. **Results:** All cell lines expressed similar levels of Her2. Both H and P alone inhibited proliferation of non-basal cell lines, and H + P had an additive cytotoxic effect. Basal cells were resistant to H, P inhibited proliferation, but H + P had no additive cytotoxic effect on cell growth in basal cells. Immunoblotting showed a significant decrease in p-Akt levels after treatment with H or H + P in non-basal cells but not in basal cells. No alterations were observed in p-ERK levels in the 4 cell lines when treated with H and H + P. Of the Her2+ patients, 33/88 (37.5%) expressed at least one basal gene. Basal Her2 tumors were associated with higher grade (p=0.04) and more ER/PR-negativity (p<0.01). CK14 expression correlated with worse overall survival by log-rank test (p=0.02), while EGFR showed a similar trend (p=0.06). **Conclusions:** Basal Her2 cell lines are resistant to Herceptin. This resistance is associated with Herceptin refractory PI3K/Akt activity. CK14 expression is predictive of worse prognosis in Her2+ breast cancer patients treated with Herceptin.

**609 General Poster Session (Board #73), Mon, 8:00 AM-11:45 AM**

**Retrospective analysis of toxicity in patients (pts) with liver metastases (mets) from phase 3 studies of trastuzumab emtansine (T-DM1) in pts with metastatic breast cancer (MBC).** *Presenting Author: David Miles, Mount Vernon Cancer Centre, London, United Kingdom*

**Background:** In two phase 3 studies in pts with HER2-positive MBC, treatment with the antibody–drug conjugate T-DM1 resulted in increased progression-free survival (PFS) and overall survival (EMILIA) and PFS (TH3RESA) v control arms. T-DM1 is associated with grade (gr) ≥3 elevations of hepatic transaminases. We examined the association between the presence of liver mets at baseline (with/without abnormal transaminases) and toxicity, as well as efficacy in pts from these 2 studies. **Methods:** EMILIA and TH3RESA data were analyzed separately. Analyses included the rates of any grade adverse events (AEs), gr ≥3 AEs (including AEs identified with hepatotoxicity), selected AEs of interest for T-DM1, ORR, and PFS. Comparisons were pts with/without liver mets at baseline in the absence or presence of abnormal (>1× upper limit of normal [ULN]) alanine aminotransferase (ALT). **Results:** Overall, the rate of gr ≥3 AEs was lower with T-DM1 v controls (Table). In pts with liver mets and elevated ALT at baseline, the incidence of gr ≥3 AEs was higher with T-DM1, with the highest incidence in the "investigations" category, which includes laboratory data such as increased transaminases (EMILIA, 18.2% v 0%; TH3RESA, 17.4% v 10.5%). Reduction in risk of progression with T-DM1 was similar in all subgroups and comparable with the overall randomized populations (Table). **Conclusions:** This retrospective analysis suggests that in the presence of liver mets (with/without elevated ALT at baseline), the clinical efficacy benefit of T-DM1 is maintained. The AEs observed with T-DM1 in pts with liver mets and elevated ALT were primarily laboratory-based. Clinical trial information: NCT00829166 and NCT01419197.

| | All pts | | No liver mets | | Liver mets | | Liver mets/ ALT ≤1 × ULN | | Liver mets/ ALT >1 × ULN | |
|---|---|---|---|---|---|---|---|---|---|---|
| | T-DM1 | Control | T-DM1 | Control | T-DM1 | Control | T-DM1 | Control | T-DM1 | Control |
| **EMILIA** | | | | | | | | | | |
| N | 495 | 496 | 311 | 304 | 176 | 178 | 142 | 148 | 33 | 28 |
| Any gr ≥3 AEs, %* | 41 | 57 | 42 | 61 | 49 | 57 | 45 | 57 | 64 | 54 |
| PFS HR (95% CI) | 0.65 (0.55–0.77) | | 0.73 (0.60–0.88) | | 0.62 (0.48–0.81) | | 0.62 (0.46–0.83) | | 0.41 (0.21–0.82) | |
| **TH3RESA** | | | | | | | | | | |
| N | 404 | 198 | 241 | 123 | 163 | 75 | 117 | 56 | 46 | 19 |
| Any gr ≥3 AEs, %* | 32 | 44 | 30 | 40 | 35 | 49 | 29 | 53 | 50 | 37 |
| PFS HR (95% CI) | 0.53 (0.42–0.66) | | 0.54 (0.40–0.72) | | 0.51 (0.36–0.73) | | 0.48 (0.31–0.75) | | 0.56 (0.28–1.13) | |

* Pts who received ≥1 dose of study drug.

**610 General Poster Session (Board #74), Mon, 8:00 AM-11:45 AM**

**Barriers to the use of trastuzumab for HER2+ breast cancer and the potential impact of biosimilars: A physician survey in the United States and emerging markets.** *Presenting Author: Philip Edward Lammers, Meharry Medical College, Nashville, TN*

**Background:** Biologics, such as trastuzumab, are an important part of oncology treatment paradigms, although access to such therapies is a challenge in emerging markets and in certain areas of more developed countries such as the United States (US). Biosimilars have the potential to increase access to biologic therapies by offering a comparable but more affordable alternative relative to the innovator biologic. This study examined access to trastuzumab and identified barriers to its use in HER2+ breast cancer patients in the US, Mexico (MEX), Turkey (TUR), Russia (RUS), and Brazil (BRZ). The study also examined whether availability of a biosimilar to trastuzumab would improve access to, and use of, HER2 monoclonal antibody therapy. **Methods:** Medical oncologists (N=500) completed a blinded survey examining their use of trastuzumab. **Results:** Across all countries, oncologists reported "not so often", "rarely", or "never" using trastuzumab in a neoadjuvant (27%), adjuvant (8%), or metastatic (8%) setting. Common barriers to the use of trastuzumab were related to insurance coverage, drug availability, cost to the patient, treatment guidelines, and patient comorbidities. Oncologists also reported having had to cancel or delay treatment with trastuzumab due to reimbursement issues (Overall=31%, US=10%, BRZ=48%, MEX=37%, TUR=16%, RUS=76%). Overall, 45% of oncologists reported that they would increase the use of HER2 monoclonal antibody therapy if a lower cost biosimilar to trastuzumab was available, including 29% of US oncologists. This percentage was higher in BRZ (53%), MEX (63%), and RUS (81%). Oncologists reported that use would increase across all treatment settings. **Conclusions:** The availability of a trastuzumab biosimilar may increase use of HER2 monoclonal antibody therapy in the breast cancer arena across all treatment settings in the US and, to an even greater extent, in the emerging markets of RUS, MEX, and BRZ. A biosimilar could provide benefit to patients who currently do not receive trastuzumab, or receive less than optimal treatment, due to insurance coverage or cost issues related to such treatment. Sponsored by Pfizer Inc.

**611 General Poster Session (Board #75), Mon, 8:00 AM-11:45 AM**

**Long-term population-based outcomes of adjuvant trastuzumab in HER2-positive early breast cancer: The British Columbia experience.** *Presenting Author: Stephen K. L. Chia, British Columbia Cancer Agency, Vancouver, BC, Canada*

**Background:** The use of adjuvant trastuzumab in women with HER2 positive early breast cancer also receiving adjuvant chemotherapy became standard of care in British Columbia in 2005. As the randomized clinical trials continue to update on the long-term efficacy of adjuvant trastuzumab, we have also recently updated our longer term outcomes from a population based publicly funded health care perspective. **Methods:** The British Columbia Cancer Agency (BCCA) Breast Cancer Outcomes Unit database includes all referred patients to the BCCA since 1989. Only patients with stage I-III HER-2 positive breast cancer diagnosed from July 2004 – Dec 2008 were included in the analysis. Demographic, pathologic and treatment data were reviewed. 5 year relapse free survival (RFS), distant relapse free survival (DRFS) and overall survival (OS) rates were calculated by Kaplan-Meir method. **Results:** 1,413 patients were identified, of which 953 were treated with adjuvant trastuzumab with a median follow-up of 5.4 years. 226 Stage I HER-2 positive breast cancers were treated with chemotherapy and trastuzumab. Of the 64 T1a-bN0 cases, 63% were ER-; while in the 162 T1cN0 cases, only 37% were ER-. **Conclusions:** 5-year population based clinical outcomes in the era of adjuvant trastuzumab are favorable, especially in node negative disease. Our 5 year RFS in T1cN0 HER2+ breast cancers treated with chemotherapy and trastuzumab is 100%. Future adjuvant clinical trials with new or multiple anti-HER 2 agents should only focus on node positive patients.

| | No. of patients | 5-year RFS (95% CI) | 5-year DRFS (95% CI) | 5-year OS (95% CI) |
|---|---|---|---|---|
| **Node-** | 400 | 95.1% (92-97%) | 95.6% (93-97%) | 95.1% (93-97%) |
| **Node+** | 552 | 82.6% (79-86%) | 83.9% (81-87%) | 86.3% (83-89%) |
| **T1a-bN0** | 64 | 92.2% (82-97%) | 93.7% (84-98%) | 94.6% (84-98%) |
| **T1c N0** | 162 | 100% (100%) | 100% (100%) | 98.1% (94-99%) |

**612 General Poster Session (Board #76), Mon, 8:00 AM-11:45 AM**

**Identification and targeting of M-phase progression downstream of HER2 in trastuzumab-sensitive and -resistant breast cancer cell lines.** *Presenting Author: E. Aubrey Thompson, Mayo Clinic, Jacksonville, FL*

**Background:** It is generally accepted that therapeutic response to HER2-targeted therapy involves both immunological and cell autonomous (signaling) events. We have used a genomic approach to define signaling processes that occur downstream of HER2 in trastuzumab-sensitive and –resistant human breast cancer cells in culture, with a view towards defining downstream effectors that could be exploited as potential therapeutic targets in tumors that are resistant to inhibition of HER2 signaling. **Methods:** RNA-seq analysis was carried out with trastuzumab-sensitive cell lines (BT474 and SKBR3), resistant variants selected from such cells, and cells that exhibit de novo resistance (MDAMB453 and HCC1954). Changes in mRNA abundance were quantified after trastuzumab treatment and after shRNA-mediated knockdown of ERBB2. Network analysis was carried to define biological processes associated with abrogation of HER2 signaling. Both pharmacological and genetic knockdown were used to test candidate downstream effectors of trastuzumab. **Results:** A prominent cohort of M-phase progression genes was consistently downregulated in sensitive but not resistant cells. These genes included PLK1, AURKB, ECT2, MCM10, BUB1, and PBK. Knockdown of PLK1 inhibited growth of both sensitive and resistant cultures. Since both PLK1 and paclitaxel inhibit process associated with the mitotic spindle, we tested for synergy between paclitaxel and the PLK inhibitor BI2536 in sensitive and resistant cell lines. At EC50 concentrations, both inhibitors significantly reduced culture growth rates. However, when both drugs were combined at EC50 concentrations, culture growth was completely obliterated. **Conclusions:** Regulation of M-phase progression is a significant component of ERBB2 signaling in HER2+ breast cancer cells. Combined therapy with low concentrations of drugs that target mitotic spindle formation by different mechanisms appears to provide a potential mechanism to target HER2+ tumors irrespective of sensitivity to HER2-targeted therapy.

**613 General Poster Session (Board #77), Mon, 8:00 AM-11:45 AM**

**Comparison of recurrent and nonrecurrent breast cancer patients undergoing AE37 peptide vaccine therapy.** *Presenting Author: Erika J Schneble, San Antonio Military Medical Center, San Antonio, TX*

**Background:** We are conducting a Phase II clinical trial of the HER2 peptide vaccine AE37 (MHC Class II binding) for the prevention of breast cancer recurrence in disease-free, node-positive or high-risk node-negative patients (pts). In this analysis, we compare disease features and immunologic responses (IR) between vaccinated recurrent (vR) pts and vaccinated non-recurrent (vNR) pts. **Methods:** After completion of standard of care therapy, pts with any level of HER2 expression (IHC1-3$^+$) who were randomized to the vaccine group received AE37+GM-CSF in 6 monthly intradermal inoculations during the primary vaccine series (PVS) followed by four boosters every 6 months. Ex vivo IR was measured by T-cell proliferation using thymidine incorporation and expressed in mean counts per minute (cpm) ±SEM at R0 and as the average of multiple time points after the PVS and throughout the booster series (R). In vivo IR was measured by delayed type hypersensitivity (DTH) immediately before (R0) and after the PVS (R6). Data was compared using student's t-test and Fisher's exact as appropriate. **Results:** Of 298 enrolled and randomized pts, 153 have been vaccinated. For this analysis, 5 patients were excluded for second malignancies leaving 14 vR and 134 vNR available for analysis. Demographics between vaccinated pts were compared with vR exhibiting a higher percentage of node positive (85.7% v 61.9%, p=0.07) disease. vR pts displayed significantly weaker proliferation than nVR pts (R0: 912±254 v 1954±350, p=0.02; R: 4463±764 v 6803±391, p=0.01). DTH between vR and vNR revealed a significantly lower initial DTH response (R0: 1.09±0.78 v 2.80±0.71mm, p<0.05), but similar post PVS DTH (R6: 33.3±9.1 v 28.9±2.0mm, p=0.68). **Conclusions:** Comparison of vR and vNR pts demonstrates that vR have more advanced disease as well as a consistently weaker intrinsic anti-HER2 immunity as measured in vivo and ex vivo at baseline. The factors responsible for the diminished endogenous immune response and reduced amplification in these pts will require further studies in larger patient populations. Of particular interest would be the response in HER2 non-overexpressing and triple negative pts, both of which appear to derive a greater benefit from AE37. Clinical trial information: NCT00524277.

**614 General Poster Session (Board #78), Mon, 8:00 AM-11:45 AM**

**Preliminary results from TRASTYVERE study: A retrospective analysis of HER2-positive (HER2) metastatic breast cancer (MBC) patients treated in Spain with lapatinib (L) plus trastuzumab (T).** *Presenting Author: Joaquin Gavila, Instituto Valenciano de Oncología, Valencia, Spain*

**Background:** Dual blockade with L and T in heavily pretreated HER2 MBC patients obtains impressive survival gain (Blackwell, 2012), yielding to the EMA approval for the HR-negative subgroup. Nevertheless, the benefit of the combination is unknown in L pretreated patients. **Methods:** We conducted a retrospective, post-authorized, multicenter study including patients treated in Spain by compassionate uses for the combination of T-L. The inclusion criteria were (1) HER2-positive metastatic or locally advanced MBC; (2) progression on at least one prior line of trastuzumab for advanced disease; and (3) T-L treatment started before DEC/2012. Concomitant endocrine therapy for HR-positive patients was allowed as well as patients with brain metastasis. Combinations with cytotoxic agents were excluded. A total of 111 patients were predefined for the primary objective: Clinical Benefit rates (CBR). In JAN/2014 independently monitored data from 72 patients was confirmed. **Results:** The median age was 59 years (39 - 83); Mean number of prior T lines 4 (range 1-13); 72% previously treated with L; 58% HR-positive; 78% visceral disease; 35% CNS involvement; 44% 3 or more organs involved. A total of 31 patients (43%) achieved a CBR (95% CI 31% – 54%); 1 CR, 12 PR and 18 SD lasting >24 weeks. The median time to progression (TTP) was 5.5 months (95% CI 4.63 – 6.54) and the median overall survival (OS) was 14.5 months (95% CI 9.69 – 17.64). The CBR was independent of L exposition: (50% L naïve vs. 40% L pretreated; p=0.46) or HR-status (HR-positive 43% vs. HR-negative 41%; p=0.86). No significant trends were observed in any pre-specified condition for ORR, TTP or OS. No cardiac toxicity occurred and less than 10% of G3 or G4 toxicity were recovered during the T-L treatment. **Conclusions:** The combination of T-L is active in heavily pretreated patients. Benefit was independent of previous treatment with L and HR-status. Future research may focus on the potential synergism of endocrine therapy in HR-positive patients.

**615 General Poster Session (Board #79), Mon, 8:00 AM-11:45 AM**

**Phase I/II study of adoptive T-cell therapy following in vivo priming with a HER2/neu vaccine in patients with advanced-stage HER2$^+$ breast cancer.** *Presenting Author: Mary L. Disis, University of Washington, Seattle, WA*

**Background:** We have reported that infusion of ex vivo expanded T cells derived from previously HER2-vaccine-primed PBMC is safe and able to mediate an anti-tumor response in patients with HER2$^+$ breast cancer (Disis 2013). In this study, we evaluated the safety and clinical efficacy of infusion of HER2 specific T cells after rapid HER2 vaccinations in patients with advanced stage HER2$^+$ breast cancer. **Methods:** 19patients were vaccinated three times weekly with a HER2 peptide based vaccine. HER2 specific T-cells were expanded 2 weeks after 3$^{rd}$ vaccine. The patients received 2-3 escalating doses of T-cells given at 7-10 day intervals. Cyclophosphamide was administrated before the first dose of T- cells. One patient underwent indium-111 labeling of T-cells for SPECT/CT scanning. **Results:** All patients received at least two doses of HER2 specific expanded T-cells. The infused T-cell products were >98% of CD3$^+$ with an average of 43% CD4$^+$ and 54% CD8+ T-cells. The total number of T-cells infused was 0.3x10$^9$ – 57.1x10$^9$ (median 17.5x10$^9$). Subjects tolerated the infusions well with 95% of adverse events of grade 1 or 2. There were no complete or partial responses. 59% had stable disease (SD) 1-3 months after infusion and 41% of the patients demonstrated progressive disease (PD). The frequencies of HER2 specific T-cells in the infused products were significantly higher in patients with SD than that in PD (p=0.039). The percentage of CD4$^+$ cells in products was positively correlated with HER2 specific T-cells (p=0.017). HER2 immunity was generated in vivo and augmented in magnitude after infusion and was maintained 3-9 months post infusion in the majority of patients. SPECT/CT of In-111 labeled T-cells demonstrated cell trafficking to all sites of metastatic disease. **Conclusions:** Adoptive transfer of HER2 specific T-cells generated from PBMC after rapid immunization is feasible and safe. Clinical outcome is associated with the frequency of HER2 specific CD4 T-cells present in the infusion product. Clinical trial information: NCT00791037.

**616 General Poster Session (Board #80), Mon, 8:00 AM-11:45 AM**

**A phase I trial of the safety and immunogenicity of a DNA-based vaccine encoding the HER2/neu (HER2) intracellular domain in subjects with HER2+ breast cancer.** *Presenting Author: Mary L. Disis, University of Washington, Seattle, WA*

**Background:** Vaccination with the intracellular domain (ICD) of HER2 in pre-clinical models is both immunogenic and protective against the development of mammary tumors. This study was designed to examine the safety and immunogenicity of a DNA-based vaccine encoding the HER2 ICD in subjects with HER2$^+$ breast cancer. **Methods:** Sixty-six patients with stage III or IV breast cancer in remission were enrolled sequentially into three vaccine arms: 1 (10$\mu$g), 2 (100$\mu$g) and 3 (500$\mu$g). Vaccines were admixed with 100$\mu$g GM-CSF and administered i.d. monthly for three immunizations. Endpoints included safety and immunogenicity (optimum dose). Toxicity and HER2 specific IFN-gamma immune responses were evaluated and DNA persistence at the vaccine site was assessed. **Results:** Sixty-four of the 66 (97%) patients enrolled completed all vaccinations. Vaccination was associated with minimal toxicity. All three doses of vaccine were able to significantly induce or boost HER2-specific T cell responses to ICD, however the incidence of subjects with augmented immunity was greatest in Arm 2 (14/22, 64%) when compared to Arm 1 (9/17, 53%) and Arm 3 (8/22, 36%). Patients in Arms 2 and 3 had immune responses to HER2 ICD of higher magnitude than patients in Arm 1, however, only patients in Arm 2 retained immunity at 1 year after vaccination. DNA persistence in the vaccine site was related to dose being found most frequently in Arm 3 patients. DNA persistence was associated with a decrease in magnitude of HER2 ICD response and long term immunity. At a median follow-up of 68 months after vaccination, patients in Arm 2 demonstrate superior overall survival (p=0.02) as compared with patients in arm 3. **Conclusions:** Immunization with a DNA-based HER2 ICD vaccine is safe and can generate robust T-cell responses in treated patients. The resulting immune response is dose-dependent, with 100$\mu$g as the optimal dose. Higher vaccine doses may have a detrimental effect on the long term retention of immunity. Clinical trial information: NCT00436254.

**617 General Poster Session (Board #81), Mon, 8:00 AM-11:45 AM**

**Effect of serum HER2, TIMP-1, and CAIX on outcome in HER2+ metastatic breast cancer patients treated in first line with lapatinib or trastuzumab combined with taxane: NCIC CTG MA.31.** *Presenting Author: Diep Ho, Penn State Hershey Medical Center, Hershey, PA*

**Background:** The lapatinib-taxane combination led to shorter PFS than trastuzumab-taxane in HER2+ metastatic breast cancer. We investigated the prognostic and predictive effects of pretreatment serum HER2, CA IX, and TIMP-1. **Methods:** MA.31 accrued 652 patients; 537 (82%) were centrally-confirmed HER2+. Biomarkers were categorized for univariate and multivariate predictive investigations with a median cut-point, ULN cut-points (15 ng/ml for HER2; 506 pg/ml for CAIX; 454 pg/ml for TIMP-1), and custom cut-points (30 and 100 ng/ml for HER2). Stratified step-wise forward Cox multivariate analysis used continuous and categorical biomarkers for PFS in the ITT and central HER2+ populations; central HER2+ biomarker results are shown. **Results:** Serum was banked for 472 (72%) of 652 patients. Higher serum HER2 (>median; >15; >30; or >100 ng/ml; p=0.05-0.002); higher CAIX (>median; >506 pg/ml; p=0.02; p=0.001); and higher TIMP-1 (>median; >454 pg/ml; p=0.001; p=0.02) had worse univariate PFS. In multivariate analysis, higher continuous TIMP-1 was associated with significantly worse PFS: HR=1.001 (95% CI=1.000-1.002; p=0.004). Continuous serum HER2 and CAIX were not significantly associated with PFS. HER2 of 15 ng/ml or higher had shorter PFS (p=0.02); higher categorical CAIX had worse PFS (p=0.01-0.08). The interaction terms of HER2, CAIX, and TIMP-1 with treatment were not significant. Multivariate PFS categorical serum results (Table). **Conclusions:** Higher levels of serum TIMP-1, CAIX, and HER2 were significant prognostic biomarkers of shorter PFS. No serum biomarker was predictive of differential response to lapatinib vs. trastuzumab. Evaluation of TIMP-1 and CAIX targeted therapy in addition to HER2 targeted therapy is warranted in patients with elevated serum levels of these biomarkers.

| | p-value | HR | Lower CI | Higher CI |
|---|---|---|---|---|
| **LTax vs TTax** | 0.001 | 1.58 | 1.20 | 2.06 |
| **Adjuvant anthracyclines** | 0.011 | 1.58 | 1.11 | 2.25 |
| **Adjuvant other therapy** | 0.043 | 3.88 | 1.04 | 14.41 |
| **EGFR (% stain)** | 0.012 | 1.01 | 1.001 | 1.01 |
| **Serum HER2 (>15 vs <15 ng/ml)** | 0.023 | 1.51 | 1.06 | 2.15 |
| **Serum CAIX (>506 vs <506 pg/ml)** | 0.005 | 1.54 | 1.14 | 2.08 |

*DH and JH contributed equally.

**618 General Poster Session (Board #82), Mon, 8:00 AM-11:45 AM**

**Correlation of $^{64}$Cu DOTA-trastuzumab positron emission tomography (PET) imaging with HER2 status by immunohistochemistry (IHC).** *Presenting Author: Joanne E. Mortimer, City of Hope, Duarte, CA*

**Background:** We have developed $^{64}$Cu-DOTA-trastuzumab for PET imaging of HER2-positive breast cancer. We have determined that administering trastuzumab (45 mg) prior to $^{64}$Cu-DOTA-trastuzumab sharply reduces liver uptake of the radiotracer. We are now testing whether tumor uptake of $^{64}$Cu-DOTA-trastuzumab correlates with variable IHC staining in women with advanced breast cancer. **Methods:** Eligibility criteria included biopsy confirmation of metastatic disease that was HER2 1+, 2+, or 3+ by IHC, no anti-HER therapy within the prior 2 mo, and at least 1 non-hepatic site of metastasis > 20 mm outside the biopsy site. Staging workup included $^{18}$F-FDG PET-CT. Patients received 45 mg of cold trastuzumab prior to $^{64}$Cu-DOTA-trastuzumab. PET-CT scans were obtained at 21-25 h (Day 1) and 47-48 h (Day 2) over axial fields of view chosen in reference to $^{18}$F-FDG. Uptake in prominent lesions was measured in terms of maximum single-voxel SUV ($SUV_{max}$) . Lesions identified on CT and judged to have image intensity > adjacent tissue by an expert radiologist were considered positive on PET. **Results:** Seventeen women (median age 59, range 35-75 y) have undergone imaging. HER2 status by IHC was 3+ in 7 pts., 2+ in 6 and 1+ in 4. Three women with IHC 2+ disease were FISH+. In the patients considered clinically HER2 positive (IHC 3+ or 2+, FISH+), $^{64}$Cu-DOTA-trastuzumab sensitivity was 75 and 90%, respectively, on Days 1 and 2, compared with 94% for $^{18}$F-FDG. Tumor uptake of $^{64}$Cu-DOTA-trastuzumab was also readily visualized in HER2-negative patients (measured detection sensitivity 78 and 80% on Days 1 and 2, respectively). There were 2 false positive findings with $^{64}$Cu-DOTA-trastuzumab. Lesion uptake of $^{64}$Cu-DOTA-trastuzumab was higher in HER2+ than in HER2- patients ($SUV_{max}$mean ± sem: Day 1 8.9±0.6 vs 4.2±0.2; Day 2 9.9±0.8 vs 4.9±0.2, $p < 0.001$). **Conclusions:** $^{64}$Cu-DOTA-trastuzumab PET visualizes HER2 1+, 2+ and 3+ metastatic breast cancers with high sensitivity and specificity. Tumor uptake of $^{64}$Cu-DOTA-trastuzumab-PET in IHC 1+ and 2+, FISH- patients implies possible benefit from anti-HER2 therapies for individuals whose cancers are currently considered HER2 negative. Research Support. DOD BC095002. Clinical trial information: NCT01093612.

**619^ General Poster Session (Board #83), Mon, 8:00 AM-11:45 AM**

**Phase II study of neoadjuvant weekly paclitaxel and carboplatin with lapatinib in HER2+ breast cancer.** *Presenting Author: Andrea Li Ann Wong, National University Health System, Singapore, Singapore*

**Background:** The optimal neoadjuvant regimen in HER2+ breast cancer is undefined. We evaluated the efficacy and tolerability of weekly paclitaxel/carboplatin with lapatinib. **Methods:** HER2+ stage I-III breast cancer patients received 4 cycles of 3 weekly PCL [IV paclitaxel (P) 80mg/m$^2$ (days 1, 8, 15), carboplatin (C) AUC 2 (days 1, 8), oral lapatinib (L) (750mg daily)] followed by surgery. Lapatinib dose reductions were not allowed. Patients with pCR (ypT0N0) received 2 cycles of adjuvant PCL; those without received 4 cycles of doxorubicin/cyclophosphamide. All received 1 year of adjuvant trastuzumab and at investigators' discretion, concurrent lapatinib 1000mg/day for 52 weeks (neoadjuvant + adjuvant). Primary endpoint was pCR; secondary endpoints were clinical CR/PR, toxicities and DFS. **Results:** 36 patients were recruited (Chinese/Malay/Others: 52.8/36.1/11.1%). Median age at diagnosis was 51 (29-78) years. 69.4%, 63.9%, 80.6% and 61.1% had cT3/4, cN+, grade 3 and hormone receptor positive tumors. 63.9% achieved CR/PR after 2 cycles. At surgery, 33.3% were ypN0, and 11.1% achieved pCR, which was limited to patients with cN0 tumors (n=8; 50% pCR). At 21 month median follow-up, 2 year DFS was 83.3%. G3/4 non-hematologic toxicities occurred in 19.4%, mainly from non-neutropenic infections (11.1%) and gastrointestinal toxicities (8.3%). None developed cardiac dysfunction. Patients with G3/4 non-hematologic toxicities had lower mean relative dose intensity of all 3 drugs (P: 0.61 + 0.33 *vs* 0.91 + 0.16, $p$=0.002; C: 0.65 + 0.30 *vs* 0.95 + 0.14, $p$=0.001; L: 0.62 + 0.34 *vs* 0.97 + 0.10, $p$<0.01) and lower clinical CR/PR rates (40% *vs* 90.3%, $p$=0.024) than those without. Dose interruptions (P: 37.1%, C: 34.4%, L: 11.4%) and reductions (P: 16.7%. C: 19.5%) were common. Serial samples from 5 patients without pCR showed general progressive decline in circulating tumor cells with treatment but remained measurable before surgery. **Conclusions:** While the low pCR rate was contributed by advanced tumors, PCL dose intensity was difficult to maintain and its efficacy/toxicity ratio not favorable in unselected patients. Tumor immunohistochemistry and pharmacogenetic studies are ongoing to select patients most likely to benefit. Clinical trial information: NCT01309607.

**620 General Poster Session (Board #84), Mon, 8:00 AM-11:45 AM**

**Prognostic significance of interferon regulating factor 4 (IRF4) in node-negative breast cancer.** *Presenting Author: Marcus Schmidt, Department of Obstetrics and Gynecology, Johannes Gutenberg University, Mainz, Germany*

**Background:** The transcription factor IRF4 (interferon regulating factor 4) regulates immunoglobulin class switch recombination as well as plasma cell differentiation. We examined the prognostic significance of IRF4 mRNA expression in node-negative breast cancer. **Methods:** Microarray based gene-expression data for IRF4 (204562_at) were analysed in four previously published cohorts (Mainz, Rotterdam, Transbig, Yu) of node-negative breast cancer patients not treated with adjuvant therapy (n=824). A meta-analysis of previously published cohorts was performed using a random effects model. Prognostic significance of IRF4 on metastasis-free survival (MFS) was examined in the whole cohort and in different molecular subtypes: luminal A ($ER^+$/$HER2^-$/aurora kinase A [AURKA]$^{low}$, luminal B ($ER^+$/$HER2^-$/$AURKA^{high}$), basal-like ($ER^-$/$HER2^-$), $HER2^+$. Independent prognostic relevance was analysed using multivariate Cox regression. **Results:** Higher RNA expression of IRF4 was related to better MFS in a meta-analysis of the whole cohort (HR 0.49, 95% CI 0.35-0.69, P<0.0001). Prognostic significance was most pronounced in the $HER2^+$ positive molecular subtype (HR 0.18, 95% CI 0.06-0.55, P=0.0008) as compared to luminal A (HR 0.75, 95% CI 0.36-1.53, P=0.425), luminal B (HR 0.39, 95% CI 0.20-0.76, P=0.0044) and basal-like (HR 0.55, 95% CI 0.32-0.94), P=0.0279) carcinomas of the breast. IRF4 showed independent prognostic significance (HR 0.394, 95% CI 0.249-0.621, P<0.0001) in multivariate analysis. In addition to IRF4, only histological grade of differentiation (HR 2.591, 95% CI 1.604-4.187, P<0.0001) and tumor size (HR 1.791, 95% CI 1.135-2.825, P=0.012), but neither age nor HER2 status nor hormone receptor status retained an independent prognostic association with MFS. **Conclusions:** The transcription factor IRF4 has independent prognostic significance in node-negative breast cancer. Higher expression of IRF4 is associated with improved outcome. The prognostic impact differs between diverse molecular subtypes and is most pronounced in $HER2^+$ breast cancer.

**621^ General Poster Session (Board #85), Mon, 8:00 AM-11:45 AM**

**Phase Ib study of BEZ235 plus either paclitaxel (PTX) in advanced solid tumors (aST) or PTX plus trastuzumab (TZ) in HER2+ breast cancer (BC).** *Presenting Author: Jordi Rodon Ahnert, Vall d'Hebron University Hospital, Barcelona, Spain*

**Background:** Preclinical data suggest BEZ235 (BEZ; dual PI3K/mTOR inhibitor) may enhance the activity of PTX ± TZ in pts with advanced cancers. In this 4-arm study (NCT01285466), BEZ or buparlisib (pan-PI3K inhibitor) were investigated in combination with PTX in pts with aST or with PTX + TZ in pts with HER2+ BC. Here, we report the BEZ arms only. **Methods:** Pts with aST or HER2+ BC who were candidates for PTX ± TZ were eligible. The primary objective was to define the MTD in each arm by assessing dose-limiting toxicities (DLT) in Cycle 1. Dose escalation was guided by a Bayesian logistic regression model with overdose control. Pts with PI3K-pathway alterations were enrolled in a BEZ + PTX safety expansion cohort. **Results:** (2 Apr 2013): BEZ + PTX: 35 pts received BEZ at 400–800 mg/d and PTX at 70–80 mg/m$^2$/wk. Median number of prior regimens was 3 (range: 1–10). DLT occurred in 5 pts: in 1 out of 4 pts at 600/80 and in 4 out of 26 pts at 800/80. The MTD was declared as BEZ 800 mg/d + PTX 80 mg/m$^2$/wk. Median exposure was 11 wks. Study drug-related Grade 3/4 AEs (>10%) included diarrhea (17%), fatigue (20%), and asthenia (11%). 29% of pts discontinued due to AEs and 63% due to progressive disease. The median $AUC_{0-24}$of BEZ at the MTD on C1D8 was 11000 (range: 1730–39000) h*ng/ml. The PK of PTX were unaffected by BEZ. Per RECIST, there were 3 PRs (ORR = 9%) and 18 SD. BEZ + PTX + TZ: 11 pts received BEZ + PTX (80 mg/m$^2$) + TZ (2 mg/kg/wk) at 2 BEZ doses: initially at 600 mg/d (5 pts) and then at 400 mg/d (6 pts). Median number of prior regimens was 4 (range: 1–10). DLT occurred in 2 pts (600 mg/d). The MTD was declared as BEZ 400 mg/d + PTX 80 mg/m$^2$/wk + TZ 2 mg/kg/wk. Median exposure was 19 wks. Study drug-related Grade 3/4 AEs (>10%) included neutropenia (27%), neurotoxicity (18%), and lymphopenia (18%). The median $AUC_{0-24}$of BEZ at the MTD on C1D8 was 3590 (range: 2190–12200) h*ng/ml. Per RECIST, there were 2 CR, 4 PR (2 with prior PTX/TZ in metastatic setting; ORR = 55%) and 3 SD. **Conclusions:** BEZ + PTX ± TZ has a challenging safety profile and substantial interpatient variability in PK parameters. However, encouraging signs of clinical activity suggest that PI3K-pathway inhibition in combination with PTX ± TZ is a promising approach for treating pts with aST. Clinical trial information: NCT01285466.

**622 General Poster Session (Board #86), Mon, 8:00 AM-11:45 AM**

**Preclinical in vitro and in vivo evaluation of antitumor activity of poly (ADP-ribose) polymerase inhibition and trastuzumab combined therapy in HER2-overexpressing breast cancer.** *Presenting Author: Ignacio Tusquets, Hospital del Mar, Barcelona, Spain*

**Background:** PARP inhibitors have provided promising results in BRCA deficient breast cancer, but not in unselected patient populations. Two lines of research in this field are needed: identification of novel subsets of patients that could potentially benefit from PARP inhibitors and the discovery of suitable targeted therapies for combination strategies. **Methods:** We tested PARP inhibition, alone or combined with the anti-HER2 antibody trastuzumab on HER2 positive breast cancer. We used two PARP inhibitors in clinical development, olaparib and rucaparib, as well as genetic downmodulation of PARP-1 for in vitro studies. DNA damage was studied by the formation of γH2AX foci and comet assay. Finally, in vivo anti-tumor effect of olaparib and trastuzumab was examined in subcutaneously implanted BT474 cells in nude mice. **Results:** In a panel of four HER2 overexpressing cell lines, but not in non-HER2 overexpressing breast cancer cell lines, both olaparib and rucaparib significantly decreased cell growth and enhanced anti-tumor effects of trastuzumab. Similar results were observed in cells with genetic downmodulation of PARP-1. Combined treatment with olaparib and trastuzumab resulted in increased DNA damage in vitro. In in vivoexperiments using the HER2 overexpression BT474 xenograft model, the combined treatment resulted in enhanced growth inhibition, as well as reduced tumor cell proliferation, increased DNA damage and apoptosis. **Conclusions:** Taken together, our results show that in HER2 overexpressing breast cancer, PARP inhibition has antitumor effects and significantly increases trastuzumab activity, which makes this novel combination a promising strategy for further development.

**623 General Poster Session (Board #87), Mon, 8:00 AM-11:45 AM**

**A multicenter randomized study comparing 6 versus 12 months of trastuzumab in combination with dose-dense docetaxel following FEC as adjuvant treatment of women with axillary node–positive or high-risk, node-negative breast cancer overexpressing HER2.** *Presenting Author: Dimitrios Mavroudis, Hellenic Oncology Research Group (HORG), Athens, Greece*

**Background:** Adjuvant trastuzumab in combination with chemotherapy improves outcome of women with HER2 positive early breast cancer. However, the optimal duration of treatment remains unknown. In this study we compared 6 versus 12 months of adjuvant trastuzumab. **Methods:** Axillary node positive or high risk node negative women with HER2 overexpressing or amplified early breast cancer were randomized following surgery to receive either 6 (arm A) or 12 (arm B) months of adjuvant trastuzumab in combination with dose dense G-CSF-supported Docetaxel (75mg/m$^2$ every 14 days for 4 cycles) following FEC (5FU 700mg/m$^2$, epirubicin 75mg/m$^2$, cyclophosphamide 700mg/m2 every 14 days for 4 cycles). The primary endpoint of the study was the 3-year disease-free survival (DFS). **Results:** Four hundred eighty one patients were randomized; 240 on arm A and 241 on arm B. Of them 83 (34%) and 100 (41%) were premenopausal, 200 (83%) and 180 (75%) were node positive, 165 (69%) and 156 (65%) were hormone receptor positive in arm A and B, respectively. Chemotherapy was completed in 98% and 99% of patients while trastuzumab therapy in 96% and 100% of patients in arm A and B, respectively. After a median follow up of 43.5 and 42 months there were 26 (10.8%) and 15 (6.2%) (p=0.07) disease relapses and the median DFS has not yet been reached (p=0.08) while the 3-year DFS rate was 92.4% and 95.1% for arm A and B, respectively. **Conclusions:** Preliminary results of this study in terms of disease relapse and DFS are in favor of 12 months of adjuvant trastuzumab administration. Clinical trial information: NCT00615602.

**624 General Poster Session (Board #88), Mon, 8:00 AM-11:45 AM**

**Long-term results on trastuzumab (T) in elderly patients (EP) with locally advanced or metastatic HER2-positive breast cancer (BC).** *Presenting Author: Christian Jackisch, Sana Kliniken Offenbach, Offenbach, Germany*

**Background:** In a prospective, non-interventional observation study, routine T treatment in advanced, HER2-positive BC was evaluated in a total of 1,843 patients (pts) enrolled between 2001 and 2010. With a follow-up duration of up to more than 11 years (y), this report focuses on the relatively large subgroup of EP (> 65 y). **Methods:** Pts were enrolled by 223 institutions in Germany. HER2-positivity was defined as 3+ staining in immunohistochemistry or a positive fluorescence in situ hybridization (FISH) test in case of 2+ staining. All types of pretreatments were acceptable. Detailed information on study treatment, its safety and the course of disease was collected for at least 1 y. Thereafter, long-term outcome data were additionally retrieved at specified follow-up time points. **Results:** The median age of the total observation group was 59.5 y (range: 21–95), with 505 pts being > 65 y (28%), 257 pts > 70 y (14%), and 58 pts even 80 y or older (3%). The percentage of EP constantly increased over the 10 y recruitment period. In EP, the proportion receiving T in combination with chemotherapy was 69% compared to 74% in younger pts (YP). Correspondingly, EP more often received T in combination with endocrine therapy only (19% vs 13%). With 11%, T monotherapy was not given more frequently in EP, but this proportion increased clearly in the cohorts > 70 y (14%) and ≥ 80 y (29%). Univariately, progression-free survival was almost identical for EP and YP (medians: 11.4 vs 10.7 months; p=0.99). Overall survival (OS) was shorter in EP with borderline significance (28.4 vs. 33.4 months; p=0.072). In multivariate analysis of OS, higher age retained its significance (HR=1.23; p= 0.022). Cardiac toxicity incidence was 2.3% overall (all grades; no grade 4 event), but distinctly higher in EP (4.2% vs 1.5%). **Conclusions:** To the best of our knowledge, our database comprises the largest population of EP with information on the longest follow-up period reported on T treatment in this disease setting. The antineoplastic efficacy of T seems to be independent of age, while the multivariately independent moderate impact of age on OS simply appears to reflect the higher background mortality of the older population.

**625 General Poster Session (Board #89), Mon, 8:00 AM-11:45 AM**

**Evidence of *PIK3CA* and *TP53* co-mutation in breast cancer identification on next-generation sequencing (NGS) of *ERBB2* (*HER2*)-amplified residual disease following preoperative anti-HER2 therapy.** *Presenting Author: Frankie Ann Holmes, Texas Oncology, US Oncology, Houston, TX*

**Background:** Understanding the molecular alterations in residual, treatment-refractory HER2-positive breast cancer (BC) following preoperative trastuzumab (H), lapatinib (L) or both (HL) in combination with chemotherapy may help identify patients at risk for not achieving pathologic complete responses as well as genomic alterations (GA) to target to overcome therapy resistance. Here we summarize the GA present in 21 pts' residual BC following preoperative anti-HER2 therapy. **Methods:** 100 pts with stage 2/3 HER2+ BC were randomized to treatment with H vs L 1250mg vs HL (L 750-1000mg) along with preoperative 5-fluoruracil, epirubicin, cyclophosphamide followed by weekly paclitaxel (Holmes F. BMC Res Notes 6:507, 2013). Following IRB-approved informed consent, targeted NGS was performed on 21 pts' FFPE residual disease (RD) after preoperative therapy at a CLIA-certified laboratory to characterize all classes of genomic alterations across 287 cancer-related genes. **Results:** 3 of 21 pts with RD were HER2-negative (1 with *TP53* mutation and *EGFR* amplification; 1 with *PIK3CA* mutation). Of the 18 HER2+ RD (5 ER- and 13 ER+), 13 (72%) had *TP53* mutations; 8 (44%) had *PIK3CA* mutations, always co-mutated with *TP53* (3 ER- and 5 ER+). Although prevalence of *TP53* and *PIK3CA* mutation was only modestly higher than published estimates for HER2+ primary BC (55% and 32% for *TP53* and *PIK3CA*, respectively - Stephens P. Nature 486:400, 2012), prevalence of co-mutations appeared significantly higher – 44% vs. 18%, $p<0.1$). Of the 4 RD post-HL, 3 were ER+, all had *TP53* mutations, 2 with *PIK3CA* mutations. Other prevalent alterations in checkpoint-related genes included truncations in *ATM* and *BRCA1*, and amplification of *EMSY*, *MDM2* and *MDM4.* Ampifications of *CCND1* and *CDK4* were also present. **Conclusions:** The enrichment of *PIK3CA* and *TP53* co-mutations in BC pts' HER2-amplifed RD following preoperative H or L or HL plus chemotherapy may predict for high sensitivity to PI3K inhibitors (Kim N, Int J Cancer 131:2456, 2012; Daemen A. Genome Biol 14:R110, 2013), and provides evidence for potentially actionable targeted treatment.

**626 General Poster Session (Board #90), Mon, 8:00 AM-11:45 AM**

**Toward clinical development of SYD985, a novel HER2-targeting antibody-drug conjugate (ADC).** *Presenting Author: Gijs Verheijden, Synthon Biopharmaceuticals BV, Nijmegen, Netherlands*

**Background:** SYD985 is a HER2-targeting ADC based on trastuzumab and vc-seco-DUBA, Synthon Biopharmaceuticals proprietary cleavable linker-duocarmycin payload. This paper describes the direct comparison of SYD985 to T-DM1 (ado-trastuzumab emtansine) in vitro and in vivo. **Methods:** Cell survival was tested in 96-wells plates using the CellTiter-Glo luminescent assay kit (Promega); cell line-based and breast cancer patient-derived tumor-based xenograft experiments were done in SPF athymic nu/nu mice (n=8 per group). A polyclonal rabbit anti-human HER2 (DAKO) antibody was used in the IHC analysis. In vitro data analysis comprised the sigmoidal dose-response equation with variable slope in GraphPad Prism. **Results:** In vitro, SYD985 and T-DM1 were compared head-to-head in a panel of 8 cell lines expressing different levels of HER2. In cell lines with high HER2 expression (HER2 3+), both SYD985 and T-DM1 show similar potencies and activities. In cell lines with low HER2 expression (HER2 2+ and 1+), SYD985 was a factor 3- to over 50-fold more potent than T-DM1. In vivoanti-tumor activity was assessed in a series of cell line and patient-derived breast cancer xenograft studies with varying HER2 levels, including FISH-positive / IHC-HER2 3+ and FISH-negative / IHC-HER2 2+ and 1+ models. Both SYD985 and T-DM1 showed anti-tumor activity in the FISH-positive / IHC-HER2 3+ models, although SYD985 appeared to be somewhat more active. Whereas SYD985 showed very potent anti-tumor activity in the FISH-negative models that were either IHC-HER2 2+ or 1+, T-DM1 was not active, indicating superior anti-tumor activity of SYD985 over T-DM1. The data are corroborated by similar results in gastric cancer models. **Conclusions:** The preclinical profile of SYD985 enables extending the target population of breast and gastric cancer patients that may respond to this treatment modality to include FISH-negative / IHC-HER2 2+ and 1+ patients. Early phase clinical trials with SYD985 in breast and gastric cancer patients with this tumor profile, besides the classical FISH-positive and/or IHC-HER2 3+ indication, appear justified and warranted.

**627^ General Poster Session (Board #91), Mon, 8:00 AM-11:45 AM**

**Phase Ib study of buparlisib (BKM120) plus either paclitaxel (PTX) in advanced solid tumors (aST) or PTX plus trastuzumab (TZ) in HER2+ breast cancer (BC).** *Presenting Author: Cristina Cruz, Vall d'Hebron University Hospital, Barcelona, Spain*

**Background:** Preclinical data show PI3K-pathway inhibition can enhance the efficacy of anticancer therapy, such as PTX or TZ. In this 4-arm Ph Ib study (NCT01285466), buparlisib (pan-PI3K inhibitor) or BEZ235 (dual PI3K/mTOR inhibitor) was combined with PTX in pts with aST or PTX + TZ in pts with HER2+ BC. Here we report the buparlisib arms only. **Methods:** Pts with aST or HER2+ BC eligible for PTX ± TZ received oral buparlisib qd + PTX (70−80 mg/m$^2$ IV) qw ± TZ (2 mg/kg IV) qw in 28-day cycles. The primary objective was to define the MTD in each arm by assessing dose-limiting toxicities (DLT) in Cycle (C) 1. Dose escalation was guided by a Bayesian logistic regression model with overdose control. Pts with PI3K-pathway alterations were enrolled in a buparlisib + PTX safety expansion cohort. **Results:** (2 Apr 2013) Buparlisib + PTX: buparlisib doses from 40−120 mg/d were tested in 53 pts, including 36 pts at 100 mg/d. Median no. prior regimens was 3 (1−12). DLT occurred in 5 pts: 3 at 120 mg and 2 at 100 mg. MTD was declared as buparlisib 100 mg qd + PTX (80 mg/m$^2$ IV) qw. Drug-related G3/4 AEs (>10%) were neutropenia (13%) and hyperglycemia (11%). Median exposure was 15 wks. Primary reason for discontinuation was PD (68%). Buparlisib exposure was lower than in the single-agent study, especially at 100 mg. Buparlisib did not modify the PK of PTX. Per RECIST, there was 1 CR, 8 PR, and 27 SD (ORR = 17%). 3 pts are ongoing. Buparlisib + PTX + TZ: all 11 pts received buparlisib at 100 mg/d. Median no. prior regimens was 4 (1−10; prior taxane, 82%; prior TZ, 100%). DLT occurred in 2 pts. MTD was declared as buparlisib 100 mg qd + PTX (80 mg/m$^2$ IV) qw + TZ (2 mg/kg IV) qw. Drug-related G3/4 AEs (>10%) were neutropenia (27%) and diarrhea (18%). 1 pt developed G4 psychosis in C2, resolving after discontinuation. Median exposure was 17 wks. Primary reason for discontinuation was PD (64%). PK of PTX and TZ were in the expected range. Per RECIST there were 3 PR (1 with prior PTX/TZ in metastatic setting) and 5 SD (ORR = 27%). 2 pts are ongoing. **Conclusions:** Buparlisib can be combined with PTX and TZ in pts with aST or HER2+ BC at the single-agent MTD, with early indications of activity, thus establishing the feasibility of PI3K blockade combined with PTX + TZ. Clinical trial information: NCT01285466.

**628 General Poster Session (Board #92), Mon, 8:00 AM-11:45 AM**

**Predictive value of CTCs biomarkers status in patients with metastatic breast cancer (MBC) receiving anti-HER2 therapy.** *Presenting Author: Zefei Jiang, Hospital Affiliated to Academy of Military Medical Science, Beijing, China*

**Background:** The value of circulating tumor cells (CTCs) enumeration has been widely accepted, but the predictive value of enumeration and the detection of HER-2 expression in CTCs (CTCs-HER2) in patients with HER2 positive disease treated with HER-2 targeted therapy has still not been prospectively demonstrated. **Methods:** One hundred one HER-2 positive (IHC HER2+++ or FISH+) patients were enrolled from Oct 2010 to Nov 2013. All of the patients received a new line of treatment with chemotherapy plus trastuzumab or lapatinib. CTC isolation, enumeration and characterization were performed by using the CellSearch technology. HER2 expression intensity in CTC was given a score of 0, 1+, 2+, or 3+, according to the trial we have conducted previously, the CTCHER2 positive criterion was defined as >30% of CTCs over-expressing HER2 (3+). Hormone receptor positive(HR+) was defined as ER or PR positive and hormone receptor negative(HR-) was defined as ER or PR negative. **Results:** 56(55.4%) out of 101 patients were detected with CTC≥1. For the patients who detected CTC, 29(51.8%) patients were CTCHER2-positive, 27(48.2%) were CTCHER2-negative. There was a statistically difference in PFS between the groups of CTCHER2-positive and the CTCHER2-negative (P=0.014). For the patients with ≥5 CTC, HR- patients benefit a longer PFS compared with HR+ patients (7m vs 4m). The PFS for CTCHER2-positive and hormone receptor negative patients versus CTCHER2- negative and hormone receptor positive patients were 8.5 months versus 2.5 months(P=0.003). **Conclusions:** This analysis demonstrates that the baseline enumeration of CTC for HER2 positive MBC patients with different HR statuses who received chemo plus anti-HER2 therapy lacks of predictive value, whereas the detection of baseline CTCHER2 status is associated with significant prediction of therapeutic benefit. Moreover, the CTCHER2 positive and HR- patients can benefit most from chemo plus anti-HER2 therapy. Routine CTCs biomarkers assessment should be prospectively evaluated in patients candidates for molecularly targeted therapies.

**629^ General Poster Session (Board #93), Mon, 8:00 AM-11:45 AM**

**Clinical effects of prior anthracycline or taxane use on eribulin as first-line treatment for HER+/- locally recurrent or metastatic breast cancer (BC): Results from two phase II, multicenter, single-arm studies.** *Presenting Author: Stefan Gluck, Sylvester Comprehensive Cancer Center, University of Miami, Miller School of Medicine, Miami, FL*

**Background:** Eribulin mesylate, a novel nontaxane microtubule dynamics inhibitor, has demonstrated an overall survival benefit relative to other commonly used agents in pts with at least 2 prior MBC therapies. Primary data presented from 2 phase 2 trials, Study 206 (eribulin in HER2- pts) and Study 208 (combination eribulin + trastuzumab [TRAS] in HER2+ pts), showed clinical activity and acceptable tolerability profiles as first-line therapy (tx). Here we present prespecified efficacy data for both trials based on prior anthracycline (A) and taxane (T) use. **Methods:** In both studies, pts received eribulin mesylate 1.4 mg/m$^2$IV on Days 1 and 8 of each 21-day cycle. Pts in Study 208 (HER2+ pts) also received initial TRAS (8 mg/kg IV/Day 1), followed by 6 mg/kg/Day 1 of each subsequent cycle. Response, progression-free survival (PFS), and tolerability were assessed. **Results:** In Study 206 (N=56), 48% and 46% received prior A and T, and in Study 208 (N=52), 21% and 44% received prior A and T, respectively. Objective response rates (ORRs), the primary endpoint, were similar in pts, regardless of prior A or T tx, except in pts w/o prior T in Study 208 whose ORR trended higher (table). In both studies, clinical benefit rate (CBR), PFS, and duration of response (DOR) were either similar or trended higher in pts w/o prior A or T. PFS was higher in HER2+ pts receiving eribulin + TRAS who had not received prior A or T compared with those who had. Grade (G) 3-5 AE rates were similar or lower in pts who had not received prior A or T. **Conclusions:** As first-line therapy, eribulin in HER2- pts and eribulin + TRAS in HER2+ pts were effective and well tolerated, regardless of prior A or T tx. However, in HER2+ pts receiving eribulin + TRAS, the lack of prior A or T tx may be a predictor of longer median PFS. Clinical trial information: NCT01268150 and NCT01269346.

| | Study 206 (N=56) (eribulin only) | | | | Study 208 (N=52) (eribulin/TRAS) | | | |
|---|---|---|---|---|---|---|---|---|
| **Prior A/T use** | **A** | **w/o A** | **T** | **w/o T** | **A** | **w/o A** | **T** | **w/o T** |
| **n** | 27 | 29 | 26 | 30 | 11 | 41 | 23 | 29 |
| **ORR, n (%)** | 7 (26) | 9 (31) | 7 (27) | 9 (30) | 7 (64) | 30 (73) | 13 (57) | 24 (83) |
| **CBR, n (%)** | 13 (48) | 16 (55) | 12 (46) | 17 (57) | 9 (82) | 41 (100) | 19 (83) | 25 (86) |
| **PFS, m (median)** | 5.8 | 6.9 | 5.8 | 7.6 | 6.7 | 11.6 | 6.8 | 13.1 |
| **DOR, m (median)** | 5.7 | 7.4 | 4.7 | 9.7 | 11.1 | 11.8 | 7.5 | 11.8 |

**630^ General Poster Session (Board #94), Mon, 8:00 AM-11:45 AM**

**Prognostic, predictive, and surrogate value of HER2 extracellular domain (ECD) for progression-free survival (PFS) in advanced breast cancer treated with lapatinib (lap): A meta-analysis.** *Presenting Author: Chee Lee, NHMRC Clinical Trials Centre, Sydney, Australia*

**Background:** We performed a meta-analysis to determine the clinical utility of HER2 ECD in advanced breast cancer patients undergoing lap therapy. **Methods:** Data from Phase 3 clinical trials (EGF30001, EGF30008, EGF100151) of patients randomized to receive lap-containing or control treatments were analyzed. Baseline HER2 ECD (bECD) and tissue HER2 status were examined for associations with PFS. We also performed a landmark analysis to quantify the association between ECD change, as measured at 10 weeks post-randomization, with PFS, and assessed the extent ECD change predicted lap benefit. **Results:** Levels of bECD were higher in HER2+ (n=378) than HER2- (n=1060) patients (61.59 vs 14.25ng/ml, p<0.0001). The effectiveness of lap was significantly associated with bECD (joint treatment-biomarker interactions P=0.001[bECD], P=0.02[HER2 tissue status]). At 10 weeks post-randomization, there was a mean 4.23ng/ml reduction in ECD with no significant difference between treatment arms (lap: 4.33ng/ml, control: 4.12ng/ml; P=0.92). In the control arms, change in ECD was prognostic for PFS (P<0.0001). The median PFS from landmark (mPFS) were 9.8 and 2.9 months for those with low ECD (≤15ng/ml) and high ECD (>15ng/ml), respectively. mPFS were 3.3 and 5.7 months for patients with ECD increase to >15ng/ml and ECD decrease to ≤15ng/ml, respectively. Similar finding was observed in the experimental arm (P<0.0001). In both treatment arms, there was 4% increase in risk of disease progression for every 10 unit ECD increment after adjustment of bECD and other factors (P<0.0001). Lap improved PFS over control (HR 0.83, P=0.002). Adjustment for ECD change yielded a similar result (HR 0.80, P<0.001), indicating that change in ECD did not explain the treatment effect of lap. **Conclusions:** Baseline HER2 ECD was predictive of lap benefit. ECD increase during lap and non-lap therapies was associated with a shorter PFS. Change in ECD had additional prognostic information in addition to baseline ECD, but was not a valid surrogate marker for lapatinib benefit as the treatment effect of lap was largely independent of ECD change. Clinical trial information: NCT00075270, NCT00073528, and NCT00078572.

**631^ General Poster Session (Board #95), Mon, 8:00 AM-11:45 AM**

**Efficacy of eribulin in patients (pts) with metastatic breast cancer (MBC): A pooled analysis by HER2 and ER status.** *Presenting Author: Chris Twelves, Leeds Institute of Cancer and Pathology, and St James's Institute of Oncology, Leeds, United Kingdom*

**Background:** Eribulin (E) has been assessed in 2 phase 3, open-label trials in pts with locally recurrent or MBC progressing after an anthracycline (A) and taxane (T). E significantly increased overall survival (OS) compared with treatment of physician's choice (TPC) in 1 study and there was a non-significant trend for improved OS with E vs capecitabine (cape) in the other. We present an unplanned pooled analysis of these data. **Methods:** In the EMBRACE trial, women had received 2-5 lines of chemotherapy for advanced disease. In this ≥ third-line setting, pts were randomized 2:1 to E mesylate (1.4 mg/m$^2$ iv on days 1 and 8 every 21 days) or TPC. In study 301, pts who had received 0–2 prior chemotherapies for advanced disease were randomized 1:1 to either E (as above) or cape (1.25 g/m$^2$orally b.i.d. days 1–14 every 21 days). We analysed OS by 2-sided stratified log-rank tests and Cox regression in the overall intent-to-treat population and in the HER2–, triple negative (TNBC) and HER2+ subgroups. **Results:** In total 1,864 pts (median age 54 yrs) were included, most treated in the second (31.5%) or third-line (32.7%) MBC settings. Overall, E provided significantly improved OS vs control; this benefit was also significant in HER2− and TNBC, but not HER2+ pts (Table). E improved progression-free survival overall (4.0 vs 3.4 months, HR = 0.90, 95%CI = 0.81, 0.997, $p$ = 0.046), in HER2– (3.7 vs 3.0 months, HR = 0.84, 95%CI = 0.74, 0.95, $p$ = 0.006) and TNBC pts (2.8 vs 2.6 months, HR = 0.78, 95%CI = 0.63, 0.96, $p$= 0.018). As reported before, the E safety profile was similar in the studies. **Conclusions:** E significantly improved OS vs standard therapies in MBC pts with HER2− and TNBC in this pooled analysis; in pts with HER2+ disease the difference did not reach statistical significance but numbers were smaller. Clinical trial information: NCT00337103 and NCT00388726.

| | Overall | | HER2− | | HER2+ | | TNBC | |
|---|---|---|---|---|---|---|---|---|
| | **E** | **Con** | **E** | **Con** | **E** | **Con** | **E** | **Con** |
| **n** | 1062 | 802 | 748 | 572 | 169 | 123 | 243 | 185 |
| **Median OS[a], months** | 15.2 | 12.8 | 15.2 | 12.3 | 13.5 | 12.2 | 12.9 | 8.2 |
| **HR (95%CI)[b]** | 0.85 (0.77, 0.95) | | 0.82 (0.72, 0.93) | | 0.82 (0.62, 1.06) | | 0.74 (0.60, 0.92) | |
| **p[b]** | 0.003 | | 0.002 | | 0.135 | | 0.006 | |

Abbreviations: Con, control; E, eribulin; HR, hazard ratio. [a]Based on survival curve adjusted by study. [b]Stratified by geographic region, prior cape use and study (plus HER2 status for overall group only; plus TNBC for HER2– group only).

**632 General Poster Session (Board #96), Mon, 8:00 AM-11:45 AM**

**Randomized phase II trial of capecitabine and lapatinib with or without cixutumumab in patients with HER2+ breast cancer previously treated with trastuzumab and an anthracycline and/or a taxane: NCCTG N0733 (Alliance).** *Presenting Author: Paul Haluska, Mayo Clinic, Rochester, MN*

**Background:** Crosstalk between the insulin-like growth factor (IGF) and HER2 pathways in multiple preclinical models suggest a mechanism of resistance to HER2-targeted therapy. Cixutumumab (CIX, IMC-A12), an anti-IGF-1 Receptor monoclonal antibody, was investigated in combination with capecitabine and lapatinib (cape/lap) to determine if the addition of an IGF target agent would improve PFS compared to cape/lap in unselected HER2+ metastatic breast cancer (mbc) patients (pts). IGF binding protein (IGFBP) levels may be important in predicting tumor dependence on IGF signaling and are potential biomarkers. **Methods:** Following an initial safety cohort, this open label phase II study randomized (2:1) pts to cape/lap with CIX (Arm B) or cape/lap (Arm A). Primary endpoint was progression-free survival (PFS) with 144 pts planned for a target hazard ratio of 0.56. PFS was estimated using Kaplan-Meier and compared using Cox regression. Secondary endpoints included assessing the overall survival and treatment tolerability. Correlative studies included assessments of IGFBPs 1-6 using a Luminex multiplex assay on pt serum. **Results:** 64 evaluable pts were accrued, including 8 to the safety cohort. The most common grade 3 events were diarrhea, fatigue and mucositis. Dose reductions in the safety cohort for 6 of 8 pts prompted a dose reduction of cape/lap in Arm B of the randomized portion. The randomized portion of the study was closed early at 56 pts due to slow accrual. Median PFS by in Arm A was 6.0 mo vs. 4.9 mo in Arm B (p= 0.89). Median overall survival (16.8 vs 14.7 mo, p=0.93), time to treatment failure (TTF) (4.6 vs 4.4 mo, p=0.66), and duration of response (4.8 vs 6.9 mo, p=0.26) were not different between arms. In Arm B, increase in IGFBP5 correlated with poor PFS (1.4 vs 9.9 mo, p= 0.02) and high IGFBP5 correlated with improved TTF (9.9 vs 3.9 mo, p= 0.03). **Conclusions:** CIX is reasonably tolerated in combination with cape/lap following a dose reduction, but does not improve PFS in unselected pts with HER2+ mbc. IGFBP5 may be an important determinant of benefit from IGF targeted therapy and warrants further investigation. Clinical trial information: NCT00684983.

**633 General Poster Session (Board #97), Mon, 8:00 AM-11:45 AM**

**Phase II feasibility study of paclitaxel (T) with trastuzumab (H) and lapatinib (L) for node-negative, HER2-positive breast cancer (BC).** *Presenting Author: Neil M. Iyengar, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** We previously demonstrated that weekly T + HL after anthracycline based therapy was not feasible due to high incidence of grade (G) 3 diarrhea, which led to modification of the ALTTO trial. Previous data showed that L could be given more safely with every (q) 3 week than weekly T. Given the low and similar diarrhea rates between T dosed q 2 versus 3 weeks (CALGB 9741), we studied dose dense (dd) T + H + full dose L (THL). **Methods:** This is a single center, phase II feasibility study of dd T + HL. Eligible patients (pts) had HER2+ BC (IHC 3+ or FISH amplified ≥ 2.0) with negative nodes (micrometastasis allowed) and tumor size ≤ 3 cm. Pts received T 175 mg/m$^2$ x 4 q 2 weeks (w), H 4 mg/kg load → 2 mg/kg qw with T, and L 1000 mg daily. Pts received pegfilgrastim after each T, during the THL phase. Afterwards, H (6 mg/kg q 3 w) + L were continued x 1 year. Left ventricular ejection fraction (LVEF) monitoring was done at baseline, months 2, 6, 9, 12, and 18 by an echocardiogram. Primary endpoint was feasibility defined as ≥ 80% of pts who completed THL without dose delay or reduction. Allowable rate of G 3 diarrhea was set at 20% and cardiac event (symptomatic heart failure or cardiac death) at ≤ 4%. **Results:** From 05/13 – 11/13, 20 of 55 planned pts were enrolled; median age 49 (range 34 – 74 years). Overall, 17/20 (85%) had ER+ tumors. Tumors were T1a (20%), T1b (30%), T1c (40%), and T2 (10%). 1 pt had immediate T hypersensitivity and was deemed inevaluable. Only 12/19 (63%) evaluable pts completed the THL phase without dose delay/reduction or unacceptable toxicities. Diarrhea rates were: all G-16/19 (84%) and G 3-3/19 (16%). Rash rates were high: all G-18/19 (95%), G 2-7/19 (37%), G 3-1/19 (5%). Other G3-4 toxicities include: lymphopenia, 2/19 (11%); anemia, 1/19 (5%); cellulitis, 1/19 (5%); transaminases, 1/19 (5%); dehydration, 1/19 (5%). There were no cardiac events and LVEF was well preserved. The study was stopped early in November 2013 due to excess toxicity. **Conclusions:** The combination of full dose L with dd T and H was not feasible. There was an unexpected high incidence of rash. G 3 diarrhea incidence was acceptable. This important negative study provides additional feasibility data as we await the release of data from ALTTO. Clinical trial information: NCT01827163.

**634 General Poster Session (Board #98), Mon, 8:00 AM-11:45 AM**

**Racial/ethnic (RE) differences in the occurrence of HER2 and hormone receptor (HR)-defined breast cancer (BC) in California (CA).** *Presenting Author: Scarlett Lin Gomez, Cancer Prevention Institute of California (CPIC), Fremont, CA*

**Background:** RE disparities in the occurrence and mortality of BC are long-standing and persistent. Examining differences in the occurrence of molecularly-defined BC subtypes by RE can inform reasons for its unequal burden and point to better targeted strategies for prevention.Objective: To describe BC subtype occurrence by RE in a contemporary, population-based cohort. **Methods:** We examined demographic and clinical factors associated with prevalence of 4 BC subtypes (HER2Neu, HR [based on estrogen and progesterone receptor status]) by RE among all female CA residents diagnosed with primary invasive BC between 1/1/2005 and 12/31/2011 in the California Cancer Registry. **Results:** A total of 131,450 BC pts (59.0% HR+/HER2-, 10.4% triple-negative (TN), 9.9% HR+/HER2+, 5.0% HR-/HER2+, and 15.6% unclassified) were identified. TN BC was substantially more likely to be diagnosed among Blacks and Hispanics (19.8% and 12.9%, respectively) than Whites and Asians/Pacific Islanders (API) (9.2% and 8.5%, respectively). However, HER2+ BC was more likely to be diagnosed among APIs than other RE groups (19.4% vs. 13-18%). TN and HER2+ BC were more common among women living in lower socioeconomic status (SES) neighborhoods (Table 1). These associations persisted in multivariate polytomous regression analysis adjusted for year, age, stage, grade, histology, marital status, and insurance status. **Conclusions:** The distribution of breast cancer subtypes vary markedly by RE and SES, with minority RE and low SES populations being more likely to have subtypes associated with worse survival.

**Distributions of BC subtypes by RE and SES, CA, 2005-2011.**

| | BC subtype (N=131,450) | | | | | |
|---|---|---|---|---|---|---|
| | HR+/HER2+ n=13053 | HR-/HER2+ n=6630 | HR+/HER2- n=77577 | TN n=13692 | Unclassified n=20498 | Total |
| **Race/ethnicity** | | | | | | |
| Non-Hispanic White | 9.0% | 4.2% | 62.3% | 9.2% | 15.3% | 82,242 |
| Black | 10.9% | 5.4% | 48.1% | 19.8% | 15.8% | 8,255 |
| Hispanic | 11.5% | 6.4% | 53.9% | 12.9% | 15.4% | 23,330 |
| API | 12.1% | 7.3% | 56.2% | 8.5% | 15.9% | 15,878 |
| Other | 8.8% | 4.0% | 48.9% | 7.6% | 30.7% | 1,745 |
| **SES quintile** | | | | | | |
| 1st (low) | 10.9% | 6.3% | 51.3% | 12.6% | 19.0% | 16,774 |
| 2nd | 10.3% | 5.5% | 55.7% | 11.3% | 17.3% | 22,959 |
| 3rd | 9.9% | 4.9% | 58.4% | 10.6% | 16.1% | 26,932 |
| 4th | 9.8% | 4.9% | 60.7% | 9.9% | 14.7% | 30,746 |
| 5th (high) | 9.4% | 4.3% | 64.1% | 9.0% | 13.2% | 34,039 |

**635^ General Poster Session (Board #99), Mon, 8:00 AM-11:45 AM**

**Clinical effects of prior trastuzumab on combination eribulin mesylate plus trastuzumab as first-line treatment for HER2+ locally recurrent or metastatic breast cancer (MBC): Results from a phase II, single-arm, multicenter study.** *Presenting Author: Shannon Puhalla, Magee Womens Hospital, Pittsburgh, PA*

**Background:** Eribulin mesylate, a novel nontaxane microtubule dynamics inhibitor in the halichondrin class of antineoplastic drugs, is indicated for women with MBC who previously received ≥2 chemotherapy regimens in the metastatic setting. Primary data from a phase 2 trial on first-line combination eribulin + trastuzumab (TRAS) in HER2+ patients (pts) showed a 71% objective response rate (ORR) and tolerability consistent with the known profile of these agents. Here we present prespecified endpoint data for this study by prior TRAS use. **Methods:** Pts with HER2+ MBC who had not received prior chemotherapy for MBC received eribulin mesylate 1.4 mg/m$^2$IV on days 1 and 8 of each 21-day cycle and initial TRAS (8 mg/kg IV/day 1), followed by 6 mg/kg/day 1 of each subsequent cycle. Response, progression-free survival (PFS), and tolerability were assessed in patients who had and had not received prior TRAS treatment. **Results:** The 52 pts (median age, 59.5 years) received combination eribulin + TRAS, for a median treatment duration of ~30 weeks; 40% (n=21) were previously treated with TRAS in the neo-adjuvant / adjuvant setting. There was median of 23 months since completion of adjuvant treatment prior to retreatment with eribulin + TRAS for first-line MBC.Efficacy, assessed by ORR, clinical benefit rate (CBR), PFS, and duration of response (DOR), was largely consistent in pts who received prior TRAS relative to pts who had not received prior TRAS (see table). Overall, Grade (G) 3-5 adverse events (AEs), treatment-related AEs (TRAEs), and discontinuations (d/c) were similar between groups (Table). **Conclusions:** In this phase 2 single-arm trial in pts with HER2+ MBC, eribulin + TRAS demonstrated activity and was well tolerated as first-line treatment, irrespective of prior (neo) adjuvant TRAS treatment. Clinical trial information: NCT01269346.

| | HER2+ pts (N=52) | |
|---|---|---|
| | w/ prior TRAS | w/o prior TRAS |
| **n (%)** | 21 (40) | 31 (60) |
| **ORR, n (%)** | 13 (62) | 24 (77) |
| **CBR, n (%)** | 17 (81) | 27 (87) |
| **PFS, m (median)** | 11.5 | 12.2 |
| **DOR, m (median)** | 9.5 | 11.8 |
| **AEs, G3-4, n (%)** | 16 (76) | 21 (68) |
| **AEs, G5, n (%)** | 0 (0) | 1 (2) |
| **TRAE, n (%)** | 21 (100) | 31 (100) |
| **AEs leading to d/c, n (%)** | 5 (24) | 6 (19) |

**636 General Poster Session (Board #100), Mon, 8:00 AM-11:45 AM**

**Anti-HER2 CD4 T helper type 1 response in breast cancer: Is there a role for immunorestoration?** *Presenting Author: Jashodeep Datta, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA*

**Background:** Tumor microenvironment infiltration of IFNγ-producing CD4 T helper 1 (Th1) cells is linked to improved prognosis in invasive breast cancer (IBC). We investigated circulating anti-HER2 CD4 Th1 response (Th1resp) involved in breast tumorigenesis, and compared Th1resp prior to after chemotherapy/trastuzumab (C/T) treatment or dendritic cell vaccination in HER2$^+$ IBC pts. **Methods:** Th1resp were compared in healthy donors (HD; n=21) and pts with benign breast biopsy (BD; n=9), HER2$^{neg}$ IBC (n=11), HER2$^+$ DCIS (n=31), and HER2$^+$ IBC (n=14). Th1resp of pts enrolled in neoadjuvant immunization trials for HER2$^+$ DCIS and found to have Stage I IBC at surgery (n=11) were analyzed pre/postimmunization, and compared with HER2$^+$ IBC pts after C/T (n=34). Th1resp were generated from PBMC pulsed with 6 HER2 MHC class II peptides, by measuring IFNγ via ELISPOT. Th1resp metrics were (1) anti-HER2 response rate, (2) # of reactive peptides (repertoire), (3) cumulative response across 6 peptides (SFC/10$^6$ cells). Contribution of regulatory T cells ($T_{reg}$) to immune profiles was assessed by IL-10 production via ELISPOT. **Results:** Stepwise decrements in response rate (100% vs 100% vs 100% vs 84% vs 21%; p<0.0001), repertoire (5.2 vs 4.6 vs 3.9 vs 2.0 vs 0.4; p<0.0001), and cumulative response (259.9 vs 218.7 vs 191.2 vs 125.2 vs 33.0 SFC/10$^6$, p<0.0001) were observed among HD, BD, HER2$^{neg}$ IBC, HER2$^+$ DCIS, and HER2$^+$ IBC cohorts respectively. HER2$^+$ DCIS and -IBC pts differed in response rate (p<0.001), repertoire (p=0.001), and cumulative response (p<0.001). HD, BD, and HER2$^{neg}$ groups did not vary significantly. After immunizing HER2$^+$ IBC pts, improvements were seen in response rate (91% vs 18%, p=0.004), repertoire (3.7 vs 0.3, p<0.0001), and cumulative response (162.8 vs 29.7 SFC/10$^6$, p<0.0001). C/T treated and untreated IBC patients did not differ significantly. IL-10 production, as well as CD4$^+$Foxp3$^+$ cell ($T_{reg}$) proportions by flow cytometry, was similar between HD, HER2$^+$IBC, and C/T treated pts. **Conclusions:** Anti-HER2 Th1resp is progressively lost in breast tumorigenesis, and is $T_{reg}$-independent. Vaccination – but not targeted therapies – restores Th1resp in IBC, providing rationale for immunization to prevent subsequent breast events.

**637 General Poster Session (Board #101), Mon, 8:00 AM-11:45 AM**

**New graded prognostic index for breast cancer patients (pts) with brain metastases (BCBM).** *Presenting Author: Manmeet Singh Ahluwalia, Cleveland Clinic, Cleveland, OH*

**Background:** Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) is frequently used for prognosis for BCBM. We evaluated DS-GPA plus other potential prognostic factors for overall survival (OS) in BCBM pts treated at a single tertiary care institution in a contemporary cohort (Preliminary data was presented at ASCO 2013). **Methods:** With IRB approval, the Cleveland Clinic's database was used to identify BCBM pts treated between 2000 and 2010. OS from the diagnosis of BCBM was the primary end point.Cox proportional hazards models with stepwise variable selection were used for data analysis. **Results:** 371 female patients were included for this analysis. Karnofsky performance scale (KPS) was 90-100 in 142 patients (42%), 70-80 in 146 (43%) and <70 in 48 (15%) patients. Median OS for the entire group was 11.9 months (95% C.I. 9.8-13.6). Median OS in Luminal B, Her 2, Luminal A and basal groups of pts was 23.3, 13.7, 11.9 and 6.0 months respectively (using Sperduto e.t al. 2012 criteria to define the subgroups). DS-GPA for BCBM is based on KPS, age at diagnosis, and subtype. Overall it was prognostic for OS (p<.0001) however separation between groups was variable. Using DS-GPA as a starting point, the number of extracranial metastases (ECM) present, control of the primary, and leptomeningeal metastases (LEP), were found to be additional independent prognostic factors (Table). Combining these factors a revised DS-GPA with 3 groups was defined: unfavorable (total points <6), intermediate (6-8 points), and favorable (>8 points) with median OS of 4.3, 11.9, and 23.4 months, respectively. **Conclusions:** A revised DS-GPA for BCBM based on the conventional GPA, and 3 additional factors is proposed.

| Factor | No. of points | Hazard ratio[1] | p |
|---|---|---|---|
| **No. ECM** | | | |
| **0 or 1** | 3 | 1.98 (1.49-2.62) | <0.0001 |
| **>1** | 0 | | |
| **Primary controlled** | | | |
| **Yes** | 2 | 1.51 (1.13-2.00) | 0.005 |
| **No** | 0 | | |
| **LEP** | | | |
| **No** | 2 | 1.54 (1.12-2.11) | .008 |
| **Yes** | 0 | | |
| **DS-GPA** | | | |
| **3.5-4** | 6 | 1.55 (1.34-1.78) | <0.0001 |
| **2.5-3** | 4 | | |
| **1.5-2** | 2 | | |
| **0-1** | 0 | | |

| Revised GPA | No. Points | Median OS (mo) | N (%) |
|---|---|---|---|
| **Unfavorable** | <6 | 4.3 | 68 (25%) |
| **Intermediate** | 6-8 | 11.9 | 118 (44%) |
| **Favorable** | >8 | 23.4 | 85 (31%) |

1 First group is the reference.

**638 General Poster Session (Board #102), Mon, 8:00 AM-11:45 AM**

**Primary analysis of the prospective, randomized, single-blinded phase II trial of AE37 vaccine versus GM-CSF alone administered in the adjuvant setting to high-risk breast cancer patients.** *Presenting Author: Elizabeth Ann Mittendorf, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** AE37 is the Ii-Key hybrid of the HER2 peptide AE36 (HER2 aa:776-790). It is a MHC class II epitope capable of stimulating $CD4^+$ helper T-cells. We have completed accrual to a prospective, randomized, multi-center, phase II trial of the AE37 vaccine for prevention of breast cancer recurrence. Here the planned primary analysis of disease free survival (DFS) is presented. **Methods:** The trial randomized clinically disease-free, node positive or high-risk node negative patients (pts) with any level of HER2 expression to receive AE37 + GM-CSF (VG) or GM-CSF alone (CG) following standard of care therapy. Pts received 6 monthly intradermal inoculations during the primary vaccine series (PVS) followed by four boosters administered every 6 months. Statistical analysis was performed in the following groups: intention-to-treat (ITT) as the entire randomly assigned trial population, HER2 non-overexpressing (nOE) pts with IHC $1/2^+$ or $FISH^-$ tumors regardless of ER/PR status, and triple negative breast cancer (TNBC) pts with HER2 nOE and ER/$PR^-$tumors. **Results:** With 298 pts (VG= 153, CG= 145) enrolled, there are no differences between groups with respect to age, rate of node positivity, tumor grade, tumor size, ER/PR status, and HER2 over-expression (all p > 0.05). The vaccine is safe and well tolerated with no grade 3 local toxicities and 1 pt experiencing grade 3 systemic toxicity. DFS analyses by Kaplan Meier demonstrated a 12% relative reduction in recurrence (RRR) in the ITT population (19/153 v 20/145 events; HR(CI) 0.89 (0.47, 1.66), p=0.70), a 40% RRR in HER2 nOE pts (10/76 v 14/78 events; HR(CI) 0.60 (0.26, 1.35), p=0.21), and 60% in TNBC pts (4/25 v 9/25; HR(CI) 0.40 (0.12, 1.32), p=0.12). **Conclusions:** AE37 + GM-CSF is a novel vaccine that is safe and well tolerated with minimal toxicity. The primary analysis of this prospective, randomized, single-blinded phase II trial demonstrates benefit in patients with HER2 nOE tumors, especially those with triple negative tumors. These data justify a phase III trial evaluating AE37 administered in the adjuvant setting to a HER nOE or specifically TNBC population. Clinical trial information: NCT00524277.

**639 General Poster Session (Board #103), Mon, 8:00 AM-11:45 AM**

**Immunohistochemical (IHC) prediction of lapatinib efficacy in HER2-positive advanced breast cancer patients.** *Presenting Author: Renata Duchnowska, Military Institute of Medicine, Warsaw, Poland*

**Background:** Molecular mechanisms of resistance to lapatinib are not well understood. We analyzed retrospectively expression of six potentially useful biomarkers and correlated their status with clinical efficacy of lapatinib. **Methods:** Study group included 199 HER2-positive advanced breast cancer patients treated with lapatinib and capecitabine after progression of trastuzumab-based therapy. Expression of MAP-K, pAMPK alpha2, HIF-2 alpha, p-P70S6K alpha, cyclin E and PTEN in tumor samples of primary tumor was investigated by IHC using tissue microarray technology and industrial kits. Staining H-score was calculated for all markers as percent of stained tumor cells x average staining intensity graded from 0 to 3, resulting in a score value between 0 and 300. The most discriminative cut-off values (Cox regression) were subjected to multivariate analysis considering other predictive variables. **Results:** Median duration of lapatinib therapy was 6 months (range 0-52). In 82% of patients lapatinib therapy was discontinued due to disease progression. Using best discriminative values, expression of p-P70S6K alpha ($P$=0.014) and cyclin E ($P$=0.05) was predictive for progression free survival (PFS), the primary endpoint, and their predictive value was confirmed in the multivariate analysis (HR 0.44; 95%CI 0.24-0.80; $P$=0.007 and HR 1.87; 95% CI 1.09-3.21; $P$=0.024, respectively). PFS was also associated with the presence of brain metastasis (HR 1.79; 95% CI 1.28=2.49; $P$=0.001). Overall survival (OS) was associated with expression of cyclin E (p=0.015), p-P70S6K alpha ($P$=0.021), PTEN ($P$=0.034) and pAMPK alpha2 ($P$=0.020), of which cyclin E and MAP-K were confirmed in multivariate analysis (HR 3.66; 95%CI 1-55-8.81; $P$=0.003 and HR 1.59; 95%CI 1.12-2.27; $P$=0.010, respectively). Another independent determinant of OS was the presence of brain metastasis (HR 1.69; 95% CI 1.17-2.40; $P$=0.005). **Conclusions:** Clinical efficacy of lapatinib is associated with activity of downstream signaling pathways – PI3K/AKT/mTOR and MAPK, that seem to play opposite roles. Further investigation may indicate potential role of combining lapatinib with MAP pathway inhibitors.

**640 General Poster Session (Board #104), Mon, 8:00 AM-11:45 AM**

**Survher: A retrospective multicenter study comparing demographic and tumor characteristics of clinical trials versus clinical practice patients with HER2-positive breast cancer.** *Presenting Author: Grazia Arpino, Medical Oncology, AOU Federico II, Naples, Italy*

**Background:** Several clinical trials (CT) have shown remarkable efficacy of trastuzumab-based adjuvant therapy in human epidermal growth factor receptor 2 (HER2)-positive breast cancers (BC). However, CT patient population may not always be representative of patients routinely seen in clinical practice (CP). The aim of this study was to compare clinical and tumoral features between CT and CP patients with HER2 positive BC. **Methods:** From January to December 2012, 696 consecutive patients with HER2+ early BC, treated in 36 Italian Hospitals were enrolled in our study. Age, treatment information, tumor size (T), nodes (N), grade (G), estrogen receptor (ER) and progesterone receptor (PgR) status, were prospectively collected in CP patients. In parallel, the same data were extracted from the adjuvant trastuzumab trials FNCLCC-PACS-04, BCIRG-006, FinHER, HERA, NSABP B31-NCCTG N9831 and pooled using the random-effects model of DerSimonian and Laird. CT and CP groups were compared by using the Cochran Q statistics. **Results:** Compared to CT patients, CP patients were more likely to be older than 50 years (65% vs 48%, respectively, p<0.0001) and have ER positive (71% vs 51%, p<0.0001) and PgR positive (60% vs 39%; p<0.0001) BC and were less likely to have tumor bigger than 2 cm (T ≥2 cm 39% vs 59%; p<0.0001), with positive N (47% vs 89%, p<0.0001) and high G (61% vs 67%, p=0.0241). Additionally, CP patients received more frequently adjuvant endocrine therapy (70% vs 57% p<0.0003) and less frequently adjuvant chemotherapy (97% vs 99.7%; p<0.0001). Among chemo-treated patients there was no difference in the type of administered chemotherapy. **Conclusions:** Most tumor and clinical characteristics significantly differed among CP and CT patients. These data raise doubts about the applicability of CT results to the CP patient population. Therefore, assessing the efficacy and tolerability of anti-cancer treatments also in a clinical scenario closer to the routine CP may be needed to further validate CT results.

**641 General Poster Session (Board #105), Mon, 8:00 AM-11:45 AM**

**Long-term follow up (FU) of patients with durable complete response (DCR) after chemotherapy (CT) and HER2-targeting systemic therapy (HER2-Tx) for HER2+ metastatic breast cancer (MBC).** *Presenting Author: Giuseppe Gullo, St Vincent's University Hospital, Dublin, Ireland*

**Background:** CT-induced DCR of MBC is reported only anecdotally. The addition of HER2-Tx to conventional CT results in increased response rates and prolonged survival for pts with HER2+ MBC. We previously reported that a minority of pts with HER2+ MBC can achieve prolonged CR but their long-term outcome remains unclear. **Methods:** We conducted a systematic retrospective review of all pts with HER2+ MBC treated at our Institution with any CT+HER2-Tx and identified DCR. DCR was defined as a complete response according to RECIST 1.1 criteria lasting >36 months. **Results:** Between January 2000 and December 2010 168 consecutive pts with HER2+ MBC were commenced on CT+HER2-Tx. We identified 17 pts (10%) who met criteria for DCR. Their characteristics are: median age: 53yrs (range 30-65), oestrogen receptors (ER): neg 53%/pos 47%, sites of distant metastases: visceral 47%/lymph nodes only 35%/bone and soft tissues 12%, unknown 6%. All pts received trastuzumab (T). Chemotherapy regimens were: docetaxel+carboplatin 64%/docetaxel+lapatinib 18%/single agent taxane 6%/capecitabine 6%/unknown 6%. Metastatic disease was biopsy-proven in 9/17 pts (53%). All pts received maintenance HER2-Tx after completion of CT. Median FU is 6.5 yrs (range 3.4-13.6). Median duration of HER2-Tx is 61 months (41-127+). Two pts (12%) had MBC relapse while on maintenance T, 1 pt had a second HER2+ primary BC and underwent curative surgery. At database cut-off date (1/2/2014) 15 pts (88%) are alive and disease-free. Their characteristics are: all 1st-line therapy, ER neg 53%, single site of distant metastases 73% (lymph nodes 40%, liver 33%). **Conclusions:** To our knowledge this is the largest series analyzing long-term outcome of HER2+ MBC pts with DCR after CT+HER2-Tx. Our mature results show that a subgroup of pts can achieve a very prolonged CR thus prompting speculations that they have been cured from HER2+ MBC. These pts are usually treated in the 1st-line setting, have more frequently ER-negative disease and limited metastatic disease. Prolonged HER2-Tx could play a role in maintaining DCR. We are currently investigating the molecular profile of this subset of pts.

**642 General Poster Session (Board #106), Mon, 8:00 AM-11:45 AM**

**Projecting the cost-effectiveness of pertuzumab with trastuzumab and docetaxel in the neoadjuvant treatment of HER2-positive, locally advanced, inflammatory or early breast cancer.** *Presenting Author: Joseph B. Babigumira, University of Washington, Seattle, WA*

**Background:** The NeoSphere trial (Gianni et al. [2012]) compared the following regimens for neoadjuvant treatment in HER2+, locally advanced, inflammatory or early breast cancer: 1) trastuzumab and docetaxel (TH) 2) pertuzumab, trastuzumab and docetaxel (THP), 3) pertuzumab plus trastuzumab (HP), and 4) pertuzumab plus docetaxel (TP). The pathological complete response (pCR) rates were 29.0% for TH, 45.8% for THP, 16.8% for HP, and 24.0% for TP. THP significantly increased the pCR rate. We performed a cost-effectiveness analysis of THP compared to other treatment regimens in the neoadjuvant setting based on the pCR results from NeoSphere. **Methods:** We constructed a combined decision-analytic (decision tree) and partitioned survival (area under the curve) model with three health states: disease-free (DF), progressive disease (PD), and death. The decision tree modeled the probability of pCR and the partitioned survival model projected life expectancy of patients who did or did not achieve pCR. Utility data for health states were assigned to calculate quality-adjusted life years (QALYs). We estimated the cost of early breast cancer systemic therapy, drug administration, drug monitoring, clinical management of adverse events, and progressive disease (PD). We performed univariate and probabilistic sensitivity analyses. **Results:** See Table. The incremental cost-effectiveness ratios (ICERs) comparing THP to TH were $34,700/LY and $38,500/QALY, THP to HP, $33,000/LY and $36,900/QALY, and THP to TP, $16,100/LY and $17,800/QALY. The ICERs (THP vs. TH) were most sensitive to pCR difference between THP and TH and the cost of pertuzumab. **Conclusions:** Pertuzumab combined with trastuzumab and docetaxel is projected to be cost-effective in the neoadjuvant setting. This study suggests that this regimen, in addition to being clinically effective, would be favorable from an economic standpoint in the U.S.

**Summary of results.**

| Treatment regimens | Lifetime cost ($) | Life years (LYs) | Quality-adjusted life years (QALYs) |
|---|---|---|---|
| **THP** | 143,000 | 18.41 | 16.51 |
| **TP** | 132,000 | 17.69 | 15.86 |
| **TH** | 124,000 | 17.85 | 16.01 |
| **HP** | 112,000 | 17.45 | 15.65 |

**643 General Poster Session (Board #107), Mon, 8:00 AM-11:45 AM**

**Trastuzumab (T) and pertuzumab (P)-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) in tyrosine kinase inhibitor (TKI)-treated breast cancer (BC) cell lines.** *Presenting Author: Denis Collins, National Institute for Cellular Biotechnology, Dublin City University, Dublin, Ireland*

**Background:** Monoclonal antibody (mAb) therapy and TKI combinations are under investigation for the treatment of HER2-positive (HER2 gene amplification/IHC 3+/2+) BC. A further ~50% of BCs can be described as HER2-low (IHC 1+/2+/non-amplified). The HER2-targeted TKI lapatinib (LAP) can modulate HER2 levels and potentiate T-mediated ADCC in pre-clinical models. This study compares the effects of three HER2-targeted TKIs, LAP, neratinib (NER) and afatinib (AFAT) on HER2 levels in HER2-positive SKBR3 and HER2-low MCF-7 cells and examines the associated effects on T and P-induced ADCC in vitro. **Methods:** MCF-7 and SKBR3 were treated with LAP, NER or AFAT (0.2, 1 and 2$\mu$M, 48 hr). Membrane HER2 protein levels were determined by high content analysis (HCA) using an extracellular domain (ECD)-targeted antibody. A flow cytometry-based ADCC assay utilized TKI pre-treated SKBR3 and MCF-7 (2$\mu$M TKI, 48 hr) and healthy volunteer CD56+ NK cells or PBMCs. **Results:** LAP treatment increased HER2 in SKBR3 and MCF-7. Following LAP treatment, T and P-induced ADCC was increased in MCF-7 and reduced in SKBR3 using PBMCs.Using NK cells, T-induced ADCC was reduced in both LAP-treated cell lines.NER decreased HER2 expression in both cell lines but reduced T-related ADCC in MCF-7 only. AFAT reduced HER2 levels in SKBR3 cells only, but did not significantly reduce ADCC response in SKBR3 cells. (Table, *p< 0.05 relative to DMSO control). **Conclusions:** ADCC optimal TKI/mAb combinations may differ between HER2-positive and HER2-low models, and PBMC sub-populations other than NK cells may be required as mediators. Further pre-clinical assessment is required to elucidate the mechanisms of ADCC modulation by TKIs.

| | SKBR3 | | | | | MCF-7 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Membrane HER2 (fold change) | PBMC (5:1, PBMC:TC) % ADCC | | CD56+ (1:1, NK:TC) % ADCC | | Membrane HER2 (fold change) | PBMC (5:1, PBMC:TC) % ADCC | | CD56+ (1:1, NK:TC) % ADCC | |
| TKI (2$\mu$M) | ECD | T | P | T | P | ECD | T | P | T | P |
| LAP | 1.4±0.2* | 11±5* | 10±6* | 3±8* | 9±4 | 1.6±0.2* | 22±4* | 9±1* | 9±3* | 8±2 |
| NER | 0.4±0.1* | 24±4 | 21±7 | 28±4 | 29±9 | 0.5±0.1* | 7±1* | 0.8±1 | 10±1* | 7±4 |
| AFAT | 0.5±0.1* | 18±3 | 16±4 | 15±8 | 17±7 | 1.1±0.7 | 8±3 | 3±3 | 5±1* | 3±1* |
| DMSO | 1.01±0.1 | 22±3 | 22±5 | 20±6 | 19±8 | 1.04±0.2 | 10±1 | 4±3 | 19±5 | 15±4 |

**644 General Poster Session (Board #108), Mon, 8:00 AM-11:45 AM**

**Effect of adjuvant trastuzumab (T) among patients treated with neoadjuvant T-based chemotherapy.** *Presenting Author: Mariana Chavez-Mac Gregor, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Neoadjuvant T-based chemotherapy is commonly used in the treatment of invasive HER2-positive breast cancer. Pathological complete response (pCR) is a surrogate of improved long-term outcomes; the impact of adjuvant T among patients achieving a pCR is unknown. Among patients treated with neoadjuvant T-based chemotherapy we evaluated the impact of completion of adjuvant T. **Methods:** Patients with primary HER2-positive breast cancer treated with T-based neoadjuvant chemotherapy at our institution between 2001-2012 were included and categorized according to adjuvant T administration and pCR (no invasive residual tumor in the breast and ipsilateral axillary lymph nodes). Descriptive statistics and Cox proportional hazard models were used. **Results:** 589 patients were included. 203 (34.5%) achieved a pCR. 109 (18.5%) did not receive adjuvant including 53 (26.1%) that achieved a pCR and 56 (14.5%) that did not achieve a pCR. Median follow up was 45 months. The 5 year-OS for patients who did and did not receive adjuvant T was 91% vs 93% (p=0.97) and the 5-year RFS was 92% vs 85% (p=0.33). Among patients that achieved a pCR, the 5-year OS was 96% vs 100% (p=0.23) and the RFS was 93% vs 100% (p=0.06) for patient that did and did not receive adjuvant T. Among those without a pCR, the 5-year OS was 92% vs 83% (p=0.28) and the RFS was 81% vs 84% (p=0.67) for patients that did and did not receive adjuvant T. In the multivariable analysis after adjusting for pCR, adjuvant T had no impact on outcome (HR=0.85 p=0.68 for OS and HR 1.05 p=0.9 for RFS). Among patients with pCR, adjuvant T did not improve OS or RFS (HR=2.7 p=0.35 and HR=8.02 p=0.93), the benefit of adjuvant T in OS and RFS did not achieve statistical significance among patients without a pCR (HR=0.64 p=0.3 and 0.76 p=0.44). **Conclusions:** Our data demonstrates that patients treated with neoadjuvant T-based chemotherapy that achieve a pCR, have excellent outcome regardless of whether they received or not adjuvant T. Among patients not achieving a pCR, the use of newer agents should be studied in order to further improve outcomes. Our results are relevant as our field evaluates the appropriate duration, therapeutic index, and cost of additional targeted therapies.

**645 General Poster Session (Board #109), Mon, 8:00 AM-11:45 AM**

**Meta-analysis of stomatitis incidence in everolimus (EVE) clinical studies and its relationship with efficacy.** *Presenting Author: Hope S. Rugo, University of California San Francisco Comprehensive Cancer Center, San Francisco, CA*

**Background:** Stomatitis is a common adverse event with EVE. This meta-analysis of individual patient (pt) data assessed the incidence, severity, and potential impact on outcomes of stomatitis and related events in EVE pts with cancer or TSC. **Methods:** 7 randomized, double-blind, phase 3 studies of EVE were included: RECORD-1 (RCC), RADIANT-2 (NET), RADIANT-3 (pNET), BOLERO-2 ($HR^+/HER2^-$ breast cancer), BOLERO-3 ($HER2^+$ breast cancer), and EXIST-1 and -2 (TSC). Only events from the double-blind period were included. Kaplan-Meier (KM) methods were used to analyze times to first stomatitis and recurrence. Stratified Cox regression analysis adjusted for known baseline prognostic factors was used to assess the association between stomatitis occurrence within 8 wk of EVE start and PFS in cancer pts and response rate in TSC pts. **Results:** 1,455 cancer and 157 TSC EVE-treated pts were analyzed. Crude stomatitis incidence was 66.9% in oncology pts (8.6% grade 3/4) and appeared early (median 0.82 mo; 95% CI 0.7-1.0; 2 mo KM estimate 60.8%). Stomatitis led to discontinuation in 1.7% of pts. Reccurence occurred in 40% and appeared less rapidly (2 mo KM estimate 28.0%). Results were similar in TSC pts. An association between stomatitis and PFS was observed in BOLERO-2 (HR 0.771; 95% CI 0.603-0.987) and RADIANT-3 (HR 0.687; 95% CI 0.465-1.014); association was maintained after correcting for exposure. A similar trend was observed in RECORD-1 (HR 0.866) but not BOLERO-3 or RADIANT-2. In all trials, EVE pts had longer PFS compared with placebo regardless of stomatitis incidence. There were too few TSC pts to reach a conclusion on the relationship between stomatitis and response. **Conclusions:** Stomatitis is common in EVE-treated pts and occurs in the initial wks of therapy. Most events are grade 1/2, rarely lead to discontinuation when actively managed according to recommendations, and recur in $<50\%$ of affected pts. Cancer pts treated with EVE who experienced stomatitis derived benefit consistent with that shown in the overall population, suggesting EVE continuation is beneficial. Ongoing prospective studies will determine the value of prophylactic measures to reduce EVE-induced stomatitis incidence and improve its management.

**646 General Poster Session (Board #110), Mon, 8:00 AM-11:45 AM**

**Disparities among older women with de novo stage IV breast cancer treated with trastuzumab from 1999 to 2009.** *Presenting Author: Ines Maria Vaz Duarte Luis, Dana-Farber Cancer Institute, Boston, MA*

**Background:** To characterize trastuzumab utilization and survival by race/ethnicity in older women with *de novo* stage IV breast cancer who were treated with trastuzumab. **Methods:** We used Surveillance, Epidemiology, and End Results (SEER)-Medicare data to identify patients (pts) ≥66 years with *de novo* stage IV BC diagnosed between 1999-2009 who received trastuzumab. We examined treatment patterns, including time to trastuzumab initiation. We then examined survival time by race/ethnicity using Kaplan-Meier methods and Cox proportional hazards models, adjusting for clinical, sociodemographic, and treatment characteristics. **Results:** Among 579 pts, 452 (78.1%) were non-Hispanic white and 76 (13.1%) were non-Hispanic black. Overall, death was recorded among 418 women (72.2%); the median survival time was 2.4 years (95% CI: 2.1-2.7) and there was a 22% survival rate at 5 years. Compared with white women, black women had a significantly increased adjusted hazard of death (hazard ratio=1.4, 95% CI: 1.04-2.0). Survival for all pts improved over time (Table 1). Overall the odds of early (within 6 months from diagnosis) vs. later (after 6 months) trastuzumab initiation did not differ by race/ethnicity (OR=1.0, 95% CI: 0.5-1.7), but when stratified by hormone receptor (HR) receptor status, white (*v*black) pts with HR negative disease were more likely to have initiated trastuzumab within 6 months (OR: 2.8, 95% CI: 1.4-5.6). **Conclusions:** Although survival times among pts receiving trastuzumab for *de novo* metastatic disease improved over time, we identified racial/ethnic disparities in survival and differences in patterns of care. Additional analyses will include examination of trastuzumab duration and associations with survival.

| Characteristic | Hazard of death (95%CI) |
|---|---|
| **Race** | |
| **Non-Hispanic White** | 1.0 |
| **Non-Hispanic Black** | 1.4 ( 1.04- 2.0) |
| **Hispanic-Other/Unknown** | 1.0 (0.7-1.6) |
| **Year of diagnosis** | |
| **1999-2001** | 1.0 |
| **2002-2005** | 0.7 (0.5-0.9) |
| **2006-2009** | 0.6 (0.4-0.8) |
| **HR** | |
| **Positive** | 1.0 |
| **Negative** | 1.3 (1.03-1.6) |
| **Initiation of trastuzumab** | |
| **Within 6 months** | 1.0 |
| **After 6 months** | 1.6 (1.2-2.0) |

* Adjusting for all variables in Table and age, race, SEER region, location of residence, socioeconomic status, marital status, comorbidity score, grade.

**647 General Poster Session (Board #111), Mon, 8:00 AM-11:45 AM**

**Quality of life (QOL) among patients (pts) with HER2+ breast cancer (bc) treated with adjuvant lapatinib and/or trastuzumab in the ALTTO study (BIG 2-06, Alliance N063D).** *Presenting Author: Amylou C. Dueck, Mayo Clinic, Scottsdale, AZ*

**Background:** The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO; NCT00490139) study was an international randomized open-label phase III study of 2 targeted therapies for HER2+ bc. Efficacy results will be reported in a separate abstract. **Methods:** Pts were randomized to 1 of 4 arms with sequential or concurrent chemotherapy: (A) trastuzumab (T) for 52 weeks (w); (B) oral lapatinib (L) for 52w; (C) T for 12w followed by 6w washout followed by L for 34w; or (D) T+L for 52w. Functional Assessment of Cancer Therapy-Breast (FACT-B) and Linear Analogue Self-Assessment (LASA) items measuring overall and 5 QOL domains, fatigue, rash, and diarrhea were administered on paper at baseline, w12, w52, year 3, and year 5 in pts enrolled in ALTTO through the US NCI CTSU. Mean scores were compared using analysis of covariance and paired t-tests. **Results:** Among 777 pts, 607, 521, and 492 completed booklets at baseline, w12, and w52. At w12, worsening of LASA domains (overall QOL, mental, physical, social wellbeing), FACT-B Trial Outcome Index (TOI), fatigue, rash and diarrhea reached statistical significance within all arms (all $p<0.05$ except FACT-B TOI for arm C $p=0.21$). Worsening was similar across arms for these LASA domains and fatigue. Diarrhea worsening was more severe in upfront L-containing (B & D) arms compared to upfront T alone (A & C) arms (B vs A, B vs C, D vs A, D vs C $p<0.001$). Rash worsening was most severe in B (vs C $p=0.02$, vs D $p=0.007$, vs A $p=0.10$). At w52, LASA domains, fatigue, and FACT-B TOI returned to baseline levels with changes similar across arms (all $p>0.05$). Rash (C vs A, D vs A $p<0.05$) and diarrhea (B vs A, C vs A, D vs A, C vs B, D vs B $p<0.05$) exhibited statistically significant worsening from baseline in L-containing arms relative to A. **Conclusions:** While L had a larger negative impact than T on diarrhea and rash, QOL did not appear to differ across arms. Patient QOL was negatively impacted similarly across arms at w12 but returned to baseline by the end of the treatment period at w52. These data enhance the understanding of QOL impact of anti-HER2 therapy in pts with early stage bc. Long term QOL collection is ongoing. Clinical trial information: NCT00490139.

**648 General Poster Session (Board #112), Mon, 8:00 AM-11:45 AM**

**Neoadjuvant chemotherapy with nonpegylated liposome-encapsulated doxorubicin (NPLD) plus cyclophosphamide followed by trastuzumab plus nabpaclitaxel for HER2-positive breast cancer (BC).** *Presenting Author: Silvana Saracchini, Pordenone, Italy*

**Background:** Using a liposomal delivery system NPLD has shown similar efficacy and less cardiac toxicity compared to conventional anthracyclines. Similarly albumin-bound paclitaxel (nabpaclitaxel) has demonstrated higher response rates and improved tolerability compared to conventional taxanes. This study aimed to evaluate the activity and safety of neoadjuvant chemotherapy with NPLD, nabpaclitaxel and trastuzumab for early or locally advanced HER2 positive BC. **Methods:** Preoperative treatment included NPLD (60 mg/mq iv) plus cyclophosphamide (600 mg/mq iv) every 3 weeks for 4 cycles followed by nabpaclitaxel (260 mg/mq iv) plus trastuzumab (8 mg/mq loading dose iv, then 6 mg/mq iv) every 3 weeks for 4 cycles. All patients received granulocyte colony-stimulating factor as prophylaxis of febrile neutropenia. Primary objective of the study was pathologic complete response (pCR) defined as the absence of residual invasive cancer both in the breast and regional nodes. Also, breast MRI, Contrast-Enhanced-Spectral-Mammography (CESM) and Ki-67 after 1 cycle of chemotherapy were exploratory investigated to assess the ability to predict pCR. **Results:** 15 pts were treated from September 2011 to November 2013. 14 pts were evaluable for response and completed the planned treatment. Median age was 52 years (range: 28-70), the majority of pts had T2 stage (64%), clinical nodes involvement N+ (71%), ER positive (64%). 6 out of 14 pts had clinical stage III BC. All tumours were grade 3 and 93% had Ki-67 ≥20%. pCR was reported in 64% (9 of 14). The most frequent grade 3 adverse event was myalgia (21%). Breast MRI after 1 cycle showed a significant difference on "signal-intensity/time" (SIT) curve between pCR pts and no-pCR pts, with an increase (type-II to type-III) in 50% of pCR pts and 0% of no-pCR pts. **Conclusions:** The nanoparticle formulations, nabpaclitaxel and NPLD, combined with trastuzumab seem to be an active and manageable regimen. It may represent an attractive and promising option in neoadjuvant treatment for HER2 positive BC. The role of Breast MRI, CESM and Ki-67 needs further exploration to predict pathologic response.

**649 General Poster Session (Board #113), Mon, 8:00 AM-11:45 AM**

**Correlation of high levels of HER2 measured by multiplex mass spectrometry with increased overall survival in patients treated with anti-HER2-based therapy.** *Presenting Author: Paolo Nuciforo, Vall d'Hebron Institute of Oncology, Barcelona, Spain*

**Background:** There is evidence that increased absolute levels of the HER2 receptor in breast cancer positively correlates with a clinical benefit from anti-HER2 therapies. The current method of HER2 evaluation, immunohistochemistry (IHC), does not allow for absolute HER2 quantification and is prone to false-positives. Thus, a significant portion of patients classified as HER2-positive actually express low levels of the receptor. We quantitated absolute levels of HER2 using a mass spectrometry-based assay and correlated expression levels with the anti-HER2 therapy benefit. **Methods:** Formalin-fixed, paraffin-embedded (FFPE) tumor sections were microdissected and proteins were solubilized and digested by trypsin in Liquid Tissue buffer. After digestion, internal standards were added and absolute quantitation for multiple proteins was performed using selected reaction monitoring (SRM) mass spectrometry. **Results:** 26 HER2-positive (IHC 3+) breast cancer samples from patients treated with anti-HER2 therapy were obtained from Vall d´Hebron Hospital. Nineteen patients were treated with trastuzumab-based therapy; six were treated with a combination of anti-Her2 therapies. HER2 quantitation by SRM revealed receptor level ranges from 283 to 12840 amol/$\mu$g. Based on the median HER2 expression of the trastuzumab-only treated patients, the patients were divided into two subgroups. The subgroup with high expression levels of HER2 protein (average of 7461 amol/$\mu$g) had an overall survival time of 82.8 months whereas the subgroup with low levels of HER2 (average of 1823 amol/$\mu$g) had a significantly shorter survival time of 55.3 months. **Conclusions:** We used a non-antibody based assay to quantify absolute levels of HER2 in samples from patients treated with anti-HER2 therapy. We found high variability in HER2 expression within a patient population that had been homogenously classified as 3+ by IHC. High levels of HER2 correlated with increased overall survival following anti-HER2 therapy. This study demonstrates the need for improved quantitation of HER2 protein levels prior to initiating anti-HER2 therapy.

**650 General Poster Session (Board #114), Mon, 8:00 AM-11:45 AM**

**T-DM1 in HER2-positive breast cancer brain metastases (BM).** *Presenting Author: Rupert Bartsch, Department of Medicine I, Clinical Division of Oncology and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria*

**Background:** Local treatment options such as radiotherapy or neurosurgery are the mainstay of BM management. Whole brain radiotherapy (WBRT), however, is associated with severe late-toxicity. The LANDSCAPE trial established lapatinib plus capecitabine (LapCap) as primary systemic treatment in oligosymptomatic patients (pts) with multiple Her2-positive BM. Limited evidence exists regarding the activity of antibodies in BM. T-DM1 is an antibody-drug conjugate linking trastuzumab (T) to an anti-microtubule agent. T-DM1 provides activity in pts progressing upon T and has lower toxicity as compared to LapCap. Here, we investigated the activity of T-DM1 in newly diagnosed or progressive BM. **Methods:** A total of six consecutive pts (median age 55 years) with Her2-positive breast cancer and BM were treated with T-DM1. In two asymptomatic pts, T-DM1 was administered as primary systemic therapy, while four subjects had already received local therapy and had documented CNS progression. T-DM1 was administered intravenously at a dose of 3.6 mg/kg body weight every three weeks; re-assessment of disease status was performed every three cycles. At baseline and restaging, MRI was performed. CNS response was defined as a reduction of lesion size of $\geq$50%. **Results:** Median follow-up was 6 months (m) and median brain metastases-free survival 11 m, respectively. All pts had received prior T, three (50%) had already received LapCap, and two (33.3%) pertuzumab. Currently, 4/6 pts (1 with primary treatment and 3 receiving T-DM1 upon CNS progression) are assessable for CNS response. 2/4 pts (50%) had partial remission, while one patient progressing upon prior local therapy had stable disease lasting for 15 cycles. One patient had minor response on MRI but no reduction of pre-existing brain oedema and increasing cortisol doses and was therefore deemed PD. A significant LVEF drop was observed in one heavily pretreated patient. **Conclusions:** This prospective case series again indicates that systemic therapy offers activity in Her2-positive BM. Currently, LapCap remains the standard of care. Still, T-DM1 offers relevant clinical activity; therefore, the role of T-DM1 in BM should be investigated in larger studies.

**651 General Poster Session (Board #115), Mon, 8:00 AM-11:45 AM**

**A phase 1 study of MM-111, a bispecific HER2/HER3 antibody fusion protein, combined with multiple treatment regimens in patients with advanced HER2-positive solid tumors.** *Presenting Author: Donald A. Richards, Tyler Cancer Center, US Oncology Research, McKesson Specialty Health, Houston, TX*

**Background:** MM-111 (111) inhibits ligand activated HER3 signaling in HER2+ tumors. This study evaluated the safety of 111 combined with standard of care (SOC) HER2-targeting regimens (Rx): capecitabine (X) + cisplatin (C) + trastuzumab (T) (Arm 1); lapatinib (L) +/- trastuzumab (Arm 2); paclitaxel (P) + trastuzumab (Arm 3); lapatinib + paclitaxel + trastuzumab (Arm 4); docetaxel (D) + trastuzumab (Arm 5). **Methods:** This was a multi-arm Phase 1, dose escalation study of 111 in combination with SOC regimens to evaluate safety, pharmacokinetics (PK), and anti-tumor activity. Patients were required to have documented advanced HER2-positive cancer and adequate organ function. Each arm was designed to run as a separate Phase 1 study to address safety and tolerability and utilized a "3 + 3" design with standard dosing of the SOC regimen. 111 was dosed weekly at 10 mg/kg and escalated up to 20 mg/kg where possible. For Arm 5, 111 was dosed q3w starting at 30mg/kg and escalated up to 40mg/kg. **Results:** A total of 86 patients (11 bladder, 46 breast, 15 gastro-esophageal, 14 other cancers) were enrolled and treated across all five arms. Dose-limiting toxicities (DLTs) included anemia, acute renal failure (assessed as cisplatin-related), chest pain, decreased appetite, diarrhea, febrile neutropenia, hyperuricemia, hypokalemia, hyponatremia, hypophosphatemia, mucosal inflammation, nausea, neutropenia, stomatitis, thrombocytopenia, and vomiting. An MTD was not reached in Arms 2-5; Arm 1 required a capecitabine dose reduction. **Conclusions:** Treatment with 111 and SOC HER2-directed regimens was feasible. The Recommended 111 Phase 2 doses are 20mg/kg QW and 40mg/Q3W. Additional safety, PK and preliminary activity data will be provided. Clinical trial information: NCT01304784.

**Patient outcomes summary.**

| Arm | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 5 |
|---|---|---|---|---|---|
| Rx (Dose) | X (1000) | T (4/2) | P (80) | P (80) | D (75) |
| Units | C (80) | L (1000) | T (4/2) | L (750) | T (8/6) |
| 111 and T (mg/kg) | T (4/2) | 111 (10-20) | 111 (10-20) | T (4/2) | 111 (30-40) |
| X, D, C and P (mg/m$^2$) | 111 (5-10) | | | 111 (10-20) | |
| N (safety population) | 17 | 31* | 23 | 9 | 6 |
| DLT | 6 | 4 | 1 | 1 | 0 |
| SAE | 5 | 12 | 6 | 4 | 1 |
| N (evaluable population) | 14 | 24 | 21 | 9 | 6 |
| CR; PR; SD | 1 CR;3 PR;6 SD | 4 PR;10 SD | 6 PR;7 SD | 4 PR; 3 SD | 1 PR; 2 SD |

*10 patients did not receive T.

**TPS652 General Poster Session (Board #116A), Mon, 8:00 AM-11:45 AM**

**Comparison of weight loss among early-stage breast cancer patients post chemotherapy: Nutrition education in combination with weight loss acupuncture versus nutrition education alone.** *Presenting Author: Jami Fukui, Mount Sinai Medical Center, New York, NY*

**Background:** Obesity and weight gain are significant concerns for breast cancer survivors. Obesity at diagnosis of breast cancer is an established negative prognostic factor and the Nurses' Health Study suggest that post-diagnosis weight gain may increase risk for recurrence. Up to 96 percent of women gain weight during treatment and once a woman has been diagnosed with breast cancer, she is at increased risk for other cancers, diabetes and cardiovascular disease. Several studies report an inverse relationship between weight gain and disease free survival. Continued efforts to identify appropriate weight management interventions aimed at promoting overall health and long term survivorship are needed. In this study, we will examine whether adding weight loss acupuncture to a nutrition education program for weight loss could improve short and long term weight loss among breast cancer survivors post treatment with chemotherapy. Vtrim is an online, evidence based, 12 week behavior modification program for weight management and has been used in breast cancer survivors, with a recent study showing weight change and safety in this population. Meta-analyses have suggested that acupuncture may be helpful for weight loss in obese women not diagnosed with breast cancer and without the common side effects found in alternative medicinal options. **Methods:** We plan to enroll obese women who have been diagnosed and treated for breast cancer in a twelve week weight loss program. The participants will be randomized to two groups: weight loss acupuncture plus nutrition intervention or nutrition intervention alone. Women in the acupuncture group will receive weekly body and/or auricular acupuncture once a week at the Pain Management and Integrative Medicine Clinic at Mount Sinai Medical Center, in addition to attending the online group-based nutritional education sessions in which all study participants will partake. All study participants' weight loss will be assessed at the end of twelve weeks, with follow-up at twenty-four weeks, then every 3 months for the first year, then every 6 months until year two, to evaluate weight loss maintenance.

**TPS653 General Poster Session (Board #116B), Mon, 8:00 AM-11:45 AM**

**A phase II randomized, double-blind, placebo-controlled multicenter trial evaluating the efficacy and safety of enzalutamide in combination with exemestane in estrogen or progesterone receptor-positive and HER2-normal advanced breast cancer.** *Presenting Author: Denise A. Yardley, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN*

**Background:** The androgen receptor (AR) is expressed in the majority of patients (pts) with ER/PgR+ breast cancer (BC)(Collins LC et al. *Mod Pathol*. 2011;24:924–931; Loibl S et al. *Breast Cancer Res Treat*. 2011;130:477–487). In ER+ cell lines, AR over-expression can lead to hormone-resistance (De Amicis F et al. *Breast Cancer Res Treat*. 2010;121: 1-11). Androgen stimulated growth of ER+/AR+ cells lines can be blocked by enzalutamide (ENZA), a potent oral inhibitor of AR. Treatment with exemestane (EXE) can increase androgen levels (Takagi K, et al. *Endocr Relat Cancer*. 2010;17:415–430), the addition of ENZA to EXE may inhibit any androgen-mediated breast tumor growth. **Methods:** This randomized placebo (PBO) controlled phase 2 trial will evaluate EXE with or without ENZA (160 mg/day) in 240 patients (pts) with advanced BC (aBC) that is ER/PgR+ and Her2 normal (NCT02007512). Two parallel enrolling cohorts (C) will each evaluate 120 pts who have received either no (C1) or 1 (C2) prior hormone therapy for aBC. Randomization (1:1) is stratified (Y/N) by prior hormone, prior aromatase inhibitor (AI) and hormone resistance. Eligible pts must have $\leq$ 1 non-hormone regimen and ECOG $\leq$1; non-measurable bone or skin disease is allowed. Pts with CNS disease or history of seizure are excluded. Tissue submission for determination of AR expression is mandatory. The co-primary endpoint (EP) is progression-free survival (PFS) in all pts and in those with AR+ disease. Cross-over is allowed following RECIST 1.1 progression. Additional EPs include clinical benefit rate (complete/partial response or stable disease at $\geq$24 weeks); response rate; duration and time to response, safety and tolerability. Efficacy analyses will be conducted on all randomized pts (ITT), a minimum of 90 PFS events/cohort is required to estimate the median PFS and hazard ratio. Approximately 55 PFS events, for a target HR = 0.67, are required in the AR+ subset. The definition of "AR+" will be determined prior to unblinding. Clinical trial information: NCT02007512.

**TPS654 General Poster Session (Board #117A), Mon, 8:00 AM-11:45 AM**

**Adjuvant palbociclib (P) plus endocrine therapy (ET) for hormone receptor positive (HR+) breast cancer: A phase II feasibility study.** *Presenting Author: Erica L. Mayer, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Cell cycle inhibition is a target of interest for novel cancer therapeutics. P is an orally active inhibitor of CDK4/6, causing cell cycle arrest at the G1-S transition. In an interim analysis of a phase II first-line study in HR+ metastatic breast cancer (MBC), patients (pts) randomized to letrozole (L) plus P had prolonged progression-free survival compared with L alone (26.1 vs 7.5 mos, HR 0.37, p<0.001) (Finn et al SABCS 2012). The most common toxicity with P is neutropenia, typically non-cumulative and uncomplicated. Given observed benefits of LP in HR+ MBC, exploring the feasibility of P in the adjuvant setting is warranted. **Methods:** This is a phase II single arm trial evaluating the feasibility of 2 yrs of combination P and adjuvant ET. Eligible pts are postmenopausal, with HR+ stage II (not T2N0)-III invasive breast cancer. Pts must have demonstrated tolerance of adjuvant aromatase inhibitor (AI) by completion of 3-24 mos of AI without significant adverse events (AE), with plan for at least 2 more yrs of AI. Pts will receive P at 125 mg daily, 3 wk on/1 wk off in a 28d cycle, plus continuous physician's choice AI (L, anastrozole, or exemestane), for planned duration 2 yrs. Neutropenia monitoring occurs every 2 wks for the first 3 cycles, then monthly for the duration of treatment. Pts may be removed from study for toxicity, non-adherence, or other events related to tolerability; pts who recur or complete 2 yrs of therapy will be censored for the primary endpoint. The primary objective is to evaluate the treatment discontinuation rate at 2 yrs; if the rate is >50%, the treatment duration will not be considered feasible, whereas a rate <33.3% would be considered feasible and worthy of further study for efficacy. Discontinuation rates at 2 yrs will be estimated by Kaplan Meier with 95% confidence bands. The total sample size is 120 pts, providing 92% power to reject the null hypothesis using a one-sided alpha = 0.025, and accounting for a censoring rate of up to 20% over the 2 yrs. Secondary endpoints include AE graded by CTCAE 4.0 and adherence to oral therapy. Two interim analyses for futility are planned when 66% and 100% of pts have received 6 mos of therapy. Clinical trial information: NCT02040857.

**TPS655^ General Poster Session (Board #117B), Mon, 8:00 AM-11:45 AM**

**Phase II, randomized, placebo-controlled study of BYL719 or buparlisib (BKM120) with letrozole for neoadjuvant treatment of postmenopausal women with HR+/HER2−, *PIK3CA* mutant or wild-type, breast cancer (BC).** *Presenting Author: Ingrid A. Mayer, Vanderbilt-Ingram Cancer Center, Vanderbilt University, School of Medicine, Nashville, TN*

**Background:** The PI3K/AKT/mTOR pathway is frequently activated in BC, with mutations in *PIK3CA* particularly common in hormone receptor-positive (HR+) tumors. In preclinical studies of HR+ BC, BYL719 (an $\alpha$-specific PI3K inhibitor) and buparlisib (a pan-PI3K inhibitor) have shown synergistic effects *in vitro* and near-complete tumor regression *in vivo*, respectively, when used in combination with hormone therapy. **Methods:** This is a Phase II, randomized, double-blind, placebo-controlled trial of BYL719 (300 mg QD) or buparlisib (100 mg QD) combined with letrozole (2.5 mg QD) for the neoadjuvant treatment of postmenopausal women with HR+/HER2– BC (NCT01923168). Key inclusion criteria are stage T1c–T3, any N, M0, operable BC; measurable disease; HR+, HER2– BC; known *PIK3CA* status (mutant or wild type) and Ki-67 level, determined centrally; Eastern Cooperative Oncology Group performance status $\leq$1; and adequate bone marrow and organ function. Key exclusion criteria are locally recurrent/metastatic disease and prior systemic therapy or radiotherapy for current BC. Patients will be assigned to 1 of 2 cohorts (*PIK3CA* mutant or wild type) and randomized to 1 of 3 arms (letrozole + BYL719, buparlisib, or placebo), stratified by Ki-67 level (<14% vs $\geq$14%) and lymph node status (+ve or –ve). Patients will be treated for 24 weeks, until surgery. The primary endpoint is pathologic complete response (pCR; defined as ypT0/Tis, ypN0) after 24 weeks' treatment. The secondary endpoints are objective response rate (complete + partial, per RECIST 1.1), safety, rate of breast-conserving surgery, correlation between pCR and Ki-67 changes from baseline to Day 15 and to surgery, response (defined as central preoperative endocrine prognostic index score of 0), and pharmacokinetic profiles of all drugs used in the combination treatments. For each cohort, pCR rates will be summarized by treatment arm. The activity signal with either combination will be established if pre-defined proof-of-concept criteria are met. Approximately 360 patients will be randomized. Global recruitment is ongoing. Clinical trial information: NCT01923168.

**TPS656 General Poster Session (Board #118A), Mon, 8:00 AM-11:45 AM**

**PERSEPHONE: Duration of trastuzumab with chemotherapy in patients with HER2-positive early breast cancer—Six versus twelve months.** *Presenting Author: Helena Margaret Earl, Department of Oncology, NIHR Cambridge Biomedical Research Centre and Cambridge Breast Cancer Research Unit, University of Cambridge, Cambridge, United Kingdom*

**Background:** PERSEPHONE is a randomised controlled trial comparing six months of trastuzumab to the standard 12 months in patients with HER2 positive early breast cancer. **Methods:** 4,000 patients will be randomised into the two arms (1:1). The power calculations assume that the disease-free survival (DFS) of standard treatment (12 months trastuzumab) is 80% at 4 years. Randomisation of 4,000 pts will allow the trial to prove non-inferiority of six months trastuzumab (5% 1-sided significance & 85% power). Non-inferiority is defined as 'no worse than 3%' below the control arm (12 month) 4 year DFS. Primary outcome is DFS, and secondary outcomes are overall survival (OS) non-inferiority; cost effectiveness; cardiac function & quality of life. Tumour blocks are collected to research molecular predictors of survival with respect to duration of trastuzumab treatment. Blood samples are analysed for single nucleotide polymorphisms (SNPs) as pharmaco-genetic determinants of prognosis, toxicity and treatment outcome. Exciting developments led to a protocol amendment (Dec 2013) which allows sites to administer IV or sub-cutaneous trastuzumab according to their standard practice. Cardiology data on the first 2,500 patients is now being analysed. PERSEPHONE is funded by the NIHR HTA programme in the UK. Results: PERSEPHONE commenced recruitment in October 2007. At abstract submission, 3,166 pts (79%) had been randomised from 154 UK sites. Recruitment is due to complete mid-2015 with the first planned interim analysis of the primary outcome mid-2016. The iDMSC reviewed all data available on HERA and PHARE in 2012 as well as a PERSEPHONE interim analysis. There were no safety findings or signals that would warrant a change of the study plan & the high quality of data was noted. Conclusion:PERSEPHONE continues the active recruitment phase as planned with the sub-cutaneous form of trastuzumab proving popular. Publication of early PHARE results have reinforced interest in the PERSEPHONE trial both nationally and internationally. There has been full support from the Breast International Group (BIG) and the international breast cancer community to answer this important shorter duration question. Clinical trial information: 52968807.

**TPS657 General Poster Session (Board #118B), Mon, 8:00 AM-11:45 AM**

**Bevacizumab plus paclitaxel optimization study with interventional maintenance endocrine therapy in advanced or metastatic ER-positive HER2-negative breast cancer: JBCRG-M04 (BOOSTER) trial.** *Presenting Author: Shigehira Saji, Department of Target Therapy Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan*

**Background:** In the standard management of inoperable or recurrent breast cancer (BC), active therapy is continued until disease progression (PD) or unacceptable toxicity. In patients (pts) receiving first-line bevacizumab (BV) plus paclitaxel (PTX), this strategy results in some pts discontinuing treatment because of PTX-related peripheral sensory neuropathy despite sustained tumor response. To overcome this problem, we propose a practical treatment strategy in pts with ER-positive HER2-negative BC, introducing temporary BV + endocrine maintenance therapy in pts responding to BV + PTX followed by BV + PTX reintroduction at first PD. This strategy may reduce the impact of peripheral sensory neuropathy, enable pts to maintain their quality of life (QOL) and prolong disease control. **Methods:** JBCRG-M04 (BOOSTER; UMIN000012179; ClinicalTrials.gov NCT01989780) is a multicenter open-label randomized phase II trial in pts with ER-positive HER2-negative inoperable or recurrent BC. After 16–24 weeks of induction therapy with BV 10 mg/kg q2w + PTX 90 mg/m$^2$ days 1, 8 and 15 q4w, pts achieving a complete or partial response or stable disease (investigator assessed) are randomized to either A: continued BV + PTX; or B: a switch to maintenance BV + endocrine therapy, followed by BV + PTX at the time of either PD or clinical PD on maintenance therapy. Tumor tissue, DNA and sequential plasma samples are collected before and during treatment for biomarker research. The primary endpoint is time to failure of strategy (TFS), defined as the interval between randomization and either PD on study therapy, change to new agent not in study regimen, first PD not followed by BV + PTX in arm B, or death. The planned sample size of 160 pts provides 80% power to detect a 6-month increase in TFS in arm B versus arm A. Secondary endpoints include overall survival, 2-year survival rate, progression-free survival, safety and QOL. Biomarker analyses include correlations between biomarkers and response, changes in angiogenesis regulators and comparison of biomarker levels between initial and reintroduced BV + PTX. Clinical trial information: NCT01989780.

**TPS658 General Poster Session (Board #119A), Mon, 8:00 AM-11:45 AM**

**A single-blind, randomized, placebo-controlled phase II study to evaluate the impact of oral bisphosphonate treatment on bone mineral density in osteopenic women receiving adjuvant aromatase inhibitors: Interim analysis of "BONADIUV" trial.** *Presenting Author: Vieri Scotti, Florence University Hospital, Florence, Italy*

**Background:** Aromatase inhibitors (AIs) are a highly effective well-tolerated treatment for post-menopausal endocrine-responsive breast cancer (BC). However, their use is associated with accelerated bone loss and increased risk of fractures. The ARIBON trial published by Lester et al in 2008 showed that monthly oral ibandronate improves bone density and normalizes bone turnover in patients treated with anastrozole. BONADIUV trial is a single-blind, randomized, placebo-controlled phase II study designed to evaluate the impact of oral ibandronate (150 mg monthly) on bone mineral density (BMD) in osteopenic women on AIs in adjuvant setting. **Methods:** All patients underwent histological proven diagnosis of BC. Patients received breast surgery and adjuvant treatment according to clinical and pathological status at Our Institute. Enrolled patients were candidate to 5 years of adjuvant AIs. Major exclusion criteria were: previous diagnosis of solid tumors, psychiatric disorders, premenopausal status, smokers patients, chronic use of steroids, ipertyroidism, iperparathyroidism, rheumatoid arthritis, severe thinness (body mass index $<16$), age less than 18 years or more than 70. All patients were treated with vitamin D supplementation for an overall treatment of 24 months. The primary endpoint was the change in BMD at lumbar spine or hip after 12 and 24 months of treatment in ibandronate-treated patients (Arm A) compared with those receiving placebo (Arm B). Patients were also stratified by menopausal age, body mass index and age. Secondary end points included adverse events monitoring. Common Terminology Criteria for Adverse Events (CTCAE) 4.0 were utilized to record toxicity related events. Recruiting is ongoing: 105 of planned 196 patients have been enrolled. Fifty-three patients were allocated in arm A and 52 patients were allocated in arm B. At 12 months' follow up visit, complete data were assessable in 86 cases. At 24 months' follow up visit, complete data were assessable in 40 patients.

**TPS659 General Poster Session (Board #119B), Mon, 8:00 AM-11:45 AM**

**A phase III randomized trial of niraparib versus physician's choice in previously treated, HER2-negative, germline-BRCA mutated breast cancer patients: Intergroup study EORTC-1307-BCG and BIG5-13.** *Presenting Author: Konstantinos Tryfonidis, EORTC Headquarters, Brussels, Belgium*

**Background:** Germline mutations of *BRCA1/BRCA2* genes are a cause of hereditary breast or ovarian cancer. Cancers arising in women with germline *BRCA1/BRCA2* mutations are defective in DNA repair, and *BRCA* deficient cancer cells are hypersensitive to PARP inhibitors (Bryant et al., 2005; Farmer et al., 2005). Niraparib is a potent,selective inhibitor of PARP-1 and PARP-2 that demonstrated activity in *BRCA1* or *BRCA2* mutated cancer cell lines. Responses have been reported with Niraparib in women with *BRCA1.2* related breast and ovarian cancer. (Michie et al, 2013). **Methods:** Patients with HER2 negative metastatic breast cancer (306), with centrally confirmed *BRCA1* or *BRCA2*germline mutations, will be randomized 2:1 open-label study, to either niraparib 300mg (3x 100 mg niraparib capsules) administered orally QD continuously or physician's choice of single-agent chemotherapy (eribulin, vinorelbine, capecitabine or gemcitabine) administered in 3 weekly cycles. Patients must have received prior therapy that included a taxane and anthracycline and should be pretreated with up to 2 prior cytotoxic regimens for advanced/metastatic disease. Patients with hormone receptor positive disease can be included if they progressed during one prior hormonal therapy. The primary objective is to compare the progression-free survival (PFS) (RECIST v 1.1) on niraparib versus physician's choice, assessed by blinded, central review. The key secondary objective is to compare overall survival between patients in niraparib versus physician's choice. Sample size is based on Overall Survival (OS). The hypothesis of median PFS improvement is 3 versus 6 months for physician's choice and niraparib respectively, with a hazard ratio of 0.5, and power of 99.6% for the primary PFS analysis. Assuming an increase in OS from 9 to 13 months, the study has 80% power at a 1-sided alpha of 0.025. Secondary endpoints are PFS by investigator-based assessment, safety, time to treatment failure, Response Rate, Duration of response, HRQoL. This trial is enrolling patients from European, North American countries and Israel and is sponsored by TESARO. Clinical trial information: NCT01905592.

**TPS660 General Poster Session (Board #120A), Mon, 8:00 AM-11:45 AM**

**Phase I dose-escalation trial of ONT-380 in combination with trastuzumab in participants with brain metastases from HER2+ breast cancer.** *Presenting Author: Otto Metzger-Filho, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Central nervous system (CNS) metastases remain an important cause of morbidity and death for patients diagnosed with HER2+ breast cancer (BC). ONT-380 is an orally active reversible and selective HER2 inhibitor. In pre-clinical studies ONT-380 showed superior CNS penetration and improved overall survival (OS) when compared with lapatinib. In a previous phase I study, ONT-380 demonstrated an acceptable safety profile, with a low incidence and severity of diarrhea and rash. Dose limiting toxicity was represented by transient and reversible transaminases elevation. Clinical activity was observed. We therefore designed a Phase I clinical trial combining ONT-380 with trastuzumab for patients diagnosed with HER2+ BC and CNS metastases. **Methods:** This is an open-label, dose finding phase I study. The primary objectives are to determine the maximum-tolerated dose and schedule of ONT-380 in combination with trastuzumab in patients with HER2+ BC and CNS metastases. Secondary objectives include CNS objective response rate by RECIST and volumetric criteria, progression-free survival and OS. Correlative science analysis includes collection of circulating tumor cells at baseline and time of progression for molecular characterization, including FISH studies for EGFR, HER2, Met, and Myc. The study has two parallel arms with two dose regimens of ONT-380, either twice-daily or once-daily, in combination with standard dose trastuzumab. The dose level of ARRY-380 in the initial and subsequent dose escalation cohorts will be 450 and 600mg for the BID regimen and 750, 900, 1200mg for the QD regimen. Eligibility criteria include measurable disease in the CNS, ECOG performance status 0 to 2, and no limit on prior therapies. We utilize a 3+3 dose escalation design with an expansion phase of 16 participants per arm, which will provide additional information on the safety and biologic activity of the treatment combination. In addition, 16 participants per arm at the MTD will give an 89% probability of selecting the best regimen under a "pick the winner" selection design if true probabilities of clinical benefit are 10% and 30% respectively. Clinical trial information: NCT01921335.

**TPS661 General Poster Session (Board #120B), Mon, 8:00 AM-11:45 AM**

**Prevention of stomatitis in patients with hormone receptor–positive advanced breast cancer treated with everolimus plus exemestane: A phase II study of a steroid-based mouthwash.** *Presenting Author: Hope S. Rugo, University of California San Francisco Medical Center, San Francisco, CA*

**Background:** Stomatitis is a frequent adverse event associated with the oral mTOR inhibitor everolimus that can impact treatment adherence. Steroid mouthwashes, gels, or pastes used to treat recurrent aphthous stomatitis have been proposed as potential preventive therapies. This phase II, single-arm study will evaluate a steroid-based therapeutic intervention to prevent stomatitis (grade ≥2) in breast cancer patients taking everolimus + exemestane. **Methods:** Eligibility includes patients with HR-positive, HER2-negative advanced breast cancer, no evidence of stomatitis or other oral pathology, and a plan to start therapy with everolimus + exemestane. A baseline oral assessment will be conducted. Treatment consists of a steroid-based mouthwash (alcohol-free 0.5 mg/5 mL dexamethasone solution), swished in the mouth for a minimum of 2 minutes 4 times per day, starting on the first day of everolimus and exemestane administration. Patients will be instructed to abstain from eating or drinking for at least 1 hour after using the mouthwash. Preventive therapy will continue for 56 days, with optional continued use for an additional 56 days. The primary endpoint of this trial is the incidence of stomatitis (grade ≥2) at 56 days, defined as meeting at least 1 of the following criteria: ≤50 on Normalcy of Diet Scale to assess oral intake and a rating of 7 on two consecutive days or a rating of 8, 9, or 10 on any one day using a visual analog scale to assess oral pain. Secondary endpoints include average number of times per day the mouthwash regimen was performed and time to resolution of stomatitis (grade ≥2). Assuming a 13% absolute reduction in the rate of grade ≥2 stomatitis from the historical control rate of 33% and 1-sided type 1 error = 0.05 and power = 80%, 73 evaluable patients are required. To account for an estimated 25% of the total patient population being nonevaluable, 97 patients will be enrolled. Support: Novartis Pharmaceuticals Corporation. Clinical trial information: NCT02069093.

**TPS662 General Poster Session (Board #121A), Mon, 8:00 AM-11:45 AM**

**A phase 1b study of ONT-380, an oral HER2-specific inhibitor, combined with ado-trastuzumab emtansine (T-DM1), in HER2+ metastatic breast cancer (MBC).** *Presenting Author: Virginia F. Borges, University of Colorado Cancer Center, Aurora, CO*

**Background:** ONT-380 is a selective small molecule inhibitor of HER2 kinase with nanomolar potency. Unlike dual HER2/EGFR agents, it does not inhibit EGFR at clinically relevant concentrations, decreasing the potential for EGFR-related toxicities. In preclinical studies, ONT-380 demonstrated greater than additive activity with trastuzumab, and was active in models of CNS metastases. In a single-agent phase 1 study in 50 patients (pts) with metastatic HER2+ cancer, the MTD was 600 mg BID, with DLT consisting of reversible Grade 3 ALT/AST in 2 of 4 pts treated at 800 mg. In 22 HER2+ breast cancer pts treated at doses ≥ 600 mg BID, the clinical benefit rate (partial response [n = 3] plus stable disease for at least 6 months [n = 3]) was 27%. Based on data supporting dual blockade of HER2, ONT-380 is now being evaluated in combination with T-DM1. **Methods:** The study objectives are to determine the safety, MTD/Phase 2 dose, and preliminary anti-tumor activity of ONT-380 given in combination with T-DM1 in pts with or without CNS metastases. Potential biomarkers of response and pharmacokinetics will also be assessed. A 3+3 design will evaluate up to four dose levels of ONT-380 (starting at 300 mg PO BID) given with T-DM1 (3.6 mg/kg IV once every 21 days). The study population includes up to 48 adult pts with HER2+ MBC who have received prior trastuzumab and a taxane, but not T-DM1, for metastatic disease. Pts with either treated CNS metastases or asymptomatic untreated CNS metastases are also eligible. Two expansion cohorts are planned, including an MTD/Phase 2 dose expansion cohort, and a cohort of pts with CNS disease, including either untreated, asymptomatic CNS metastases or CNS metastases that have progressed after local therapy. Systemic disease response will be evaluated using RECIST 1.1. CNS response will be evaluated by RECIST 1.1, modified RECIST 1.1, and volumetric criteria. Potential biomarkers of response include the presence of p95 HER2 and HER2 mutations in archived tumor biopsies. Treatment will continue until unacceptable toxicity, disease progression, or withdrawal of consent. Clinical trial information: NCT01983501.

**TPS663 General Poster Session (Board #121B), Mon, 8:00 AM-11:45 AM**

**A phase 1b study of ONT-380, an oral HER2-specific inhibitor, combined with capecitabine and trastuzumab, in HER2+ metastatic breast cancer (MBC).** *Presenting Author: Erika Paige Hamilton, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN*

**Background:** ONT-380 is a selective small molecule inhibitor of HER2 kinase with nanomolar potency. Unlike dual HER2/EGFR agents, it does not inhibit EGFR at clinically relevant concentrations, decreasing the potential for EGFR-related toxicities. In preclinical studies, ONT-380 demonstrated greater than additive activity with trastuzumab, and was active in models of CNS metastases. In a single-agent phase 1 study in 50 patients (pts) with metastatic HER2+ cancer, the MTD was 600 mg BID, with DLT consisting of reversible gr 3 ALT/AST in 2/4 pts at 800 mg. In 22 HER2+ breast cancer pts treated at doses ≥ 600 mg BID, the clinical benefit rate (partial response [n = 3] plus stable disease for at least 6 months [n = 3]) was 27%. Based on data supporting dual blockade of HER2, as well as preclinical activity of ONT-380 in the CNS, ONT-380 is now being evaluated in combination with capecitabine and trastuzumab. **Methods:** The study objectives are to determine the MTD/Phase 2 dose and preliminary anti-tumor activity of ONT-380 given with capecitabine alone, trastuzumab alone, and both capecitabine and trastuzumab in pts with and without CNS metastases. The study population includes adult pts with HER2+ MBC who have received trastuzumab and ado-trastuzumab emtansine (T-DM1) but not capecitabine for metastatic disease. A 3+3 design will evaluate up to three dose levels of ONT-380 (starting at 300 mg PO BID) given in combination with either capecitabine (1000 mg/mg$^2$ PO BID for 14 days of a 21-day cycle) or trastuzumab (8 mg/kg IV loading dose; 6 mg/kg IV once every 21 days). If both combinations are tolerable, ONT-380 will be evaluated with both capecitabine and trastuzumab. Expanded cohorts of pts with and without CNS metastases may be enrolled for either doublet or triplet combinations. Tumor response will be evaluated using RECIST 1.1. CNS response will be also evaluated by modified RECIST 1.1 and volumetric criteria. Potential biomarkers of response, including p95 HER2 and HER2 mutations, will be assessed in archived tumor biopsies. Treatment will continue until unacceptable toxicity, disease progression, or withdrawal of consent. Clinical trial information: NCT02025192.

**TPS664 General Poster Session (Board #122A), Mon, 8:00 AM-11:45 AM**

**RTOG 1119: Phase II randomized study of whole brain radiotherapy with concurrent lapatinib in patients with brain metastasis from HER2-positive breast cancer—A collaborative study of RTOG and KROG (NCT01622868).** *Presenting Author: David M. Peereboom, Cleveland Clinic, Cleveland, OH*

**Background:** The addition of trastuzumab to cytotoxic chemotherapy has improved outcomes for patients with HER2 positive breast cancer. Increased survival coupled with limited blood-brain barrier (BBB) penetration of trastuzumab may contribute to the increased incidence of brain metastasis in these patients. Half of these patients die of intracranial disease progression rather than extracranial disease. Therefore, strategies to improve survival must include increased CNS disease control in these patients. Lapatinib crosses the BBB and demonstrates modest activity against intracranial metastases. Based upon preclinical data and results of a phase I study, we hypothesize that lapatinib plus WBRT can improve the intracranial disease control compared to WBRT alone. **Methods:** We initiated a randomized phase II trial of WBRT (37.5 Gy/3 weeks) plus or minus concurrent lapatinib (1000 mg qd x 21 during WBRT and for 21 days after). Non-CNS penetrating HER2 targeted therapy is permitted throughout the study, but patients not on trastuzumab, pertuzumab or any other breast cancer therapy at study entry are not permitted to begin this therapy while on protocol treatment, but may begin it 24 hours after completion of protocol treatment. Eligibility includes HER2+ breast cancer with at least one measurable, unirradiated parenchymal brain metastasis (≥10 mm on enhanced MRI). The two populations targeted for accrual include patients with 1) newly diagnosed, multiple brain metastases or 2) progressive brain metastases after stereotactic radiosurgery (SRS) or surgical resection of 1-3 metastases. Patients are stratified by breast-specific graded prognostic assessment; use of non-CNS penetrating HER2 targeted therapy; and prior SRS or surgical resection. The primary endpoint is complete response rate in the brain 12 weeks after WBRT. Secondary endpoints include objective response rate, lesion-specific response rate, CNS progression free survival, and overall survival. 29 of 143 planned patients have enrolled. Supported by NCI U10 grants CA21661 & CA37422. Clinical trial information: NCT01622868.

**TPS665^ General Poster Session (Board #122B), Mon, 8:00 AM-11:45 AM**

**Targeting HSP90 in breast cancer: Enchant-1 (NCT01677455) phase 2 proof of concept study of ganetespib in first-line treatment of women with metastatic breast cancer.** *Presenting Author: David A. Cameron, University of Edinburgh, Edinburgh, United Kingdom*

**Background:** Hsp90 is a chaperone protein required for the activation of several client proteins critical to breast cancer growth and aggressiveness, including HER2, HIF1-$\alpha$, EGFR, ER, PI3K, AKT, p53 and VEGFR. Ganetespib, a novel Hsp90 inhibitor, has preclinical activity in HER2+, ER+/PR+ and triple negative breast cancer (TNBC) models. Clinical trials showed a favorable safety profile with early signals of activity in patients (pts) with HER2+ disease, as well as TNBC. The ENCHANT-1 trial aims to further evaluate ganetespib single-agent activity in metastatic breast cancer (mBC) and identify biomarkers predictive of outcome. **Methods:** ENCHANT-1 is an international, Phase 2 study in 1st line mBC. Pts are assigned to one of the following 3 cohorts: Cohort A, HER2 amplified (n=35), Cohort B, TNBC (n=35), Cohort D, Hormone receptor (HR) positive (n=35). Pts with previously untreated mBC are eligible for treatment with ganetespib twice weekly on a 3 out of 4 wk schedule, for a total of up to 12 wks. HER2+ and HR+ pts must have received prior anti-HER2 therapy and endocrine therapy, respectively. At disease progression, pts will receive combination therapy of weekly ganetespib (150 mg/m$^2$) and weekly paclitaxel (80 mg/m$^2$) on a 3 out of 4 wk schedule. Primary endpoint: ORR assessed using RECIST1.1 criteria. Key secondary endpoints include metabolic response assessed by PET/CT at wk 3 utilizing modified EORTC criteria. Tumor genetic signature and proteomic profiling are performed on patient's tumors in an effort to develop biomarkers of response. At the time of submission, a total of 46 pts were enrolled; TNBC (n= 38) and HER2+ (n=8). Clinical trial information: NCT01677455.

**TPS666 General Poster Session (Board #123A), Mon, 8:00 AM-11:45 AM**

**Phase I/II trial of ruxolitinib in combination with trastuzumab in metastatic HER2-positive breast cancer.** *Presenting Author: Kevin Kalinsky, Columbia University Medical Center, New York, NY*

**Background:** Integrated analysis of whole genome RNAi screening with computationally reverse engineered interactome models identified IL6/JAK/STAT as a master regulator pathway essential for growth of ErbB2/HER2 positive breast cancer. Ruxolitinib (R), FDA-approved treatment for myelofibrosis, inhibits JAK1 and JAK2. The combination of R plus Trastuzumab (T) is synergistic in tumor growth inhibition in mouse xenografts of HER2 amplified breast cancer cell lines. These data provide a strong rationale for studying the efficacy of combination R and T in a clinical trial. **Methods:** A multi-center, open-label, phase I/II (P1/2) trial of R plus T in HER2+ metastatic breast cancer (MBC) who have progressed on T-based therapy. P1 will be an adaptive design with 10 patients, using the time-to-event continual reassessment method. The recommended P2 dose (RP2D) will be used in a non-randomized, open-label P2 trial with 30 evaluable patients. Given the anticipated limited overlapping toxicities, 33 patients are expected for the P1/2 (range: 33-42 pts). The duration of a treatment cycle will be 21 days. R will be taken orally twice a day continuously. The P1 dosing range will be 10-25 mg BID. T will be administered on Day 1 of each cycle at standard dosing. The primary endpoint is progression-free survival (PFS). Assuming a historical PFS of 8 weeks with single-agent agent HER2-targeted therapy in HER2+ MBC after progressing on T-based therapy, we predict that patients receiving the combination of R plus T will have a PFS of at least 13 weeks. With a 2-sided alpha of 0.05, we have 80% power to detect a difference with 30 pts. Objective Response Rate (ORR) will be assessed by imaging every 9 weeks. Blood samples will be obtained for biomarker analysis pre-treatment, on-treatment on cycle 2 day 1, and then at progression. Pre-treatment biopsies from archival tissue or new biopsy, prior to cycle 2 day 1, and upon progression of disease will be discussed with pts with accessible disease. Predictive markers include tumor pSTAT3 expression(tumor), tumor gene expression, and serum IL-6, IL-8, and C-reactive protein.

**TPS667 General Poster Session (Board #123B), Mon, 8:00 AM-11:45 AM**

**A phase II study with lead-in safety cohort of cabazitaxel (C) plus lapatinib (L) as therapy for HER2+ metastatic breast cancer (MBC) with intracranial metastases (mets).** *Presenting Author: Denise A. Yardley, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN*

**Background:** Although HER2-targeted therapy has improved outcomes in HER2+ breast cancer (BC) patients (pts), CNS mets continue to be a significant source of morbidity and mortality. Inability of drugs like trastuzumab to cross the blood-brain barrier (BBB) renders the CNS a sanctuary site for mets. L is a small molecule tyrosine kinase EGFR1/HER2 inhibitor that crosses the BBB and is active against CNS mets. C is a new taxane approved for prostate cancer that is also active in taxane-resistant metastatic breast cancer (MBC) and distinguishes itself by its ability to cross the BBB. The activity shown by C in taxane-resistant MBC as well as the CNS penetrance of both C and L make this an attractive combination for HER2+ MBC pts with CNS mets. **Methods:** This is an open-label, non-randomized, phase II study with a lead-in safety cohort (NCT01934894). Pts $\geq$ 18 yrs with HER2+ (by FISH or IHC 3+) MBC and CNS mets are eligible. Patients must have either at least 1 untreated measurable CNS lesion $\geq$ 5mm in longest dimension on MRI or at least 1 previously treated (by WBRT and or/SRS) CNS lesion with evidence of intra-cranial disease progression following WBRT or SRS. Pts must have had at least 1 prior HER2 therapy; first line MBC pts are eligible only if they progressed during or within 6 mos of adjuvant therapy. Prior treatment (tx) with C is not permitted. During the lead-in, cohorts of 3 pts will be treated with escalating doses of q 3 weeks (wks) C and daily L to determine the tolerability and optimal dose. Subsequent pts will be treated with the identified optimal dose combination. Each tx cycle is 3 wks and systemic and intra-cranial disease restaging will occur every 2 cycles for the first 8 cycles and then every 3 cycles until PD or unacceptable toxicity. The primary study objectives are to determine the safety and CNS ORR (ORR=CR+PR) of the combination of C and L in HER2+ MBC pts. Secondary objectives include evaluation of the clinical benefit rate ([CBR]CR+PR+SD $\geq$ 6 mos), 3- and 6-mo PFS rate for CNS mets, and response rate and CBR for extra-cranial mets. The trial is ongoing. Clinical trial information: NCT01934894.

**TPS668 General Poster Session (Board #124A), Mon, 8:00 AM-11:45 AM**

**A phase II study of eribulin mesylate in combination with trastuzumab and pertuzumab in patients (pts) with metastatic, human epidermal growth factor receptor 2-positive breast cancer.** *Presenting Author: Rachel A. Freedman, Dana-Farber Cancer Institute, Boston, MA*

**Background:** As a single agent, eribulin is associated with prolonged overall survival compared to treatment of physician's choice in pts with heavily pre-treated metastatic breast cancer (MBC). In the first-line setting, pertuzumab improves progression-free and overall survival when added to trastuzumab and chemotherapy; however there are limited data in the second line or beyond. This study will evaluate the efficacy of eribulin in combination with trastuzumab and pertuzumab in pts with HER2+ MBC who have progressed after at least 1 line of trastuzumab-based therapy. **Methods:** This is a single center, single-arm, phase II study. Prior to the start of the phase II study, a safety run-in was conducted and enrolled 6 patients. The established dose of eribulin was 1.4mg/m$^2$ on days 1, 8 of a 21 day cycle. Pts will undergo mandatory metastatic biopsies at baseline and optional biopsies at progression. Circulating tumor cells (CTC) will also be collected. The primary aim is objective response rate, RECIST 1.1. Secondary aims include: (a) Clinical benefit rate, progression free and overall survival (b) safety and tolerability, and (c) mechanisms of response and resistance to HER2-directed therapy, including MET and HER2 co-amplification in CTCs, comparisons of mutational profiles and copy number variation in primary vs. metastatic tumors and in pre-treatment vs. resistant tumors, and exploration of correlations between tumor characteristics and pts outcomes. This is a two-stage Simon Minimax design. In the first stage, 34 pts will be entered. If there are at least 9 responses, the study will continue to the second stage where another 22 pts will be entered. If there are at least 18 responses among the 56 pts, the regimen will be declared worthy of further study. There is a 90% chance of declaring the regimen worthy of further study if the true response rate is 40% and a 10% chance of declaring the regimen worthy of further study if the true response rate is 24% (90% power, 10% Type I error rate). The phase II portion began enrollment in January 2014. The estimated accrual rate is 3-5 patients/month. Clinical trial information: NCT01912963.

**TPS669 General Poster Session (Board #124B), Mon, 8:00 AM-11:45 AM**

**Phase Ib trial of trastuzumab emtansine (TE) in combination with lapatinib (L) plus nab-paclitaxel in metastatic HER2-neu overexpressed breast cancer patients: STELA trial.** *Presenting Author: Tejal Amar Patel, Houston Methodist Cancer Center, Houston, TX*

**Background:** Therapies directed at HER2 establish a successful treatment paradigm, but de novo and acquired resistance exist. Multiple large randomized clinical trials have demonstrated that dual HER2 targeted therapies are synergistic and result in improved efficacy. We hypothesize that dual targeted therapy with trastuzumab-emtansine and lapatinib will affect both PI3K and ERK1,2 MAPK pathways. This trial was designed to determine the maximum tolerated dose (MTD) and dose limiting toxicities (DLTs) of trastuzumab-emtansine (TE) and lapatinib (L), together with Nab paclitaxel (A). **Methods:** Eligible patients have stage IV HER2 positive breast cancer, normal LVEF, and Peripheral neuropathy $<$ grade 2. Phase IB planned for up to 9 patients in a standard 3+3 dose de-escalation design. Starting dose level of TE 3.6mg/kg, Lapatinib 750mg and Abraxane(A) 80 mg/m2. DLTs were defined as $\geq$ grade 3 non hematological toxicity attributed to the study drugs. Currently, our lead cohort has three patients with manageable toxicities and we will start expansion cohort soon. The secondary endpoint includes the description of DLT and other toxicities, document anti-tumor activity as assessed by RECIST 1:1 criteria as well as plasma pharmacokinetics and pharmacodynamics of TE in combination of L and A as well as potential biomarkers of response including HER2 expression levels, PTEN, PI3K and others.

**TPS670^ General Poster Session (Board #125A), Mon, 8:00 AM-11:45 AM**

**Phase 2 feasibility study of dose-dense doxorubicin and cyclophosphamide (AC) followed by eribulin mesylate with or without prophylactic growth factor (GF) for adjuvant treatment of early-stage breast cancer (EBC).** *Presenting Author: Tiffany A. Traina, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** In a previous phase 3 randomized, open-label trial, eribulin mesylate demonstrated antitumor activity and significantly improved overall survival (OS) in patients (pts) with heavily pretreated locally advanced or metastatic breast cancer. This trial will assess feasibility of eribulin as adjuvant therapy following dose-dense AC for pts with HER2-normal EBC. The study required prophylactic pegfilgrastim with each AC cycle; with eribulin, GF was used following a neutropenia episode (Cohort 1). Based on neutropenic events without prophylactic GF in Cohort 1 and to improve feasibility, Cohort 1 was closed and the study was amended to require prophylactic GF with eribulin (Cohort 2). **Methods:** Pts with confirmed HER2-normal, stage I-III invasive EBC and adequate bone marrow, liver, and renal function may enroll. Pts receive dose-dense AC (doxorubicin 60 mg/m$^2$ IV + cyclophosphamide 600 mg/m$^2$ IV) on Day 1 of a 14-day cycle x 4 cycles, followed by 4 cycles of eribulin mesylate (1.4 mg/m$^2$ IV) on Days 1 and 8 every 21 days. A protocol amendment established 2 cohorts. Cohort 1 includes the 55 pts enrolled, who received GF at physician's discretion following a neutropenic event during eribulin treatment (per original protocol). Cohort 2 will include 55 new pts who will receive prophylactic GF on Days 3, 4, 10, and 11 of each eribulin cycle. Feasibility is determined by the ability to complete the eribulin portion of the regimen with no dose delay/reduction due to eribulin-related AE. A feasibility target of 80% was set. Feasibility rates will be calculated separately in the 2 cohorts. Relative dose intensity of eribulin and toxicities will be summarized by cohort. Exploratory objectives include efficacy endpoints of 3-year disease-free survival and OS. Clinical trial information: NCT01328249.

**TPS671^ General Poster Session (Board #125B), Mon, 8:00 AM-11:45 AM**

**A single-arm, open-label, phase 2 study of MGAH22 (margetuximab) [fc-optimized chimeric anti-HER2 monoclonal antibody (mAb)] in patients with relapsed or refractory advanced breast cancer whose tumors express HER2 at the 2+ level by immunohistochemistry and lack evidence of HER2 gene amplification by FISH.** *Presenting Author: Mark D. Pegram, Stanford University, Stanford, CA*

**Background:** Response to trastuzumab (T)-based chemoimmunotherapy in metastatic breast cancer segregates according to expression of the Fcg receptor, CD16A, allotypes with patients homozygous for the 158V variant having superior outcomes to patients expressing the 158F variant (Musso-lino, J Clin Oncol 2008, 26:1789-1796). Margetuximab is a chimeric anti-HER2 mAb with antigen specificity and affinity similar to T's and an Fc domain engineered for increased binding to both allotypes of CD16A. Margetuximab exhibited enhanced ADCC against HER2-positive tumor cells, including T-resistant and HER2-low expressing cells. Margetuximab demonstrated increased activity against HER2-low expressing human tumor xenografts. In toxicology, margetuximab was well tolerated (15-150 mg/kg) (Nordstrom, Breast Cancer Research 2011, 13:R123). In Phase 1 testing involving 34 heavily pre-treated patients with HER2-positive neoplasms, margetuximab was well tolerated - MTD not exceeded at 6 mg/kg qw. The major safety findings were infusion reactions, which responded promptly and were largely ameliorated by pre-medications. Margetuximab produced clinical benefit at doses as low as 0.1 mg/kg qw and best responses of PR were noted in 5 patients [Burris, J Clin Oncol 2013, 31 (suppl; abstr 3004)]. **Methods:** The current study employs a Simon 2-stage design to determine if margetuximab has sufficient activity (>/= 5 responses in 41 evaluable) to justify further development in advanced breast cancer patients whose tumors exhibit 2+ HER2 expression and lack evidence of gene amplification by central testing. Time-delimited endpoints will be captured. Exploratory objectives include: PK/PD, FcgR allotype-response, and cytokine-AE relationships, ability of patient PBMCs to mediate ADCC, lymphocyte subsets and activation markers; circulating tumor cells and circulating nucleic acids. Three evaluable patients have participated thus far in the study. Clinical trial information: NCT01828021.

**TPS672 General Poster Session (Board #126A), Mon, 8:00 AM-11:45 AM**

**Phase I study of BYL719 and trastuzumab-MCC-DM1 (T-DM1) in HER2-positive metastatic breast cancer (MBC) patients with progression on trastuzumab and taxane-based therapy.** *Presenting Author: Sarika Jain, Northwestern University, Robert H. Lurie Comprehensive Cancer Center, Chicago, IL*

**Background:** Despite the considerable efficacy of trastuzumab, eventually all HER2-positive MBC patients develop resistance and disease progression. Upregulation of the PI3K pathway and oncogenic activating mutations of *PIK3CA* mutations have been implicated in trastuzumab resistance. Simultaneously targeting HER2 and PI3K pathways may allow for a more effective treatment option in this population. **Methods:** This investigator-initiated phase I, open-label, single arm study employs a dose-escalating 3+3 design to determine safety and efficacy of T-DM1 (an antibody-drug conjugate that incorporates the HER2-targeted properties of trastuzumab with a microtubule-inhibitory agent) in combination with an oral PI3K inhibitor BYL719 in patients with HER2-positive locally advanced or MBC whose disease has progressed on trastuzumab and taxane-based regimens in the metastatic setting or within 6 months in the adjuvant setting. Three to 6 patients are being enrolled in 3 successive cohorts with dose escalation of daily BYL719 (Cohort 1: 300 mg, Cohort 2: 350 mg, Cohort 3: 400 mg). T-DM1 is given at the FDA approved dose of 3.6 mg/kg every 3 weeks. At the maximum tolerated dose (MTD), an additional 10 patients will be enrolled to gain further knowledge on safety. The primary objectives are to determine safety, tolerability, feasibility, and MTD. The secondary objectives will evaluate pharmacokinetics of BYL719 and efficacy. Exploratory endpoints will examine alterations of the *PIK3CA* gene, decrease of PTEN expression and other Akt/mTOR downstream markers. This will be performed on archival metastatic tumor tissue or an optional baseline tissue biopsy and compared to optional tissue biopsy after 3 cycles of treatment. Clinical trial information: NCT02038010.

**1000^** **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**Association of increased tumor-infiltrating lymphocytes (TILs) with immunomodulatory (IM) triple-negative breast cancer (TNBC) subtype and response to neoadjuvant platinum-based therapy in PrECOG0105.** *Presenting Author: Shaveta Vinayak, University Hospitals Case Medical Center/ Case Western Reserve University School of Medicine, Cleveland, OH*

**Background:** Increased TILs are prognostic and predictive of therapy response in TNBC. PrECOG 0105, a neoadjuvant trial of carboplatin, gemcitabine and iniparib, enrolled 80 pts with clinical stage I-IIIA TN or BRCA1/2 mutation-associated BC. This correlative study was designed to assess the association of pre-therapy TILs in PrECOG 0105 with pathologic response, germline BRCA1/2 genotype & gene expression profiles, including TNBC subtypes. **Methods:** Evaluable pts had TNBC and completed at least 4 of 6 planned cycles of therapy. H and E stained tumor sections from pre-therapy biopsies were evaluated by a central pathologist for density of stromal (sTILs) and intratumoral (iTILs) lymphocytes. Pathologic response was assessed by the residual cancer burden (RCB) index. All patients had comprehensive BRCA1/2 genotyping. TNBC subtypes were derived from Affymetrix U133 plus 2.0 arrays. **Results:** 70 pts were included in this analysis. Median age = 47 yrs, median T size = 3.2 cm, 20% BRCA1/2 mutant & 48% node positive. 76% of tumors had at least 10% sTILs (range 10-80%) & 31% at least 10% iTILs (range 10-40%). Lymphocyte-predominant BC (LPBC), defined as ≥50% sTILs, was seen in 13%. pCR rate was highest (56%) in LPBC, though not significantly different from the non-LPBC group (38%, p=0.47). sTILs were significantly associated with TNBC subtype; median sTIL = 40% in the IM subtype, 15% in BL1, 20% in BL2, 10% in LAR, 0% in M, and 10% in MSL (p=0.0005). iTILs were also significantly associated with TNBC subtypes (p=0.0003); iTIL>0 for 10/14 (71%) in IM subtype, 1/7 (14%) in BL1, and 0 in others. Association with BRCA1/2 mutation status was not significant. In a multivariate model, each 10% increase in iTILs (OR 2.62 [95% CI 1.08 – 6.35]; p=0.03), but not sTILs (OR 1.17 [95% CI 0.87 – 1.58];p=0.28) was independently associated with pCR (RCB=0). However, both sTILs (p=0.02) and iTILs (p=0.009) were significantly associated with continuous RCB value. **Conclusions:** Both sTILs and iTILs are predictive of response to platinum-based neoadjuvant therapy and are significantly associated with TNBC subtypes, with the highest frequency in the IM subtype. Clinical trial information: NCT00813956.

**1001** **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**Expression of novel immunotherapeutic targets in triple-negative breast cancer.** *Presenting Author: Gargi Dan Basu, Caris Life Sciences, Phoenix, AZ*

**Background:** Triple negative breast cancer (TNBC) is an aggressive form of breast cancer that lacks expression of ER, PR and HER2. Targeted treatment options for TNBC are limited, and novel potential molecular targets need to be evaluated. This study examined biomarkers involved in immune evasion including PD-L1 and its association with other biological pathways as potential treatment options for TNBC patients. **Methods:** We analyzed 511 TNBC samples using a multiplatform approach including whole genome mRNA expression (HumanHT-12 v4 BeadChip Illumina Inc., San Diego, CA), protein expression (immunohistochemistry), gene copy number changes (in situ hybridization) and gene sequencing. PD-L1 IHC was performed on 22 samples. **Results:** Within the TNBC patient cohort, there were subsets with elevated mRNA expression of immune markers including PD-L1, CTLA4, IDO1 and B7-H3. Cancer cell-specific over-expression of PD-L1 protein was present in 50% of TNBC tumors. Androgen receptor (AR) was over-expressed in 17% of the TNBC cohort and AR-negative TNBC patients were more likely to express PD-L1 (p =.05), CTLA-4 (p =.001), and IDO1 (p = 2.8e-05). Spearman correlation test showed a positive correlation of PD-L1 with CTLA-4 (0.52), IDO1 (0.48), PIK3CA (0.39), and PTEN (0.11). Differential expression analysis between high and low PD-L1 expressing tumors identified 144 genes. Pathway analysis of the 144 genes indicated significant enrichment of DNA repair genes. Consistent with these findings, PD-L1 expression was negatively associated with BRCA1 expression (p=0.001) and positively correlated with HUS1 and FANCA expression (p=8e-13). **Conclusions:** The expression of immune regulatory targets in the TNBC population suggests that immune- targeted therapies may be effective in subsets of TNBC. This is particularly true for patients with AR-negative TNBCs who may benefit from PD-L1 and CTLA-4 targeted therapies. The positive correlation of PIK3CA and PD-L1 may indicate that combination therapy targeting both pathways may be beneficial. In addition, the inverse correlation of BRCA1 with PD-L1 suggests a potential role for platinum-based therapy in combination with anti-PD-L1. Further prospective validation of these findings is ongoing.

**1002** **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**RNA-sequencing of residual triple-negative breast cancers after neoadjuvant chemotherapy compared to matched pretreatment biopsies from the Hoosier Oncology Group trial BRE09-146.** *Presenting Author: Milan Radovich, Indiana University School of Medicine, Indianapolis, IN*

**Background:** Residual disease after neoadjuvant chemotherapy in triple-negative breast cancer (TNBC) patients entails a high risk of disease recurrence. We investigated the transcriptomes of residual disease versus matched pre-treatment biopsies from a post-neoadjuvant TNBC trial to understand mechanisms of treatment resistance and to identify potential therapeutic interventions. **Methods:** RNA-sequencing of 44 TNBC tumors with high tumor cellularity (22 matched pre- and post-neoadjuvant specimens) was performed using the Ion Proton Next Generation Sequencer. RNA-seq data was aligned to the genome followed by expression and network analysis. **Results:** Statistical analysis resulted in 1,022 genes differentially expressed between matched pre- and post-neoadjuvant chemotherapy samples (p<0.01). Pathway analysis identified significant down-regulation of immune genes ($P<1x10^{-5}$), which correlated with histologic observation of the depletion of lymphocytic cells in the post-neoadjuvant specimens (p=0.018). To identify novel therapeutic modalities, we employed upstream regulator analysis which predicts transcriptional regulators that are activated based on differentially expressed genes. Our top activated regulator in post-neoadjuvant specimens is MAPK1 ($p=1.13x10^{-4}$), a key component of the MEK/ERK pathway. To further identify novel markers of residual disease, we analyzed for precursor microRNAs. Differential expression identified significant up-regulation of our top hit, miR-663B ($P=2x10^{-4}$, Fold-Change=3.4) in residual disease tumors. **Conclusions:** RNA-seq and histology identified significant depletion of immune cells in residual disease, which has been previously associated with poor prognosis in breast cancer. We further identified a highly activated MAPK1 network, suggesting the potential use of MEK/ERK inhibitors in clinical trials for this population. Lastly, we identified a novel clinical biomarker, miR-663B, which is known to mediate in vitro TNBC resistance to doxorubicin, cyclophosphamide, and docetaxel.

**1005** **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**Pathological complete response (pCR) rates after carboplatin-containing neoadjuvant chemotherapy in patients with germline *BRCA* (g*BRCA*) mutation and triple-negative breast cancer (TNBC): Results from GeparSixto.** *Presenting Author: Gunter Von Minckwitz, German Breast Group/ University Frankfurt, Neu-Isenburg, Frankfurt, Germany*

**Background:** We previously showed in participants with TNBC of the neoadjuvant phase II GeparSixto study (NCT01426880) that the addition of carboplatin can substantially improve the pCR rates from 36.9% with weekly paclitaxel/non-pegylated liposomal doxorubicin (PM) to 53.2% with PM plus weekly carboplatin (AUC2) (PMCb) (von Minckwitz et al, Proc ASCO 2013). We aimed to assess how far this benefit is correlated with g*BRCA* mutation or with a family history for breast or ovarian cancer. **Methods:** Full blood samples with sufficient amount of DNA were available in 295 (94%) out of 315 participants of GeparSixto with TNBC. We searched for gBRCA mutations by MLPA and Fluidigm screening for recurrent pathogenic *BRCA1/2* alterations. In combination, both methods enable us to detect approximately 60% of all expected mutation carriers. Participants with so far undetected mutations are currently under investigation by employing next generation sequencing (NGS) techniques to detect additional pathogenic germline alterations in *BRCA1/2* or other breast cancer predisposing genes. **Results:** At total of 38 mutation carriers (35 BRCA 1, 3 BRCA 2) have so far been identified (31 by central testing and 7 known results from local testing). Additional 78 patients have a known family breast cancer history. 179 patients have so far neither a mutation nor a family history. Overall pCR (ypT0 ypN0) rate increased from 40.2% in patients with no identified risk, to 44.9% in patients with family history only, to 57.9% for patients with g*BRCA* mutation. Adding carboplatin to PM increased the pCR rate by 14% (odds ratio, OR 1.79) in patients without increased risk, by 20% (OR 2.29) in patients with family history only, and by 25% (OR 2.75) for patients with g*BRCA* mutation. **Conclusions:** g*BRCA* mutation and family history are predictors for higher pCR rates after neoadjuvant anthracycline/taxane based chemotherapy in TNBC. Additive effect of carboplatin is most prominent in patients with g*BRCA* mutation. Updated results after complete g*BRCA* mutation analysis will be presented at the meeting. Clinical trial information: NCT 01426880.

**1006 Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**Adoption of hypofractionated radiotherapy (HyRT) for ductal carcinoma in situ (DCIS): A SEER-Medicare study.** *Presenting Author: Aaron David Falchook, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

**Background**: Multiple randomized trials published in 2008-2010 demonstrated that for women with early-stage invasive breast cancer receiving adjuvant radiotherapy (RT) after a lumpectomy, shorter course (hypofractionated) RT is non-inferior to conventionally fractionated RT (CRT). However, the role of HyRT has not been evaluated prospectively for DCIS. The purpose of this study is to examine adoption of HyRT in DCIS. **Methods**: DCIS patients diagnosed from 2004-9 in the Surveillance Epidemiology and End Results (SEER)-Medicare database were included, with Medicare claims data available through 2010. A total of 4,459 women received lumpectomy followed by external beam RT. The number of RT treatments received by each patient was determined from Medicare claims, and grouped into: accelerated partial breast irradiation (APBI, ≤12 treatments), HyRT (13-24), or CRT (≥25). Proportions of women receiving different fractionation schemes were described per year of RT, and in subgroups based on patient and disease factors. Multivariate logistic regression was used to examine factors associated with receipt of HyRT (vs. CRT). **Results**: Utilization of HyRT increased from ~4% to 8.8% in 2008 and 11.2% in 2009-10, with corresponding decreases in CRT (Table); external beam APBI utilization was low and stable during the study years. HyRT was more common in older women. On multivariate analysis, older age (OR 1.8 for age 80+ vs. age 66-69, p=.002), later RT years (OR 2.8 for 2009-10 vs. 2005, p<.001) and higher regional education were significantly associated with increased utilization of HyRT, while higher grade was associated with less HyRT (OR .8 for Grade 3 vs. Grade 1, p=.06). Race, marital status, comorbidity, and laterality (left vs. right) were not significantly associated with HyRT. **Conclusions**: Utilization of HyRT increased after 2008 coinciding with trial publications for invasive cancer, even though the efficacy of this treatment for DCIS has not been clearly established.

| | APBI (%) | HyRT (%) | CRT (%) | Univariate p |
|---|---|---|---|---|
| **RT year** | | | | |
| **2004** | 2.7 | 4.3 | 93.0 | <.001 |
| **2005** | 2.0 | 3.8 | 94.3 | |
| **2006** | 4.0 | 4.0 | 92.0 | |
| **2007** | 3.3 | 4.2 | 92.5 | |
| **2008** | 2.6 | 8.8 | 88.6 | |
| **2009-10** | 2.5 | 11.2 | 86.3 | |
| **Age (yrs)** | | | | |
| **66-69** | 3.6 | 4.7 | 91.7 | <.001 |
| **70-75** | 2.1 | 6.1 | 91.7 | |
| **76-79** | 2.4 | 8.6 | 89.1 | |
| **80+** | 3.1 | 8.1 | 88.8 | |

**1007 Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**Trends in treatment patterns and outcomes for DCIS patients: A SEER population-based analysis.** *Presenting Author: Mathias Worni, Department of Surgery, Division of Surgical Oncology, Duke University Medical Center, Durham, NC*

**Background:** Ductal carcinoma in situ (DCIS) is considered a precursor lesion of invasive ductal cancer of the breast, and current therapy aims to prevent progression to invasive disease. However, the impact of contemporary treatment options on breast-cancer survival remains poorly defined. **Methods:** The Surveillance, Epidemiology, and End Results (SEER) registry was queried from 1991-2010 for patients with DCIS. Age-adjusted incidence rates were calculated, and trends in treatment patterns were analysed using the Cochran Armitage trend test. Survival analyses were performed with inverse probability weight (IPW) adjusted competing risk analysis for cancer specific (CSS) and cox proportional hazard regression analysis for overall survival (OS). **Results:** 121,080 DCIS patients were included in the analysis. Age-adjusted incidence rates increased from 23.2/100,000 females in 1992 to 36.4/100,000 in 2010. Highest incidence rate was found among females age 60-79 years in 2010 (83.8/100,000). Most patients were treated with lumpectomy and radiation therapy (breast conservation therapy, BCT) (43.0%), followed by lumpectomy alone (26.5%), unilateral (23.8%) or bilateral mastectomy (4.5%), and no treatment (2.3%). Rates of unilateral mastectomy significantly decreased from 1991 (44.9%) to 2010 (19.3%), as did lumpectomy alone (29.8% to 22.3%), while increased rates of BCT (24.2% to 46.8%) and bilateral mastectomy (0% to 8.5%) were observed (p for trend <0.001 for all comparisons). On IPW adjusted analysis, CSS was superior to BCT compared to mastectomy (hazard ratio HR: 1.16, 95% CI: 1.00-1.33, p=0.048) while no difference was found for lumpectomy alone over mastectomy (HR: 0.90, CI: 0.77-1.05, p=0.17). Compared to mastectomy, patients undergoing BCT demonstrated improved OS (HR: 1.17, CI: 1.12-1.22, p<0.001) while patients undergoing lumpectomy alone demonstrated worse OS (HR: 0.79, CI: 0.76-0.83, p<0.001). **Conclusions:** The incidence of DCIS in females continues to rise, particularly in women 60-79. There has been a significant shift in treatment patterns towards BCT and bilateral mastectomy. Using IPW adjustment, CSS and OS were best for patients undergoing BCT compared to all other treatment groups.

**1008 Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**Predicting local recurrence using PAM50 in postmenopausal endocrine responsive breast cancer patients.** *Presenting Author: Florian Fitzal, Medical University of Vienna, Vienna, Austria*

**Background:** Breast conservation may lead to increased local recurrence rates compared with mastectomy. We investigated whether genetic expression profiling using PAM50 may predict local recurrence free survival (LRFS) independent of established factors **Methods:** Tumor blocks from patients randomized within the ABCSG 8 trial comparing tamoxifen with tamoxifen followed by anastrozole after surgery were analysed by the PAM50 assay (Prosigna, NanoString Technologies). Postmenopausal patients with endocrine responsive her2neu negative breast cancer were included. The risk of recurrence (ROR) score as well as biological subtypes (Luminal A and B) were correlated with LRFS. **Results:** 1,308 patients were analysed. 59% were <65 years, 79% had breast conservation (BCT) followed by radiotherapy and 32% were nodal positive. 72% had a low ROR score, 68% were luminal A while 28% had a luminal B cancer. After a median follow up of 11 years, 34 locoregional recurrences were observed, defined as ipsilateral in breast or axillary recurrences. Cox regression model showed that the ROR score significantly predicted LRFS independent from nodal status, tumor size and age (p<0.0081). Patients with high risk (ROR ≥ 57) had a LRFS of 94.4% while low risk patients (ROR < 57) showed a 98.4% 10-year LRFS (p=0.0005). Biological subtype analysis did also show a significant difference in LRFS comparing luminal A (98.1% 10-year LRFS) and luminal B cancer (95.9% 10-year LRFS, p=0.022). Multivariate analyses demonstrated that BCT did not significantly influence LRFS and was oncologically "safe" even in high risk patients (p=0.174). **Conclusions:** The PAM50 ROR score and intrinsic subtype are independent predictors for LRFS. Mastectomy seems unlikely to imporve LRFS in high risk patients. Clinical trial information: NCT00291759.

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| **Age category** | ≥65 years vs <65 years | 0.873 (0.426 1.789) | p=0.7101 |
| **Tumor stage** | T2/T3 vs T1 | 0.911 (0.419 1.980) | p=0.8139 |
| **Node status** | N1 vs N0 | 1.325 (0.635 2.764) | p=0.4540 |
| **Type of surgery** | Mastectomy vs BCT | 0.468 (0.161 1.357) | p=0.1620 |
| **Treatment** | Tam/Ana vs Tam alone | 0.685 (0.346 1.358) | p=0.2784 |
| **Risk group** | High vs low | 3.621 (1.822 7.199) | p=0.0002 |

**1009 Poster Highlights Session (Board #1), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**German Adjuvant Intergroup Node Positive (GAIN) study: A phase III trial to compare IDD-ETC versus EC-TX in patients with node-positive primary breast cancer—Final efficacy analysis.** *Presenting Author: Volker Jochen Moebus, Klinikum Frankfurt Hoechst, Frankfurt, Germany*

**Background:** Intense dose-dense (idd) epirubicin (E), paclitaxel (T), cyclophosphamide (C) (idd-ETC) resulted in a superior disease-free (DFS) and overall survival (OS) compared to conventionally dosed EC-T (q3w) chemotherapy in primary breast cancer patients (pts) with ≥4 involved lymph nodes (LN) (Möbus et al, JCO 2010). The GAIN trial had a 2x2 factorial design for investigating two different dose-dense chemotherapy regimens as well as the use of adjuvant ibandronate treatment. Ibandronate results have been reported previously (von Minckwitz et al, JCO 2013). Here we report the final results of the chemotherapy comparison. **Methods:** Pts were randomized to idd-ETC (E:150 mg/m², T:225 mg/m², C:2500-2000 mg/m², i.v. day 1, q15 for 3 cycles each) or EC followed by T plus capecitabine (X) (EC-TX) (E: 112.5 mg/m² + C: 600 mg/m², i.v. day 1, q 15 for 4 cycles followed by T: 67.5 mg/m² i.v. day 1, q 8 for 10 weeks + X: 2000 mg/m² p.o. day 1-14, q 22 for 4 cycles). After recruitment of 1,500 patients the dose of C was reduced to 2000 mg/m². Pts aged 18-65 years with involved axillary LN were eligible. 3000 pts with 801 events were needed to show an increase of 5-year DFS (primary endpoint) from 75% to 79% for patients receiving EC→TX after 8 years total study duration. **Results:** 3,023 patients were randomized from 06/2004 until 08/2008. Median age was 50 years; pN1 (37.7%), pN2 (35.4%), pN3 (26.9%); 46.6% were grade 3. With a median follow up of 74 months we observed 644 DFS events (327 with idd-ETC; 317 with EC-TX) (HR 0.94; log-rank p=0.47). 5-year DFS was 80% with idd-ETC and 82% with EC-TX. No different treatment effect was observed in predefined subgroups. 383 pts have died (205 with idd-ETC; 178 with EC-TX) (HR 0.85; log-rank p=0.10). Hematological toxicity was higher in the idd-ETC arm, but 3 and 11 treatment related deaths occurred in the idd-ETC and EC-TX arm, respectively. **Conclusions:** Both dose-dense regimens achieved a highly favorable 5-year DFS superior to our assumptions mainly based on the preceeding idd-ETC study. The addition of a fourth cytostatic drug (here capecitabine) did not improve efficacy of dose-dense therapy, but led to higher toxicity. Clinical trial information: NCT 001 968 72.

**1010 Poster Highlights Session (Board #2), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Adjuvant gemcitabine for high-risk breast cancer (BC) patients: Final survival results of the randomized phase III SUCCESS-A study.** *Presenting Author: Wolfgang Janni, Department of Gynecology and Obstetrics, University of Ulm, Ulm, Germany*

**Background:** Gemcitabine (G) has shown to have a relevant single agent efficacy and to improve chemotherapy response to taxanes in advanced BC patients. Aim of this study was to evaluate the effect of G on disease free survival (DFS) in high risk adjuvant BC patients. **Methods:** This is a phase III, randomized, open label trial of FEC-Doc vs. FEC-DocG (3 cycles of FEC (500/100/500 mg/m$^2$) followed by 3 cycles of docetaxel (Doc; 100mg/mg$^2$) every three weeks (q3w) *vs.* 3 cycles of FEC followed by 3 cycles of G (1,000 mg/m$^2$ d1,8) and Doc (75 mg/m$^2$) q3w). Key inclusion criteria: stage N1 or T2–T4 or grade 3 or age ≤ 35 or hormone receptor (ER/PR) negative. Key exclusion criteria: locally recurrent/metastatic disease; prior systemic therapy or radiotherapy for current BC. Strata for randomization: nodal, ER/PR, menopausal and HER2 status and grading. Primary and secondary study aims were DFS and overall survival (OS). Survival rates were estimated by the Kaplan-Meier method. Cox regression models were fitted to estimate unadjusted hazard ratios (HRs). Further exploratory analyses investigated treatment differences within patient subgroups. **Results:** 3,754 patients were randomized to FEC-Doc (n=1898) or FEC-DocG (n=1856). Median observation time was 5.3 ys with 456 (238 vs. 218; FEC-Doc vs. FEC-DocG) events for DFS and 269 (140 vs. 129) events for OS. Mean age was 53.5 ys and 58.7% were ≥ T2, 66.1% were nodal positive, 29.3% ER and PR negative and 23.5% HER2 positive. 5-year DFS rate was 0.87 for both randomization arms and 5-year OS was 0.93 for both arms. HRs for DFS and OS were 0.93 (95%CI: 0.78-1.12; p=0.46) and 0.94 (95%CI: 0.74-1.19; p=0.60). Further analyses, accounting for age, body mass index, tumour stage, grading, lymph node status, tumor type, hormone receptor and HER2neu status, did not generate any hypothesis for subgroup-specific efficacy. **Conclusions:** AdjuvantGemcitabine does not improve the efficacy of FEC-Doc chemotherapy for high risk breast cancer patients. With regard to the risk-benefit ratio, we do not recommend adjuvant Gemcitabine for the adjuvant treatment of high risk breast cancer patients. Future analyses will report on circulating tumor cells, serum markers and pharmacogenomics. Clinical trial information: 2005-000490-21.

**1011 Poster Highlights Session (Board #3), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Phase III study of vinflunine plus gemcitabine versus paclitaxel plus gemcitabine in the first-line treatment of anthracycline pretreated advanced breast cancer.** *Presenting Author: Antonio Llombart, Arnau de Vilanova Hospital, Valencia, Spain*

**Background:** Paclitaxel (PTX), plus gemcitabine (GEM) showed survival advantage over paclitaxel in advanced breast cancer (ABC) patients who relapsed after adjuvant anthracycline. This was associated with increased toxicity, especially neurotoxicity. Vinflunine (VFL) plus GEM was confronted to PTX- GEM in this clinical setting. **Methods:** This open-label phase 3 study enrolled 1004 Her-2 negative ABC patients who had received neo- or adjuvant anthracycline more than 12 months prior to study entry. Patients were randomised to VFL 320 mg/m$^2$ on day 1 plus GEM 1000 mg/m$^2$ on days 1 and 8 every 3 weeks (N = 503) or PTX 175 mg/m$^2$ on day 1 plus GEM 1250 mg/m$^2$ on days 1 and 8 every 3 weeks (N = 501). Randomisation was stratified by PS, (neo)adjuvant taxane, disease measurability and visceral lesions. The primary objective was to test the non-inferiority of VFL-GEM vs PTX-GEM in terms of PFS assessed by a blinded independent review committee in the intent-to-treat population assuming a median PFS of 5.2 months in the control arm and a 20% margin. **Results:** Patients had a median age of 54 years [range: 22-79]; visceral disease for 84.5% and 33.7% had received adjuvant taxane. The median number of cycles was 6 in both arms. Median PFS was 8 months for VFL plus GEM and 8.4 months for PTX plus GEM (HR 1.05, 95%CI: 0.91-1.20, P = 0.54). The upper limit of HR 95% CI being below 1.25, non-inferiority was demonstrated. Response rates were 11.3% for VFL plus GEM and 14.6% for PTX plus GEM (P = 0.10). Median OS were similar: 18.9 months for VFL plus GEM and 19.1 months for PTX plus GEM. Rate of toxic deaths was 1.6% for VFL plus GEM and 0.4% for PTX plus GEM. Grade 3 - 4 neutropenia was common in both arms (74.3% of patients for VFL plus GEM vs 60% for PTX plus GEM), but rarely complicated (< 5% of febrile neutropenia or neutropenic infection in both arms). Grade 3 - 4 constipation was more frequent for VFL plus GEM (7.3% vs 0.2%) and grade 3 - 4 peripheral sensory neuropathy for PTX plus GEM (6.7% vs 0.8%) as well as alopecia (63.5% vs 40.4%). **Conclusions:** VFL plus GEM can be seen as an alternative option to PTX plus GEM considering its similar efficacy and its reduced neurotoxicity.

**1012 Poster Highlights Session (Board #4), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Randomized phase III study of taxane versus TS-1 as first-line treatment for metastatic breast cancer (SELECT BC).** *Presenting Author: Fumikata Hara, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan*

**Background:** Taxanes have been standard regimen as the first-line chemotherapy for metastatic breast cancer. However side effects such as neutropenia, peripheral neuropathy, edema or alopecia are important concerns. Phase II clinical trials of TS-1, an oral 5-fluorouracil derivatives (tegafur, 5-chloro-2,4-dihydropyrimidine, and potassium oxonate), have shown good clinical efficacy and tolerability. Therefore, we conducted a phase III open-label randomized controlled trial (SELECT BC) to verify the non-inferiority of TS-1 in overall survival (OS) to taxane as first-line chemotherapy for metastatic breast cancer. **Methods:** Six hundred eighteen patients receiving first-line chemotherapy for metastatic breast cancer were randomly assigned to either taxane group (n=309) or TS-1 group (n=309). In the taxane group, patients received docetaxel 60-75mg/m2 q3w, paclitaxel 80-100mg/m2 q1w or paclitaxel 175 mg/m2 q3w at the discretion of the treating physician. In the TS-1 group, patients received TS-1 40–60 mg twice daily based on the patient's body surface area for 28 days on, 14-day off. The primary endpoint was OS, with a non-inferiority margin of 1.333. Secondary endpoints were time to treatment failure (TTF), progression free survival, adverse events, health-related quality of life and cost-effectiveness. **Results:** After a median follow-up of 34.6 months, median OS was 37.2 months in the taxane group and 35.0 months in the TS-1 group (hazard ratio 1.05, 95% CI 0.86–1.27, p=0.015). Median TTF was 8.9 months in the taxane group and 8.0 months in the TS-1 group (hazard ratio 1.10, 95% CI 0.93–1.30, p=0.022). The incidences of diarrhea, mucositis and nausea were higher with TS-1, whereas the incidences of edema, peripheral neuropathy, arthralgia, allergic reaction, fatigue and alopecia were higher with taxanes. Utilities measured by EQ5D during treatment were similar (repeated measures ANOVA p=0.66) between two groups. **Conclusions:** SELECT BC clearly demonstrated that OS with TS-1 is not inferior to that with taxane in patients receiving first-line chemotherapy for metastatic breast cancer. TS-1 monotherapy would be one of the standard regimens for this patient population. Clinical trial information: C000000416.

**1013^ Poster Highlights Session (Board #5), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Vinflunine plus capecitabine for advanced breast cancer previously treated with or resistant to anthracycline and resistant to taxane: A phase III study versus capecitabine.** *Presenting Author: Matti S. Aapro, Clinique de Genolier, Genolier, Switzerland*

**Background:** Vinflunine (VFL) is a microtubule inhibitor with single-agent activity in advanced breast cancer (ABC) pretreated with anthracycline (A) and resistant to taxane (T). Synergy with capecitabine (CAPE) was demonstrated in this setting. This phase 3 study compared VFL plus CAPE with CAPE alone in A pretreated or resistant and T-resistant ABC. **Methods:** Open-label, multicenter study, in which 770 ABC patients with up to 3 prior chemotherapy (CT) regimens were randomised to VFL 280 mg/m$^2$ on day 1 plus CAPE 1,650 mg/m$^2$ (N = 384) or to CAPE alone at 2,500 mg/m$^2$ (N = 386) on days 1 to 14 every 3 weeks. Randomization was stratified by resistance to anthracycline, performance status, disease measurability and number of prior lines of CT for ABC. Primary endpoint was PFS assessed by a blinded independent review committee (IRC) in the ITT population. **Results:** Patients had a median age of 54 years (range: 27 - 81); metastatic disease for 97%; anthracycline resistance for 63%; received study treatment as first (20%), second (48%) or > third (32%) CT line for ABC. The median number of cycles was 6 for VFL plus CAPE and 5 for CAPE. VFL plus CAPE prolonged PFS compared to CAPE (median 5.6 vs 4.3 months, HR = 0.84, 95% CI 0.71-0.99, P = 0.0426). The response rate assessed by IRC was numerically greater for VFL plus CAPE than for CAPE (22.9% vs 17.9%, P = 0.1030); the disease control rate was statistically superior with the combination (57.3% vs 47.9%, P = 0.0089). Median OS analysed after 643 deaths (83.5%) was 13.9 months for VFL plus CAPE and 11.7 months for CAPE (HR = 0.98, 95% CI = 0.83-1.15, P = 0.7657). The most frequent grade 3-4 drug-related adverse events were neutropenia for VFL plus CAPE (11% of patients vs 3.7% for CAPE) and hand-foot syndrome for CAPE (18% vs 3.7% for VFL plus CAPE). Quality of life global health status score (QLQ-C30) was preserved for VFL plus CAPE while there was a deterioration for CAPE from week 12. **Conclusions:** VFL plus CAPE demonstrates a statistically significant improvement in PFS and a clinically meaningful improvement in OS compared to CAPE alone. VFL plus CAPE is a new well tolerated option for A/T pretreated/resistant patients with ABC. Clinical trial information: NCT01095003.

**1014 Poster Highlights Session (Board #6), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**ARTemis: A randomised trial of bevacizumab with neoadjuvant chemotherapy (NACT) for patients with HER2-negative early breast cancer—Primary endpoint, pathological complete response (pCR).** *Presenting Author: Helena Margaret Earl, Department of Oncology, NIHR Cambridge Biomedical Research Centre and Cambridge Breast Cancer Research Unit, University of Cambridge, Cambridge, United Kingdom*

**Background:** Bevacizumab (bev) has been used with NACT in breast cancer trials. Geparquinto reported benefit for bev in triple negative (neg) patients (pts) (pCR 36.4% v 27.8% p=0.02), as did CALGB 40603 (pCR 52% v 44%, p=0.057), although the NSABP-B40 study showed benefit in ER-positive (pos) pts (pCR 23.3% v 15.2%, p=0.008). **Methods:** ARTemis is a randomised phase 3 trial adding bev to NACT (docetaxel (D)-FEC). Pts with HER2-neg invasive breast cancer were eligible. Stratification was by age, ER status (neg: weak pos: strong pos), tumour size (T2:T3/4), clinical involvement of axillary nodes and inflammatory/locally advanced disease. Pts were randomised (1:1) to bev+D-FEC or D-FEC. The primary endpoint was pCR, defined as no residual invasive cancer in the breast or axillary lymph nodes after NACT. 800 pts were required to detect 10% differences in pCR rates, at the 5% (2-sided) level of significance with 85% power. **Results:** 800 pts were randomised from 66 UK centres (May'09 to Jan'13). 68% were <50 years old, 19% had inflammatory and/or locally advanced disease, 79% of tumours <50mm, 52% clinical node pos and 33% ER-neg. A 2-reader independent review of pathology reports was carried out. Significantly more pts on bev+D-FEC had a pCR (22% (18-27%) vs 17% (13-21%) with D-FEC; p=0.03 [adjusted for stratification factors]). pCR rates differed significantly across ER groups (neg 38%, weak pos 39%, strong pos 7%; p<0.0001). Treatment effect of bev remained significant after adjustment for ER (p=0.03). **Conclusions:** ARTemis showed a significant improvement in pCR with the addition of bev to D-FEC. ER-neg and ER-weak pos / HER2-neg breast cancer pts appeared to benefit most from bev, whilst pCR rates in ER-strong pos pts were lower and did not appear to show improvement from the addition of bev. Our results are similar to those reported in Geparquinto and CALGB 40603. Clinical trial information: 68502941.

| Factor | D-FEC pCR (95% CI) | bev+D-FEC pCR (95% CI) | p* |
|---|---|---|---|
| **ER-neg (Allred 0-2) (n=253)** | 32% (24-41) | 44% (36-54) | 0.03 |
| **ER-weak pos (Allred 3-5) (n=67)** | 26% (13-44) | 52% (34-69) | |
| **ER-strong pos (Allred 6-8) (n=461)** | 7% (4-11) | 6% (3-10) | |

* p-value across treatment groups, after adjusting for ER.

**1015 Poster Highlights Session (Board #7), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Resource utilization in patients with breast cancer treated with generic versus branded docetaxel.** *Presenting Author: Stephen E. Jones, US Oncology Research, LLC, McKesson Specialty Health, The Woodlands, TX*

**Background:** This study was to assess health resource utilization in patients with breast cancer (BC) treated with generic (available in US since 2011) vs branded docetaxel. **Methods:** A retrospective inception cohort was analyzed in Clinformatics DataMart healthcare claims database. Patients (female, aged ≥18 years) were identified between Apr 1, 2011 and Jun 30, 2012 if they had an ICD-9:174 for BC, initiated docetaxel, and had 6-month continuous insurance coverage pre (baseline) and post (follow-up) docetaxel initiation. The 50 most frequent claims for clinical diagnoses, procedures and prescriptions were evaluated between generic and branded docetaxel along with health resource utilization and expenditures, with hierarchical mixed effects model adjustment for potential confounding. **Results:** 1,955 patients diagnosed with BC were identified, of which a total of 98 generic and 262 branded docetaxel users were included in the final analysis. For the majority of patients, the source of docetaxel was not apparent. Patient characteristics were comparable at baseline between study groups. During follow-up, the generic cohort showed a higher rate of claims for neutropenia (67.3% vs 48.9%; p<0.01) and malaise and fatigue (22.4% vs 13.7%; p<0.05) among medical diagnoses. The branded was higher in nausea and vomiting (43.5% vs 29.6%; p=0.02). The rate of neutropenia remained higher in generic vs branded (73.9% vs 52.8%; p<0.01) even after adjusting for history of neutropenia and baseline use of G-CSF and fosaprepitant. The generic cohort had more fosaprepitant use at follow up (54.1% vs 30.2%; p<0.01). The higher odds of neutropenia was observed in generic with (OR=2.49; p= 0.03) or without (OR=1.41; p= 0.31) fosaprepitant use during follow up. Mean outpatient costs excluding docetaxel drug costs were higher in the generic ($59,177 vs $50,243; p<0.01), and remained significantly higher ($54,282 vs $46,698; p=0.03) after adjustment for baseline healthcare costs, inpatient admissions, etc. **Conclusions:** Use of generic vs branded docetaxel in BC was associated with about 40% more medical claims for neutropenia and higher ambulatory care costs at 6 months follow up. Further research is needed to confirm these findings.

**1016 Poster Highlights Session (Board #8), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Outcome of male patients and black patients enrolled in S0221, an intergroup chemotherapy study.** *Presenting Author: G. Thomas Budd, Cleveland Clinic, Cleveland, OH*

**Background:** Assessment of the outcome of minority populations within clinical trials may give insight into important tumor and host factors relevant to those populations. **Methods:** S0221 is a phase III trial of various dose-schedules of doxorubicin, cyclophosphamide and paclitaxel. S0221 allowed enrollment of male patients, and was sufficiently large to enroll significant numbers of minority populations. Here, we report the outcome of male patients and patients of black race. **Results:** Among 3236 total patients entered on S0221, 23 (0.7%) were male and 378 (12%) were of self-reported black race. Non-significant differences in male/female patients were seen in HER2 positivity (9%/19%), hormone receptor (HR) positivity (100%/66%), lymph node negativity (17%/26%), and treatment completion rate (70%/74%), but men were more often ≥60 years old (48%/21%, p=0.006). Males had significantly worse disease-free survival (DFS), with 5-year DFS 49%/82%; HR=3.16, Log-Rank p=0.0003. Male sex remained an adverse factor for DFS in a Cox model adjusted for treatment, HER2 status, HR status, age, and nodal status (HR=3.53, p<0.001). Black/non-black patients did not significantly differ in HER2 positivity (22%/18%). Black patients were less likely to be HR-positive (51%/69%, p<0.001), to have >4 nodes involved (29%/36%, p=0.02), to be age >60 years (15%/22%, p=0.008) and to complete treatment (63%/75%, p<0.001). Black patients had worse DFS, with 5-year DFS of 75%/82%; HR=1.55, Log-Rank p=0.0001. Black race remained an adverse factor for DFS in a Cox model adjusted for treatment, HR status, HER2, age, and nodal status (HR=1.48, p=0.001) or when analysis was limited to those completing therapy, adjusted for treatment (HR=1.48, p=0.01). **Conclusions:** Male patients enrolled in S0221 had a markedly worse DFS, a finding which persisted after adjustment for tumor characteristics. Black patients in S0221 treated with 3rd generation regimens had a worse DFS than non-black patients. These results are similar to those for post-menopausal HR+ black patients treated with a 2nd generation regimen (5FU/doxorubicin/cyclophosphamide) in S8814, suggesting a generalized phenomenon which is not improved with contemporary regimens. Clinical trial information: NCT00070564.

**1017 Poster Highlights Session (Board #9), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Randomized phase II study of weekly paclitaxel with or without carboplatin followed by cyclophosphamide/epirubicin/5-fluorouracil as neoadjuvant chemotherapy for stage II/IIIA HER2-negative breast cancer.** *Presenting Author: Kenji Tamura, Department of Breast and Medical Oncology, National Cancer Center Hospital, Tokyo, Japan*

**Background:** Platinum based neoadjuvant chemotherapy (NAC) in HER2-negative breast cancer (HNBC) has a potential to improve pathological complete response (pCR). We evaluated the efficacy and safety of carboplatin (CBDCA) and weekly paclitaxel (wPTX) followed by cyclophosphamide, epirubicin, and 5-fluorouracil (CEF) as NAC for HNBC. **Methods:** Patients with stage II-IIIA HNBC were randomly assigned to preoperatively CP-CEF arm (4 cycles of CBDCA [area under the curve 5 mg/mL. min, day 1, every 3 weeks] and wPTX [80 mg/m$^2$, day 1, 8, 15, every 3 weeks] followed by 4 cycles of CEF [500/100/500 mg/m$^2$, day 1, every 3 weeks], or P-CEF arm (4 cycles of wPTX followed by 4 cycles of CEF). The primary endpoint was pCR rate. Breast tumor tissues by preoperative biopsy were tested for Ki-67, EGFR, Cytokeratin (CK) 5/6, BRCA1, vimentin, ERCC1 and ZEB1 by immunohistochemistry (IHC). **Results:** Of 181 eligible patients, 89 were randomly assigned to the CP-CEF arm and 92 to the P-CEF arm. Two patients in each arm refused to receive NAC. Overall 88 patients in the CP-CEF arm and 91 patients in the P-CEF arm were assessable for efficacy and safety. The primary endpoint; pCR rate in the CP-CEF arm was significantly higher than that in the P-CEF arm (31.8 vs. 17.6%, p = 0.01). Among patients with triple-negative breast cancer (TNBC), the pCR rate in the CP-CEF arm was significantly higher than that in the P-CEF arm (61.2% vs. 26.3%, p = 0.003). Grade 3-4 neutropenia was observed in the CP-CEF arm more frequently than in the P-CEF arm (65.9% vs. 38.5%). We gained 46 tumor samples from the registered patients (26%). EGFR, CK5/6 and BRCA1 expressions were significantly frequent in TNBC. EGFR expression was significantly associated with pCR rate in the 46 patients (45.0% vs. 11.5%, P=0.010), and in patients in CP-CEF arm (63.8% vs. 18.2%, P=0.040), but not in patients in P-CEF arm. **Conclusions:** Adding CBDCA to neoadjuvant wPTX followed by CEF for HNBC statistical significantly improved pCR rate with a favorable safety profile. EGFR expression by IHC is a potent predictive biomarker of response to the CP-CEF regimen as NAC. Clinical trial information: 000003355.

**1019^ Poster Highlights Session (Board #11), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Cisplatin with or without rucaparib after preoperative chemotherapy in patients with triple-negative breast cancer (TNBC): Hoosier Oncology Group BRE09-146.** *Presenting Author: Sujaata Dwadasi, Indiana University, Indianapolis, IN*

**Background:** Patients (pts) with triple negative breast cancer (TNBC) who have residual disease after preoperative chemotherapy have a high risk of recurrence. No standard systemic therapy has proven benefit. Data suggest that some pts with TNBC and/or BRCA mutations may be sensitive to DNA-damaging chemotherapy and PARP inhibition. **Methods:** Eligible pts with TNBC or known BRCA mutations who had residual lymph node involvement or > 2 cm invasive disease after anthracycline or taxane neoadjuvant therapy were assigned 1:1 to postoperative cisplatin (C: 75 mg/m$^2$D1 q3 wks x 4) +/- rucaparib (R: 24-30 mg IV D1,2,3 q3 wks x 4 followed by rucaparib 30 mg IV or 100 mg orally wkly for 24 wks). BROCA analysis (U. Washington) was used to identify deleterious germline mutations. The primary objective is 2-yr DFS. **Results:** 128 pts were enrolled. Median age was 48; 6 pts were known at study entry to have BRCA1 or BRCA2 mutations. Neoadjuvant therapy included anthracyclines in 57% and taxanes in 91%. Median tumor size at surgery was 1.9 cm (0-11.5) with median LN involvement 1 (0-38); Toxicity required C dose reduction (20% of pts) or delay (~43% of pts) in both arms. R dose reduction was uncommon (6%). Overall 73% of pts completed planned C. With a median follow-up of 9 months, 1-yr DFS was similar (~76%) in both treatment groups. BROCA identified deleterious mutations in 22/101 (22%) pts (8 BRCA 1, 12 BRCA 2, 2 BRIP1). 1-yr DFS in the 22 pts with mutations was ~85% compared to 79% without mutations. Whole transcriptome sequencing of paired pre vs. post preoperative chemotherapysamples will be reported separately (Radovich et al, ASCO 2014). **Conclusions:** The addition of low dose rucaparib (current phase II monotherapy dose 600 mg orally twice daily) did not impact the toxicity of cisplatin or improve 1-yr DFS. Comparison to predicted DFS based on residual cancer burden (RCB) is planned to investigate potential benefit from cisplatin. Genetic testing was underutilized in this high risk population with only 30% of BRCA1 and BRCA2 mutations identified as part of routine clinical care. Clinical trial information: NCT01074970.

**1020 Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**Identification of biomarkers to predict response to single-agent platinum chemotherapy in metastatic triple-negative breast cancer (mTNBC): Correlative studies from TBCRC009.** *Presenting Author: Steven J. Isakoff, Massachusetts General Hospital Cancer Center, Boston, MA*

**Background**: TNBC has a poor prognosis compared to other BC subtypes and lacks therapeutic targets. We previously reported TBCRC009, a multicenter single-arm phase II study of single-agent platinum in 86 patients (pts) with mTNBC: the objective response rate (ORR) was 25.6% overall and 54.5% vs. 19.7% (p=0.02) in BRCA1/2 carriers (n=11) vs. noncarriers (n=66). Six long-term responders remain disease free at median follow up of ~4 yrs. Here we explored biomarkers of response to platinum in TBCRC009. **Methods**: Participants had measurable disease, available archival tumor, ≤1 prior metastatic therapy, and no prior platinum chemotherapy. By physician choice, pts received cisplatin 75mg/m$^2$or carboplatin AUC=6 every 21 days. Co-primary endpoints were: 1) ORR and 2) p63/p73 expression by RT-PCR as a predictor of response. Tumor-based exploratory studies included: gene expression (GE) profiling, PIK3CA and p53 mutational status, and homologous recombination deficiency (HRD) assays correlating with BRCA1/2 inactivation. **Results**: Among 61 pts evaluable for co-primary endpoint 2, 28 (46%) had the pre-specified p63/p73 ratio ≥2, which did not predict response to platinum (ORR 18% vs. 27% in p63/p73 ≥2 vs. <2, respectively, p=0.54). 36/54 pts (67%) had p53 mutations, and 9/55 pts (16%) had PIK3CA mutations, but neither correlated with ORR. PAM50 analysis from global GE profiling identified 60% (32/53) basal-like tumors, which showed a higher ORR that did not reach significance (28% vs. 10% in basal vs non-basal, p=0.17). All HRD assays, including Loss Of Heterozygosity (LOH), Telomere Allelic Imbalance (TAI), and Large-scale State Transition (LST), scored higher in BRCA1/2 carriers than non-carriers, and in responders than nonresponders among the small group of 22 non-carriers with available tissue (HRD-LST responders vs. nonresponders, p=0.0016). **Conclusions**: Single-agent platinum is effective in both *BRCA1/2*-associated and sporadic mTNBC. Although established biomarkers failed to predict responses, HRD assays may identify sporadic TNBC tumors that are BRCA1/2-like and responsive to platinum chemotherapy. Clinical trial information: NCT00483223.

**1021 Poster Highlights Session (Board #14), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Phase II trial of single agent PARP inhibitor ABT-888 (veliparib [vel]) followed by postprogression therapy of vel with carboplatin (carb) in patients (pts) with stage BRCA-associated metastatic breast cancer (MBC): California Cancer Consortium trial PHII-96.** *Presenting Author: George Somlo, City of Hope, Duarte, CA*

**Background:** We reported on a phase I trial showing 54% confirmed partial response (PR) with carb + vel. Here we describe single agent vel activity and, upon progression, the feasibility and efficacy of continuing administration of vel + carb. **Methods:** Pts with MBC with BRCA1 or 2 mutations, an ECOG performance status of ≤ 2, and measurable disease were eligible. Prior PARP-inhibitor therapy (Rx) , platinum Rx for MBC, or central nervous system metastasis requiring Rx were exclusions. Vel was administered orally at 400 mg twice daily (BID). Cohorts (BRCA1 and BRCA2) were studied independently: 2 or more PRs to vel out of 10 pts were required to proceed to accrual of 22 pts per cohort. Upon progression, carb (AUC of 5) iv every 21 days, and vel 150 mg orally BID were prescribed. **Results:** Between 10/2012 and 1/2014, 44 pts enrolled (41 treated) carrying BRCA1 (N=21) or BRCA2 (N=20) mutations. The median age was 43-years (range; 28-68); 50% of pts had hormone receptor + BC. Pts received 3 prior chemo-regimens (0-7). The current PR rate in pts with at least 4 cycles of follow-up is 2/12 (17%) for BRCA1 and 3/13 (23%) for BRCA2. Three pts withdrew from treatment during the first cycle of vel due to grade 2 seizure (1), grade 3 thrombocytopenia (PLT [1]), grade 2 PLT and neutropenia (1). Time to failure (TTF) on vel is 2.0 months (0-10.5+), and 5.1 months (0.9-10.3+) for the two cohorts (BRCA1, BRCA2, respectively). Twenty pts are still on vel (8 BRCA1, 12 BRCA2). Of the 10 pts to proceed to vel + carb so far, 1 PR in a BRCA1 pt was observed. **Conclusions:** Vel is active when given at 400 mg BID daily. Further trials are indicated to assess its benefit whether in combination or as a single agent in both BRCA1 and BRCA2-associated BC. Clinical trial information: NCT01149083.

**1022 Poster Highlights Session (Board #15), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Efficacy of neoadjuvant carboplatin/docetaxel chemotherapy in sporadic and *BRCA*-associated triple-negative breast cancer (TNBC).** *Presenting Author: Priyanka Sharma, University of Kansas Medical Center, Westwood, KS*

**Background:** Recent studies demonstrate that addition of carboplatin to anthracycline/taxane chemotherapy improves pathological complete response (pCR) in TNBC. In vitro data exhibits synergy between platinum compunds and taxanes in TNBC. Efficacy of anthracycline-devoid neoadjuvant platinum/taxane combination in sporadic and *BRCA*-associated TNBC is not well known. Aim: To evaluate the efficacy of neoadjuvant Carboplatin/Docetaxel in sporadic and *BRCA*-associated TNBC utilizing clinical and *BRCA* mutation data from a prospective registry. **Methods:** 205 patients with stage I (T>1cm) II or III TNBC were enrolled in a prospective multisite registry between 2011-2013, out of which 42 patients received neoadjuvant chemotherapy regimen of Carboplatin AUC 6 + Docetaxel 75 mg/m$^2$every 21 D (4-6 cycles). Following neoadjuvant therapy, all patients underwent breast surgery. pCR (no evidence of invasive tumor in the breast and axilla) and Residual Cancer Burden(RCB) was evaluated. RCB of 0 or1 was designated as near pCR (pCRn). All patients underwent comprehensive BRACAnalysis (Myriad). **Results:** For the 42 eligible patients, median age was 51 years (range 27-80), 19%: African-American and 57%: postmenopausal. Median tumor size was 3 cm and 33% LN positive. 90% of patients received 6 and 10% received 4 cycles of chemotherapy. The overall pCR and pCRn rates were 62% and 74%, respectively. 33% (14/42) of patients carried deleterious *BRCA* mutation (11 *BRCA1*, 3 *BRCA2*). For *BRCA*mutation carriers, both pCR and pCRn rates were 86%(12/14). For sporadic TNBC (N=28), pCR and pCRn rates were 50% and 68%, respectively. Tumor size, LN status, age and number of cycles of chemotherapy did not impact pCR rate. pCR was higher in BRCA mutation carriers compared to sporadic TNBC (p=0.04). **Conclusions:** We report very encouraging near pathologic response in both sporadic (68%) and *BRCA*-associated (86%)TNBC with a neoadjuvant platinum/taxane chemotherapy regimen. This Carboplatin/Docetaxel combination yielded pCR rates similar to observed rates with A/C plus Carboplatin however, is devoid of potential cardiac and secondary leukemia side effects and should be explored further in randomized studies.

**1023 Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**Does pathologic complete response predict for outcome in *BRCA* mutation carriers with triple-negative breast cancer?** *Presenting Author: Shani Paluch-Shimon, The Breast Cancer Unit, Institute of Oncology, Sheba Medical Center, Modiin, Israel*

**Background:** Pathological complete response (pCR) has been demonstrated to serve as a surrogate for outcome in patients receiving neo-adjuvant systemic therapy (NAT) for triple negative (TN) breast cancer (BC). To date no data has been published to establish if this is also true for *BRCA1/BRCA2*mutation carriers with TNBC. **Methods:** From a prospective NAT database of 588 BC cases, 80 TN cases who had undergone BRCA genotyping were identified. All received dose-dense chemotherapy with an anthracycline and a taxane. pCR was defined as absence of invasive disease in breast and lymph nodes. A logistic regression model was fitted to examine association between BRCA1/2 status and pCR. Survival outcomes were evaluated using Kaplan-Meier method, differences between study groups calculated by log-rank test. **Results:** 37 BRCA1/2 carriers and 43 non-carriers were identified. The BRCA1/2 carriers had superior pCR compare with non-carriers (61% vs. 39% , p=0.007). Despite the higher pCR, there was no difference in Relapse Free Survival (RFS) between the BRCA1/2 carriers and non-carriers. Amongst those that achieved pCR there was superior RFS for non-carriers compared with BRCA1/2 carriers (Log-rank p=0.043). Conversely, amongst those that did not achieve a pCR, the RFS was superior amongst BRCA1/2 carriers (Log-rank p=0.024). No difference in RFS were noted amongst BRCA1/2 carriers with or without pCR (Log-rank p=0.712), while in the non-carrier group RFS was superior for those achieving pCR compared with those not displaying a pCR (Log-rank p<0.0001). Preliminary translational data demonstrate ALDH1 over-expression in the BRCA1/2 carriers pre-treatment biopsies but not in the non-carriers. **Conclusions:** BRCA1/2 associated TN BC differs to non-BRCA TN in chemo-sensitivity as demonstrated by superior pCR, We demonstrate here for the first time that pCR in BRCA1/2 carriers, is not a surrogate for RFS as opposed to pCR in non-BRCA TN BC. The chemo-sensitivity in BRCA associated TNBC may increase the mutational spectrum in these tumors due to predisposition to DNA breaks, resulting in selection of more aggressive, metastases prone clones, in addition, BRCA1/2 tumors may be enriched for breast cancer stem cells.

**1024 Poster Highlights Session (Board #17), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Triple-negative breast cancer subtypes and pathologic complete-response rate to neoadjuvant chemotherapy: Results from the GEICAM/2006-2003 study.** *Presenting Author: Angela Santonja, Instituto de Investigacion Biomedica de Malaga, IBIMA, Malaga, Spain*

**Background:** Triple negative breast cancer (TNBC) is a heterogeneous disease with distinct molecular subtypes that differentially respond to chemotherapy (CHT) and targeted agents. In a recent study, Lehmann et al. (JCI 2011) identified six molecular subtypes of TNBC, characterized on the basis of gene ontologies and differential gene expression. However, their clinical utility remains unclear. We aimed to explore the clinical relevance of these molecular subtypes in TNBC determining differences in response to neoadjuvant chemotherapy in a randomized phase II trial, the GEICAM/2006-03. **Methods:** The GEICAM/ 2006-03 study evaluated a regimen of anthracyclines and taxanes +/- carboplatin in the neoadjuvant treatment of patients (pts) with TNBC (Alba, BCRT 2012). We determined TNBC molecular subtypes in FFPE pre-treatment tumor biopsies from pts recruited in this study. Gene expression profile was determined using HTA 2.0 arrays (Illumina). Subtypes were identified with the online tool TNBC type (http://cbc.mc.vanderbilt.edu/tnbc). Finally, we explored the association of the Lehmann subtypes with the pathological complete response (pCR) in breast and axilla (Miller and Payne criteria) using Fisher's exact test. **Results:** From the 94 enrolled pts, we processed 46 pre-treatment tumor samples in a central lab and isolated high-quality RNA for microarray analysis in 39 (42%); 7 samples are still pending to be analyzed. Tumors were classified as follows: 4 BL1, 2 BL2, 8 IM, 5 LAR, 3 M, 3 ML with 7 pts that couldn't be assigned to any subtype and were not included in this analysis. Three (75%) of the BL1 subtype pts achieved a pCR (p-value=0.075). In contrast, IM and LAR achieved the lowest pCR rates (12% and 20%, respectively). In the carboplatin-treated patients, 100% of BL1 patients showed pCR (p-value=0.033) in contrast with none of the IM and LAR pts. **Conclusions:** Our preliminary findings suggest that TNBC subtypes can predict tumor response to neoadjuvant CHT, supporting their potential clinical utility in diagnosis, treatment selection and drug development, bringing TNBC pts a step closer to personalized medicine.

**1025 Poster Highlights Session (Board #18), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**In silico analysis of a multifactorial consensus signature (ConSig) for predicting response to anthracycline (A)-based neoadjuvant chemotherapy (NAC) in triple-negative breast cancer (TNBC) patients (pts).** *Presenting Author: Natalie Heather Turner, Sandro Pitigliani Medical Oncology Department, Hospital of Prato, Istituto Toscano Tumori, Prato, Italy*

**Background**: There are no validated predictive biomarkers for A response. While A is effective therapy in some, many breast cancer pts do not benefit. Due to the complex processes required for A-induced cytotoxicity, a prospectively defined multifactorial consig may improve prediction of A sensitivity in TNBC pts, a group whose only standard systemic treatment option is chemotherapy. **Methods**: ConSigs were constructed using various combinations of components (genes/gene signatures) that were based on five steps required for A function: drug penetration, nuclear topoisomerase IIα (topoIIα) protein location, increased topoIIα mRNA expression, induction of apoptosis, and immune response. The performance of each ConSig to predict pathologic complete response (pCR) in TNBC pts treated with A without taxane (T) NAC was assessed by in silico analyses of publicly available gene expression data. Correlation between ConSig expression and pCR was evaluated using ROC analyses. To assess specificity for A, ConSigs were reassessed in pts receiving A + T NAC. **Results**: 147 TNBC pts treated with A without T and with gene expression data derived using the same platform (Affymetrix HG-U133) were identified, 28 with pCR. Single components significantly correlated with pCR were drug penetration measured by HIF1α signature (AUC 0.64, p=0.005), nuclear topoIIα location measured by LAPT4MB mRNA (AUC 0.61, p=0.03) and immune response measured by STAT1 signature (AUC 0.65, p=0.03). The most powerful combination for prediction of A response was *ConSig1*, which included these three components plus topoIIα mRNA. It performed better than single components, showing higher correlation with pCR (AUC 0.71, $p=5.3x10^{-6}$), high negative value (NPV) value and high odds ratio (OR) for no pCR (see Table). *ConSig1* was A-specific with no correlation with response seen in pts treated with A + T. **Conclusions**: With further validation, *ConSig1* may allow improved selection of TNBC pts for A treatment.

| | Performance of *ConSig1* | | |
|---|---|---|---|
| **Cohort** | **NPV (95% CI)** | **OR** | **P value** |
| **A (n=147)** | 93% (84%-98%) | 5.53 | 0.001 |
| **A + T (n=301)** | 67% (58%-75%) | 1.04 | 0.85 |

**1026 Poster Highlights Session (Board #19), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Biomarker panel (TheraPrint) analyzed as a predictor of response to neoadjuvant chemotherapy in patients with locally advanced breast cancer.** *Presenting Author: Peter D. Beitsch, Dallas Surgical Group, Dallas, TX*

**Background:** TheraPrint for breast cancer patients is a novel genomic assay that provides information on clinically relevant markers for likely sensitivity and resistance to therapies. The aim of the current study was to correlate chemosensitivity in a neo-adjuvant trial to TheraPrint results. **Methods:** The mRNA level of 55 genes was measured in formalin fixed paraffin embedded (FFPE) tumor samples submitted from 42 institutes in the US as part of the NBRST trial and compared to a large reference population (TheraPrint). The prospective Neo-adjuvant Breast Registry Symphony Trial (NBRST) study includes informed consenting women aged 18–90 with histologically proven breast cancer, who are scheduled to start neo-adjuvant chemo- or endocrine therapy. The correlation of chemosensitivity to TheraPrint results is measured by pathologic Complete Response (pCR) defined as the absence of invasive carcinoma in both the breast and axilla at microscopic examination of the resected specimen, regardless of the presence of carcinoma in-situ. Differentially expressed genes were identified by Analysis of Variance (ANOVA) with corrected p-value (FDR) <0.05. **Results:** 204 Patients (T1-4 N0-3) received neo-adjuvant chemotherapy and had definitive surgery. The overall pCR rate was 24%. Listed in the table are those genes that were significantly differentially expressed between patients with a pCR versus those with residual disease (p>0.05, Fold change >1.5). **Conclusions:** This study has identified 13 genes with statistically significant correlation between expression and response to neo-adjuvant chemotherapy indicating that TheraPrint can give indication for response prediction to chemotherapy. Clinical trial information: NCT014799101.

| TheraPrint gene | Corrected p-value | Fold change | Up or downregulated in patients with pCR |
|---|---|---|---|
| **Ki67** | 0.01473 | 1.2 | ↑ |
| **LYN** | 0.01803 | 1.2 | ↑ |
| **EPHA2** | 0.05190 | 1.3 | ↑ |
| **MET** | 0.05190 | 1.3 | ↑ |
| **ESR1** | <0.00000 | -3.3 | ↓ |
| **ESR2** | 0.00077 | -1.6 | ↓ |
| **PgR** | 0.00002 | -2.4 | ↓ |
| **CCND1** | 0.00077 | -1.6 | ↓ |
| **IGF1R** | 0.00387 | -1.7 | ↓ |
| **HER3** | 0.01473 | -1.6 | ↓ |
| **HER4** | 0.00412 | -1.7 | ↓ |
| **BCL2** | 0.01797 | -1.6 | ↓ |
| **AR** | 0.01803 | -1.5 | ↓ |

This list of genes is significantly associated with PTEN activation, ER inhibition and estrogen-related signaling pathways (Ingenuity Pathway Analysis).

**1027 Poster Highlights Session (Board #20), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Quantitative assessment of CD3, CD8, and CD20 in tumor-infiltrating lymphocytes and predictive value for response to neoadjuvant chemotherapy in breast cancer.** *Presenting Author: Jason R. Brown, Yale School of Medicine, New Haven, CT*

**Background:** Tumor infiltrating lymphocytes (TILs) have been associated with response to neoadjuvant therapy. However, typical analysis of TILs is subjective, semi-quantitative and does not differentiate between subpopulations. Here we describe a quantitative objective method for measurement of TIL subsets, including CD3, 8, and 20 and assess their predictive value for therapeutic response. **Methods:** We used a quantitative immunofluorescence (QIF) assay to measure stromal expression of CD3 (T cell), CD8 (cytotoxic T cell), and CD20 (B cell) on a single slide using AQUA technology. This method was validated by comparison to flow cytometry on fresh tonsil tissue. To assess the predictive value of TIL markers, we used a cohort of 105 consecutive (2002 - 2010) invasive breast cancer patients that received neoadjuvant therapy and had obtainable pre-surgical biopsy tissue. Percentage TIL infiltrate in the tumor stroma was estimated by two pathologists on H and E stained slides of these biopsies. Images from each specimen were collected in 4 to 118 fields of view, and we obtained summary scores for CD3, 8 and 20. **Results:** In tonsil specimens, lymphocyte percentage and proportions of CD3, CD8, and CD20 positive lymphocytes were similar between flow cytometry and QIF. Pathologist TIL count (H&E TIL) was predictive of pCR ($p = 0.0171$, OR: 6.458) despite fair interobserver reproducibility ($k = 0.390$). AQUA scores for CD3 ($p = 0.0193$, OR: 1.960), CD8 ($p = 0.0225$, OR: 2.021), and CD20 ($p = 0.0033$, OR: 1.868) within the stroma predicted pathologic complete response (pCR) in univariate analysis. CD3 ($p = 0.0369$, OR: 2.504) and CD20 ($p = 0.0062$, OR: 3.371) also predicted pCR in multivariate analysis with age, size, nuclear grade, nodal status, and ER, PR, and HER2 status, but only CD20 was significant with Ki-67 AQUA score added ($p = 0.0341$, OR: 5.532). CD20 was more sensitive and specific than CD3 and CD8 and equivalent to H&E TILs (AUC: 0.690 vs. 0.655 vs. 0.629 vs. 0.692). **Conclusions:** We have developed and validated an objective quantitative assay for measuring TILs. H&E TIL, CD3, CD8, and CD20 all predict therapeutic response, and CD20 is independently predictive including all variables.

**1028 Poster Highlights Session (Board #21), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Next-generation sequencing (NGS) in relapsed/refractory triple-negative breast cancer (TNBC) in Israel.** *Presenting Author: Noa Ben-Baruch, Department of Oncology, Kaplan Medical Center, Rehovot, Israel*

**Background:** Relapsed/metastatic TNBC is an aggressive form of the disease that typically responds initially to chemotherapy, but eventually progresses in the majority of patients (pts). We hypothesized that a comprehensive NGS assay (FoundationOne) could identify novel therapy targets not routinely interrogated in TNBC pts. **Methods:** Hybridization capture of 3,769 exons from 236 cancer-related genes and 47 introns of 19 genes commonly rearranged in cancer was applied to ≥ 50 ng of DNA extracted from 26 TNBC FFPE specimens and sequenced to high, uniform coverage. Genomic alterations (GA) including base substitutions, small indels, copy number alterations, and select gene fusions, were characterized and reported for each pt sample. Actionable GAs were defined as those identifying anti-cancer targeted therapies on the market or in registered clinical trials. **Results:** The 26 TNBC pts had a mean age of 49.6 yrs (range, 28-74). All 26 tumors were ER-/PR-/HER2- on routine slide-based testing. Samples used for NGS originated from breast (42%), lymph nodes and axilla (23%), chest wall and muscle (12%), skin (8%) and serous effusion (4%). All 26 cases harbored ≥1 GA, with a total of 113 GAs and a mean of 4.35 GAs per tumor. The most frequent currently unactionable GAs were *TP53* (21, 81%) and *MYC* (8, 31%). Twenty two cases (85%) harbored ≥1 actionable GA; mean, 2.73 actionable GAs per tumor. The most common actionable GAs were *PIK3CA* (7, 27%), *MCL1* (4,15%), *PTEN* (3,12%), *BRCA1* (3,12%), and *BRCA2* (2,8%). One pt (4%) had *ALK* amplification. Activating *ERBB2* point mutations not detectable by IHC/FISH, potentially targetable with anti-HER2 therapies were identified in 2 pts; *EGFR* amplifications, potentially treatable with anti-EGFR TKI were identified in 2 pts (1 pt had both of these GAs). One pt with *ERBB2*mutation received neratinib monotherapy and one pt with EGFR amplification received capecitabine plus cetuximab; both had partial response lasting 8+ months. **Conclusions:** For TNBC, comprehensive genomic profiling can identify a significant number of actionable GAs not currently tested for in routine practice. Results point to the potential of MTOR, anti-HER2, and anti-EGFR targeted therapies for a significant subset of pts.

**1029 Poster Highlights Session (Board #22), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Genomic and protein alterations in 126 triple-negative (TN) metaplastic breast cancers.** *Presenting Author: Sherri Z. Millis, Caris Life Sciences, Phoenix, AZ*

**Background:** Metaplastic breast cancer (MpBC) is a rare subtype (less than 1% of all breast cancers), is generally ER, PR and HER2-negative (TN), demonstrates a claudin-low gene expression profile, and is poorly responsive to cytotoxic therapy. Little is known about the genomic alterations (GA) in MpBC nor about overexpressed proteins that may be amenable to targeted therapy. **Methods:** Of 2000 TN breast cancers (TNBC) referred to Caris Life Sciences since 2009 from 50 states and 59 countries, 126 cases were TN MpBCs based on local pathology evaluation. Specific testing was performed per physician request and included sequencing (Sanger or next generation sequencing [NGS]), protein expression (immunohistochemistry [IHC]), and/or gene amplification (CISH or FISH). **Results:** The Table shows the percent gene mutations, amplifications, and IHC findings for biomarkers that were different between TNBC and MpBCs, as a percentage of total patients tested. **Conclusions:** Comparison of the genomic and protein expression profiles highlights some differences between the two cancers-.Multiplatform profiling shows that most MpBCs have gene alterations in the PI3K pathway. The low RRM1 expression rate suggests possible gemcitabine effectiveness. Other potential therapeutically targetable gene alterations are present at low incidence in this large series of MpBCs.

| | Gene mutation | | | | | ISH *EGFR* | | IHC | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Gene** | TP53 | PIK3CA | PTEN | HRAS | cMET | cMET | EGFR | PTEN loss | AR | cMET | RRM1 | TOPO1 |
| **TNBC** | 60 | 14 | 3 | 0 | 0 | 0 | 22 | 31 | 17 | 13 | 34 | 70 |
| **Metaplastic** | 33 | 45 | 7 | 10 | 7 | 7 | 17 | 41 | 9 | 4 | 28 | 50 |

**1030 Poster Highlights Session (Board #23), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Uncovering the dynamic relationship between Ki-67 and mitotic indices in breast cancer.** *Presenting Author: Guilherme Cantuaria, Northside Hospital Cancer Institute, Atlanta, GA*

**Background:** The generation of intra-tumor genetic diversity and metastatic clones relies on frequent passage of cancer cells through error-prone mitoses. Thus, we postulate that low-grade tumors undergo rapid mitotic turnover to drive clonal heterogeneity, while high-grade tumors focus more on their "metastasis program". Metastasis, a multistep dissemination process, requires a phenotypic switch from cell proliferation to migration, since these are mutually-exclusive cellular states. Currently in breast cancer diagnostic practice, the percentage of Ki67-positive "proliferating" cells (Ki67 Index, KI) and number of mitoses/10 high power fields (mitotic index, MI) are evaluated independently and their relationship remains elusive. Here we propose a "mitotic frequency" index (MFI) that rationally combines KI and MI, and provides better prediction of metastatic risk. **Methods:** The relationship between KI and MI was analyzed retrospectively in pathology reports from 2,500 breast carcinoma cases at Northside Hospital, Atlanta, GA. In addition, for an accurate assessment of mitotic frequencies, we measured MI and KI on the same scale and within the same field by optimizing a four-color immunofluorescence staining protocol to co-immunostain paraffin-embedded breast tumor tissues (n=100) for α-tubulin, Ki67, and phospho-histone H3 (p-H3, to identify all mitotic phases including prophase), and stain DNA with Hoechst. **Results:** Retrospective data analysis of 2500 cases show that although KI and MI increased with tumor grade, the grade-wise increase in MI was much slower; consequently, the Ki67-adjusted mitotic scores decreased across grades. In effect, we found a striking grade-wise decrease in frequency of mitoses amongst Ki67-positive cells. Immunofluorescence data (n=100) found lower mitotic frequencies in grade-matched patients with metastatic disease as compared to those without metastasis. **Conclusions:** The KI-MI relationship varies dynamically during tumor progression, with a lower MFI representing a shift in the tumor's agenda from mitosis to metastasis, which indicates elevated metastatic risk. The integrated MFI may thus reveal a new layer of valuable risk-predictive information.

### 1031 Poster Highlights Session (Board #24), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM

**Evaluation of the adjuvant radiation treatment-effect heterogeneity using genomic signature for locoregional relapse and long-term outcome.** *Presenting Author: Maggie Chon U Cheang, Clinical Trials and Statistics Unit at the The Institute of Cancer Research, Surrey, United Kingdom*

**Background:** In a retrospective analysis of two similar randomized radiation therapy (RT) trials (i.e. British Columbia (BC) and DBCG 82b), we reported significant survival benefits for post-mastectomy RT in Luminal A. Here we examined the predictive value of additional genomic profiles in the BC trial for loco-regional recurrences (LRR) and breast cancer survival (BCSS) in node-positive, pre-menopausal breast cancer patients randomized to adjuvant chemoradiation or chemotherapy. **Methods:** In the BC trial, 318 patients received adjuvant cyclophosphamide, methotrexate, fluorouracil and were randomized to with or without postmastectomy RT. From 145 formalin fixed paraffin embedded tissues available, expression profiles of 66 genes were done with the Nanostring nCounter. Treatment effects on LRR and BCSS events were examined by subpopulation treatment effect pattern plots. The research-based PAM50 proliferation score, Risk of Recurrence score (ROR-T and ROR-PT), and genes related to basal-like (ie. 13-genes VEGF-signature (*VEGF*-s), *RAD17, RAD50* and *RB1)* were calculated. **Results:** Overall, patients in the RT arm (n= 69) were significantly associated with better LRR and BCSS than the non-RT-treated arm (n = 76). No significant treatment-effect heterogeneity was detected for *VEGF*-s, *RAD17* and *RAD50* score. Patients with lower *RB1* mRNA level, and higher proliferation score, had better LRR survival when they received RT (Table). The patterns of treatment efficacy on LRR and BCSS were the most significant for the varying levels of risk score (ROR-T, -PT), particularly for patients with higher scores (Table) who showed the poorest prognosis, but whom may still benefit from adjuvant RT. **Conclusions:** *RB1*, proliferation score and ROR-T predicted LRR and BCSS benefit for adjuvant RT. The clinical utility of these biomarkers as predictor requires confirmation in a second independent trial.

**STEPP analysis of the treatment effect of adjuvant RT at 10-years.**

| Covariate | Interaction test P | LRR | BCSS |
|---|---|---|---|
| ***RB1 mRNA* level** | KM | 0.08 | 0.49 |
| | HR | 0.03 | 0.41 |
| **Proliferation score** | KM | 0.02 | 0.17 |
| | HR | 0.06 | 0.24 |
| **ROR-T** | KM | 0.01 | < 0.001 |
| | HR | 0.21 | 0.02 |
| **ROR-PT** | KM | 0.02 | 0.09 |
| | HR | 0.1 | 0.04 |

Abbreviations: KM, Kaplan–Meier; HR, hazard ratio.

### 1032 Poster Highlights Session (Board #25), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM

**Patterns of care for omission of radiation therapy for elderly women with early-stage breast cancer receiving hormonal therapy.** *Presenting Author: Peyman Kabolizadeh, Department of Radiation Oncology, University of Pittsburgh Cancer Institute, Pittsburgh, PA*

**Background**: For well-selected elderly women who undergo segmental mastectomy for early-stage, ER+ breast cancer, hormonal therapy alone is emerging as an acceptable adjuvant therapy option since the initial publication of CALGB 9343 study in 2004 and update in 2013. The rate of adoption of adjuvant hormonal therapy alone in lieu of radiation therapy (RT) and its associated patterns of care is the subject of this study. **Methods**: The National Cancer Data Base (NCDB) is a oncology outcomes database, which captures 70% of all newly diagnosed cancer patients in the US. We utilized NCDB to identify women aged ³70 diagnosed with T1N0/T1Nx invasive breast cancer who underwent segmental mastectomy from 1998-2011. Only those who received hormonal therapy were included in this analysis. Univariate and multivariable exploratory analyses were performed. **Results**: Of the 182,115 patients who met inclusion criteria, 97,530 (53.6%) patients underwent hormonal therapy and were included in the analysis. The rate of utilization of RT in this subset decreased with time from 84.9% in 1998 to 75.1% in 2011 ($p<0.001$). Academic sites decreased RT utilization most rapidly over this time period where in 2011 the rate of RT utilization was 70.7% as compared to 75.0% and 77.0% in community and comprehensive community facilities respectively ($p<0.001$). From 2003 to 2005 (prior to and following the initial publication of CALGB 9343), RT utilization rate decreased from 88.2% to 78.4%. Multivariable analysis revealed that the factors associated with decreased use of RT include (in order of association): older age, later year of diagnosis, lack of insurance, low grade histology, treatment at academic site, race, rural location, greater comorbidity score, lower median income, and distance from center. **Conclusions**: This study comprehensively assesses the patterns of care associated with the omission of radiation therapy in elderly women with early-stage breast cancer who only received adjuvant hormonal therapy. Since the publication of major clinical trials, this strategy has been increasingly adopted. The strongest predictors of the use of this strategy included advanced patient age at presentation and low-grade disease.

### 1033 Poster Highlights Session (Board #26), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM

**Late axillary recurrence after negative SLNB.** *Presenting Author: Cindy Brown Matsen, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** SLNB is the standard axillary evaluation method for clinically node-negative patients with invasive breast cancer. While axillary recurrence (AR) in the early years after negative SLNB is <2%, studies with longer (>8 yrs) follow-up on large patient numbers are lacking. With concern that current multimodality therapy may delay time to AR, we reviewed long-term SLNB patient outcomes. **Methods:** We identified patients with invasive cancer from a prospective, single-institution database who had a negative SLNB without additional axillary surgery from 1/97-12/00. Cancer, demographic, and treatment data were obtained for all patients. Primary outcome was AR. Overall survival (OS) and distant disease-free survival (DDFS) after AR were secondary endpoints. **Results:** 1529 eligible patients were identified. See table for patient and tumor characteristics. At 10.8 yrs (0-16) median follow-up, overall incidence of AR as a first event was low, n= 13. Median OS after AR was 4.6 yrs and median DDFS after AR was 3.8 yrs. The cumulative incidence of AR was 1.0% (CI 0.5-1.6) overall; cumulative incidence of 0.6% (CI 0.2-0.9) in the first 5 years, 0.4% years 5-10. Late AR (>5 yrs) occurred in 5 patients: 4 ER+, 1 HER2+. In comparison, in a group of contemporaneous SLNB-positive patients undergoing axillary dissection (n=902), overall cumulative incidence of AR was 0.8% (CI 0.2-1.5) at over 10 yrs follow-up. On univariate analysis of AR in SLNB-negative patients, high nuclear grade was the only significant predictor of AR (p=0.01). **Conclusions:** Late AR was an infrequent event after negative SLNB alone emphasizing its long-term safety as a staging procedure. AR after SLNB, like AR after ALND, portends a poor prognosis.

**Patient and tumor characteristics of study population.**

| Characteristic | # Evaluable | |
|---|---|---|
| **Age** | 1,529 | 57 (12-88) |
| | | **N (%)** |
| **Surgery** | 1,529 | |
| **Conservation** | | 1,297 (85) |
| **Mastectomy** | | 232 (15) |
| **Nuclear grade** | 1,190 | |
| **Low** | | 147 (12) |
| **Intermediate** | | 712 (60) |
| **High** | | 331 (28) |
| **Path tumor size (median)** | 1,489 | 1.0 cm (0.1-5.0) |
| **ER+** | 1,088 | 874 (80) |
| **PR+** | 1,079 | 671 (62) |
| **HER2 status** | 772 | |
| **Positive** | | 111 (14) |
| **Negative** | | 571 (74) |
| **Equivocal** | | 90 (12) |
| **Radiation** | 1,454 | 1,099 (76) |
| **Chemotherapy** | 1,451 | 536 (37) |
| **Hormone therapy** | 1,398 | 866 (62) |

### 1034 General Poster Session (Board #127), Mon, 8:00 AM-11:45 AM

**Predictors of surgery types after neoadjuvant therapy for advanced stage breast cancer.** *Presenting Author: Jamila Alazhri, University of Miami Hospital, Miami, FL*

**Background:** Despite the established guidelines for breast cancer treatment, there is still variability in surgical treatment after neoadjuvant therapy among women with large breast tumors, leading to variability in the outcome. Our objective was to identify possible predictors of the type of surgical treatment; mastectomy versus breast conserving surgery (BCS) in women with T3/T4 breast cancer who received neoadjuvant therapy. **Methods:** Population-based Florida Cancer Registry and U.S. Census from 1996 to 2009 were linked to select women diagnosed with T3/T4 breast cancer who then received neoadjuvant therapy followed by BCS or mastectomy. A multivariable logistic regression model was used to identify significant predictors of type of surgery by including sociodemographic characteristics (race, ethnicity, socioeconomic status, age, marital status, urban/rural residency), tumor characteristics (ER/PR status, histology, grade, SEER stage, regional nodes positivity), treatment facilities (hospital volume, teaching/non-teaching), comorbidities and type of neoadjuvant therapy. Adjusted odds ratios (OR) and 95% confidence intervals (95%CI) were calculated. Type-I error rate was set to 5%. Statistical analyses were performed with SAS v9.3. **Results:** Out of 1,056 patients treated with neoadjuvant therapy for T3/T4 breast cancer, 107 (10%) had BCS and 949 (90%) had mastectomy. After adjusting for the aforementioned characteristics, Hispanic patients were more likely to have mastectomy (OR=3.50; 95%CI:1.38-8.84; p=0.008) than BCS. Compared to localized SEER stage, regional stage with direct extension (OR=3.24; 95%CI:1.60-6.54; p=0.001), regional direct extension and nodes (OR=4.35; 95%CI:1.72-11.03; p=0.002) and distant stage (OR=4.44; 95%CI:1.81-10.88; p=0.001) were significantly more likely to have mastectomy than BCS. Patients who received hormonal neoadjuvant therapy only (OR=0.29; 95%CI:0.12-0.68; p=0.004) were less likely to undergo mastectomy compared to patients receiving both chemo/hormonal therapy. **Conclusions:** Our study suggests that Hispanic ethnicity, advanced SEER stage, and type of neoadjuvant therapy are significant predictors of mastectomy after neoadjuvant therapy.

**1035 General Poster Session (Board #128), Mon, 8:00 AM-11:45 AM**

**Final results of a phase 2 study of ramucirumab (RAM) plus eribulin (E) versus E in advanced metastatic breast cancer (MBC).** *Presenting Author: Denise A. Yardley, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN*

**Background:** RAM, a recombinant human IgG1 monoclonal antibody, targets VEGFR-2 and blocks the interaction of VEGF ligands and VEGFR-2. E is a microtubule inhibitor active in MBC. The primary goal of this multicenter US study was to identify if the addition of RAM to E would increase progression-free survival (PFS) in comparison to E alone as third- to fifth-line therapy in patients (pts) with MBC. **Methods:** Pts with locally recurrent or MBC and 2-4 prior chemotherapy regimens in the advanced setting were randomized 1:1 to receive RAM+E or E (E 1.4 mg/m$^2$ days 1 and 8; RAM 10 mg/kg day 1; q21 days). Stratifications included prior antiangiogenic therapy and triple negative status. Prior anthracycline and taxane treatment, normal LVEF, and ECOG PS 0-1 were required. Treated, stable brain metastases were allowed. **Results:** 141 pts with a median age of 56 yrs were in the ITT population (RAM+E, n=71; E, n=70). Median PFS was 4.4 mo in RAM+E and 4.1 mo in E (HR=0.8: 95% CI 0.6-1.2; p=0.4) with a median overall survival (OS) of 13.5 mo and 11.5 mo in the RAM+E and E arm (HR=0.8: 95%CI 0.5-1.3; p=0.4), respectively. Objective response rate was 20% for RAM+E and 24% for E. Median duration of response in RAM+E was 5.5 mo and 3.0 mo in E. Relative mean dose intensity was 95.3% for RAM and 80.7% for E in RAM+E, and 79.0% in E. All-cause treatment emergent adverse events (TEAEs) ≥20% and grade 3 ≥5% are shown (Table). Any grade TEAEs of special interest in RAM+E vs. E included bleeding (18.8% vs. 4.6%), hypertension (HTN) (13% vs. 1.5%), and congestive heart failure (1.4% vs. 0%). RAM+E bleeding included 7 events of epistaxis and 1 grade 3 GI hemorrhage. 3 RAM+E pts and 1 E pt had grade 3 HTN. **Conclusions:** Addition of RAM to E did not improve PFS. Higher rates of fatigue, headache, hypertension, diarrhea, and bleeding were observed in the RAM+E arm. Clinical trial information: NCT01427933.

| | RAM+E (n=69) | | E (n=65) | |
|---|---|---|---|---|
| TEAE, n (%) | Any grade (≥20%) | Grade ≥3 (≥5%) | Any grade (≥20%) | Grade ≥3 (≥5%) |
| Fatigue | 44 (64) | 11 (16) | 37 (57) | 4 (6) |
| Neutropenia | 29 (42) | 27 (39) | 29 (45) | 24 (37) |
| Nausea | 28 (41) | | 27 (42) | |
| Headache | 27 (39) | | 10 (15) | |
| Constipation | 20 (29) | | 19 (29) | |
| Vomiting | 19 (28) | | 17 (26) | |
| Diarrhea | 17 (25) | | 10 (15) | |
| Dyspnea | 15 (22) | | 14 (22) | |
| Peripheral neuropathy | 15 (22) | 4 (6) | 16 (25) | 3 (5) |
| Anemia | 14 (20) | | 16 (25) | 3 (5) |
| Leukopenia | 4 (6) | | 8 (12) | 7 (11) |

**1036 General Poster Session (Board #129), Mon, 8:00 AM-11:45 AM**

**Prophylactic ciprofloxacin to prevent febrile neutropenia in adjuvant breast cancer patients receiving docetaxel (nonanthracycline) regimens.** *Presenting Author: Meena Okera, Adelaide Cancer Centre, Adelaide, Australia*

**Background:** Febrile neutropenia (FN) is a serious adverse effect of adjuvant chemotherapy for breast cancer. Primary GCSF prophylaxis is recommended for patients at > 20% risk of FN, but is not funded in Australia with docetaxel (non-anthracycline) regimens in adjuvant breast cancer patients (TC and TCH), despite literature reporting rates of FN of up to 50%. Prophylactic antibiotics can prevent FN, but are not routinely incorporated into chemotherapy guidelines for TC and TCH regimens. This retrospective study evaluates the usage and benefit of primary ciprofloxacin prophylaxis, in patients receiving TC and TCH chemotherapy. **Methods:** Retrospective review of breast cancer patients receiving adjuvant TC or TCH chemotherapy between 1.1.11 and 30.6.13 (single centre). Logistic regression analysis used to model the contribution of regimen, primary GCSF use (pegfilgrastim), and prophylactic antibiotic use on presence of FN. **Results:** 131 eligible patients, mean age 55 years (28-77). 96/131 (73%) received TC chemotherapy, 35/131 (27%) received TCH chemotherapy. 97/131 (74%) received primary ciprofloxacin prophylaxis from cycle 1. Primary ciprofloxacin prophylaxis was more frequently prescribed with TC rather than TCH chemotherapy (93% vs 26%). 26 admissions occurred with FN (24 patients). 21/26 admissions for FN occurred after cycle 1 or 2 of chemotherapy. Primary ciprofloxacin prophylaxis significantly reduced the risk of FN (12% vs 41%) and on logistic regression analysis, was the only predictive factor reducing risk of FN (p=0.019). There was no interaction between use of antibiotics and growth factors. Further evaluation of interactions was limited by small numbers. **Conclusions:** There is a high rate of FN amongst breast cancer patients receiving TC and TCH chemotherapy. Primary ciprofloxacin prophylaxis significantly decreases the risk of FN. Primary ciprofloxacin prophylaxis should be considered for patients receiving TC and TCH chemotherapy, where primary GCSF prophylaxis is unavailable.

**Admissions of FN.**

| | Number (%) patients | Number (%) FN admissions |
|---|---|---|
| Ciprofloxacin prophylaxis | 97/131 (74%) | 12/97 (12%) |
| No ciprofloxacin prophylaxis | 34/131 (26%) | 14/34 (41%) |

**1037 General Poster Session (Board #130), Mon, 8:00 AM-11:45 AM**

**Outcomes of 3-weekly doxorubicin and cyclophosphamide followed by paclitaxel (AC/T) in a randomized trial (RCT) compared to a case-control matched British Columbia (BC) breast cancer population.** *Presenting Author: Sheridan Marie Wilson, BC Cancer Agency, Vancouver, BC, Canada*

**Background:** NCIC CTG MA.21 was a North American RCT of 3 adjuvant chemotherapies (adjCT), of which one was 3-weekly AC/T. We compared Relapse Free Survival (RFS) for this standardised adjCT given in MA.21 to that in a general population from a BC database, using a matched case-control design. **Methods:** Matching was based on age +/- 3 years (y) and MA.21 stratification factors: number of positive nodes [NP], surgery type, and estrogen receptor (ER). Patients (pts) who received > 1 cycle of AC/T were included. RFS was defined as time from randomisation (per protocol, AC/T started within 5 days) to recurrence for MA.21, and from first AC/T to recurrence for BC. A sensitivity analysis using HER2 negative (HER2-) pts was done, as testing and trastuzumab (TZ) use changed over time. RFS was estimated with Cox survivor plots, adjusting for factors significant in multivariate Cox step-wise forward regression. **Results:** 473 of 671 BC pts were matched to 473 of 696 MA.21 pts. Median follow up was 8 y and median time from surgery to AC/T was 48 days for both. After matching 52% were ER +; 37% node negative (NN); 62% of MA.21 and 56% of BC cases were HER2-. 76% of NN BC cases were grade 3; grade was unavailable for MA.21. Unadjusted 5 y RFS was 85% (95% confidence interval [CI] 81, 88) for BC and 82% (CI 78, 85) for MA.21. For HER2-only, 5y RFS was 85% (CI 80, 89) for BC and 79% (74, 83) for MA.21 pts. The Table shows multivariable analysis (ER and age were not significant). The HR in HER2- only cases was 0.68 (CI 0.47, 0.98, p = 0.04) for BC vs MA.21 pts. **Conclusions:** BC pts had superior adjusted RFS compared with matched pts who received AC/T in a RCT. We were unable to compare adherence to ET and ethnic distribution, which may explain some of the disparity. Also, BC has long had a low threshold for offering radiation for NP. It is reassuring that RCTs do not appear to overestimate adjCT RFS benefits in the general breast cancer population.

| Variable | Hazard ratio (Hz) | 95% CI | P |
|---|---|---|---|
| BC vs MA.21 | 0.65 | 0.48, 0.89 | 0.008 |
| Endocrine therapy (ET) | 0.44 | 0.33, 0.60 | <0.001 |
| NP (NN as reference) | | | |
| 1-3 NP | 1.24 | 0.86, 1.78 | 0.252 |
| 4-10 NP | 2.46 | 1.65, 3.66 | <0.001 |
| >10 NP | 7.26 | 4.33, 12.19 | <0.001 |
| TZ use | 0.53 | 0.28, 0.991 | 0.047 |

**1038 General Poster Session (Board #131), Mon, 8:00 AM-11:45 AM**

**ABCB1 polymorphism as a prognostic factor in breast cancer patients with neoadjuvant chemotherapy.** *Presenting Author: Hee Jun Kim, Chung-Ang University Hospital, Seoul, South Korea*

**Background:** Expression of the adenosine triphosphate-binding cassette B1(ABCB1) transporter and P-glycoprotein are associated with resistance to anticancer drugs. The purpose of this thesis was to investigate the role of single nucleotide polymorphism (SNP) in the ABCB1 and CYP3A genes in breast cancer patients who were treated with neoadjuvant docetaxel and doxorubicin chemotherapy. **Methods:** Stage II or III breast cancer patients were treated with 3 cycles of neoadjuvant, after which the patients received curative surgery and adjuvant chemotherapy with the same regimen. The polymorphisms of ABCB1 (C3435T, G2677T/A, and C1236T) and CYP3A were genotyped. The correlation of genetic polymorphisms of ABCB1, CYP3A, and clinical outcomes was analyzed. **Results:** Among the 216 patients, *ABCB1 3435*TT genotype had a longer OS than CT/TT. With univariate analysis, good PS, invasive ductal carcinoma, initial operable stage, ER-positivity, non-triple negative phenotype, breast conserving surgery and the TT genotype of C3435T were associated with a lower risk of death. Multivariate analyses demonstrated that good PS, invasive ductal carcinoma, non-triple negative phenotype and initial operable stage were significantly associated with the OS. *ABCB1 3435*TT genotype had a higher AUC than CC/CT genotype for docetaxel ($p$=0.031). These higher AUCs in the C3435TT genotype was associated with increased toxicities of neutropenia ($p$=0.037) and diarrhea ($p$=0.017). **Conclusions:** This study showed that the genetic polymorphism of ABCB1 C3435T might be associated with a longer OS. Our results also suggest that the prediction of docetaxel toxicity might be possible for C3435T polymorphism. Larger prospective studies as well as functional studies in human subjects are warranted.

**1039 General Poster Session (Board #132), Mon, 8:00 AM-11:45 AM**

**The effects of omega-3 fatty acids on chemotherapy-induced neuropathy and inflammation in patients with breast cancer.** *Presenting Author: Ali Esfahani, Hematology and Oncology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*

**Background:** Axonal sensoryperipheral neuropathy is the major dose-limiting side effect of paclitaxel. Omega-3 fatty acids have beneficial effects on neurological disorders from their effects on neurons cells and inhibition of the formation of proinflammatory cytokines involved in peripheral neuropathy. **Methods:** This study was a randomized double blind placebo controlled trial to investigate the efficacy of omega-3 fatty acids in reducing the incidence and severity of paclitaxel-induced peripheral neuropathy (PIPN). Fifty seven eligible patients with node positive breast cancer were randomly assigned to take omega-3 fatty acid soft gel capsules, 640 mg t.i.d during chemotherapy with paclitaxel for 12 weeks or sun flower soft gel capsules as placebo. Incidence and severity of PIPN, serum level of inflammatory markers: IL-1 beta, IL- 6, TNF-alpha and HsCRP, as well as concentrations of EPA and DHA in the serum phospholipids of the patients, were assessed before the onset of chemotherapy and after the cessation of therapy. **Results:** Twenty one patients (70%) of the group taking omega-3 fatty acid supplement did not develop PN while it was 40.7 %( 11 patients) in the placebo group. A significant difference was seen in PN incidence (OR=0.3, .95% CI= (0.10-0.88), p=0.029), but there was not a statistically significant difference of PIPN severity between the two study groups. The serum levels of aforementioned inflammatory markers were not statistically different between the active group and the control group but, a considerable difference was observed according to the serum concentrations of EPA and DHA after the end of the supplementation period (P<0.001). **Conclusions:** Omega-3 fatty acids may be an efficient neuroprotective supplement for prophylaxis against PIPN. They were able to reduce the incidence of PIPN in these study patients. Patients with breast cancer have a longer disease free survival rate with the aid of therapeutical agents. Finding a way to solve the disabling effects of PIPN would significantly improve the quality of life of these cancer patients. Clinical trial information: NCT01049295.

**1040 General Poster Session (Board #133), Mon, 8:00 AM-11:45 AM**

**Phase II clinical studies of UTD1, an epothilone analog, in metastatic breast cancer.** *Presenting Author: Binghe Xu, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China*

**Background:** UTD1, a genetically engineered epothilone analog, is a microtubule stabilizing agent that showed promising activities in phase I trials. In this report, two open-label, multicenter phase II studies of UTD1 alone or UTD1 plus capecitabine (CAP) were carried out to evaluate its efficacy and safety in metastatic breast cancer (MBC) patients (pts). **Methods:** In both studies, MBC patient who was pretreated with taxanes, anthracyclines and/or CAP received UTD1 at a dose of 40mg/m$^2$/d intravenously on day 1 to day 5 or at 30mg/m$^2$/d (d1-d5) in combination with CAP (2000mg/m$^2$/d, orally) on d1-d14, every 21 days until disease progression or unacceptable toxicity occurred for a maximum of 6 cycles. The primary endpoint was objective response rate (ORR) and the secondary endpoints were toxicity and progression-free survival (PFS) for the combination. **Results:** 25 pts received a total of 128 cycles in the combination with a median of 6 cycles (range 1-6 cycles) per patient. Among 24 pts who were evaluable for efficacy, responses included one complete response (CR), 11 partial responses (PR), 9 stable diseases (SD), and a median PFS of 7.5 months. In the UTD1 monotherapy, 34 pts received a median of 4 cycles of UTD1 and 30 pts were evaluable for efficacy. One patient had a confirmed CR, 7 had PR and 13 had SD. Peripheral neuropathy (PN) was the major adverse event associated with UTD1 toxicity in both studies, but was manageable. 40% of pts in the combination had grade 3 PN or/and foot syndrome compared to 11% in the monotherapy. One patient was removed from the monotherapy after the first cycle because of grade 3 neurotoxicity, which was reversed after 3 weeks. There were no drug-related deaths in the two studies. Other grade 3 toxicities included neutropenia (12% *vs* 3%, combination *vs* monotherapy), diarrhea (4% *vs* 3%), myalgia/arthralgia (8% *vs* 0%), dizziness (4% *vs* 0 %). **Conclusions:** UTD1 was well-tolerated in both studies with the primary toxicity being PN, and demonstrated notable antitumor activities in MBC pts. 27% of ORR was seen for the monotherapy or 50% of ORR and a median PFS of 7.5 months for the combination. A multicenter, phase III study of UTD1 plus CAP *vs* CAP alone in MBC is underway. Clinical trial information: TRC-13004205.

**1041 General Poster Session (Board #134), Mon, 8:00 AM-11:45 AM**

**Randomized phase II trial comparing docetaxel with or without low-dose metronomic oral cyclophosphamide in first-line treatment of non-triple-negative advanced breast cancer.** *Presenting Author: Leiping Wang, Fudan University Shanghai Cancer Center, Shanghai, China*

**Background:** Oral metronomic chemotherapy may target tumor cells indirectly via antiangiogenic activity, restoration of anticancer immune response, or induction of tumor dormancy. This phase II study (NCT01526499) aims to evaluate the efficacy of metronomic oral cyclophosphamide in addition to docetaxel as first-line therapy. **Methods:** Eligible patients with ER or PR positive or HER-2-overexpressed ABC who previously untreated were randomly assigned to receive docetaxel 75 mg/m$^2$on day 1 with or without continuous oral cyclophosphamide 50mg daily in a 21-day cycle. Patients with HER-2-overexpressed tumors also receive trastuzumab. All patients received docetaxel until disease progression or unacceptable toxicity or withdrawal of consent. Maintenance endocrine and/or trastuzumab were allowed. The primary endpoint was PFS. **Results:** Between Dec 2011 and Nov 2012, 31 patients were randomized to docetaxel (T) group while 35 to cyclophosphamide plus docetaxel (Metro-TC) group. The majority of the patients (83.3%) were hormonal receptor positive; 31.8% were HER2 over-expressed; 84.8% had visceral metastasis and 48.5% had ≥3 metastatic organ sites. Patients' characteristics were well balanced. Median treatment cycles of docetaxel for both groups were eight cycles. In intention-to-treat population with median follow-up of 18 months, median PFS was statistically longer in the Metro-TC group ( not reached) than it was in the T group (13.6 months, 95%CI, 7.0 to 20.2) (P =.04). Median OS had not been reached. The ORR were 51.6% (16/31) in the T and 71.4% (25/35) in Metro-TC group, respectively (P =.09). There was no significant difference of grade 3/4 toxicities between the two groups. Adverse effects were mainly docetaxel-related, including grade 3/4 neutropenia (100%) and febrile neutropenia (n=19, 29.2%). The only significant difference between the two treatment was mucositis (all grade, 10% versus 43%, P=0.003). **Conclusions:** The addition of metronomic cyclophosphamide to standard chemotherapy as first-line treatment for non-triple-negative ABC shows a benefit in PFS without significant increase in toxicity. Clinical trial information: NCT01526499.

**1042 General Poster Session (Board #135), Mon, 8:00 AM-11:45 AM**

**Comparison of six cycles of epirubicin and paclitaxel (ET) versus four cycles of epirubicin and cyclophosphamide, followed by four cycles of paclitaxel (EC-T) as adjuvant therapy for operable breast cancer in women with positive axillary nodes.** *Presenting Author: Peng Yuan, Department of Medical Oncology, Cancer Institute and Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

**Background:** To determine if 6 cycles of ET has similar efficacy to 4 cycles of EC followed by 4 cycles of T, but with shorter treatment time and reduced toxicity. **Methods:** Patients with operable breast cancer and positive lymph nodes were enrolled and randomized to receive ET (75/175 mg/m$^2$ X 6 every 21 days) or EC (90/600 mg/m$^2$ X 4 every 21 days) followed by T (175 mg/m$^2$ X4 every 14 days). The primary end point was DFS. The trial was designed to detect the upper limits of the 95% confidence interval of the hazard ratio of ET versus an EC-T < 1.30. A sample size of 905 patients was required to detect the difference ($a$=0.05, $\beta$=80%). Assuming a drop-out rate of 10%, 996 patients were required. The first analysis of DFS was planned at the time when 50% of patients were enrolled. **Results:** Between August 2009 and October 2013, 496 patients were enrolled in the study and 445 patients completed the study treatment protocol, among which 214 patients were in the EC-T arm and 231 patients were in the ET arm. The patient characteristics were well-matched between the two arms. The median age was 49 years in both groups. Of the patients in the EC-T and ET arms, 87.4% and 92.2% were ER/PR-positive, respectively. After a median follow-up of 35.5 months, 28 events were observed (14 each in both arms). The 4-year DFS was 91.3% in the EC-T arm and 91.4% in the ET arm (log-rank p= 0.719,HR = 0.873, 95%CI = 0.416-1.832). Both regimens were well-tolerated. Of the patients in the EC-T and ET groups, 92.1% and 88.7%, respectively, completed all treatment cycles per protocol. Dose reductions were required in 24.8% and 35.5% of the patients in the EC-T and ET arms, respectively. The most frequent grade 3 / 4 toxicities were neutropenia, nausea, and anemia, with no significant difference between the two regimens. **Conclusions:** The toxicity from six cycles of ET were similar to eight cycles of EC-T in patients with node-positive early breast cancer. The efficacy of the two chemotherapy regimens should await the enrollment of additional patients and a longer follow-up. Clinical trial information: NCT01134523.

**1043 General Poster Session (Board #136), Mon, 8:00 AM-11:45 AM**

**Prognostic effect of eribulin-induced liver dysfunction in metastatic breast cancer.** *Presenting Author: Takayuki Kobayashi, Department of Medical Oncology, the Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan*

**Background:** Eribulin is a non-taxane, microtubule dynamics inhibitor with a survival benefit for patients with metastatic breast cancer. Although eribulin is well tolerated in patients with heavily pretreated disease, eribulin-induced liver dysfunction (EILD) occasionally occurs in clinical practice, which may results in treatment discontinuation, with subsequent poor disease control. We conducted a retrospective study to clarify the effect of EILD in patients. **Methods:** The medical records of 157 metastatic breast cancer patients treated with eribulin between Jul 2011 and Nov 2013 at Cancer Institute Hospital were retrospectively analyzed. EILD was defined as 1) an increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels >3 times the upper limit of normal, and/or 2) starting liver-supporting oral drug therapy such as ursodeoxycholic acid and glycyron. Fatty liver was defined as a decrease in the liver-to-spleen attenuation ratio on computed tomography to <0.9. **Results:** The median age was 56 years, median treatment duration was 4.0 months, and mean body mass index (BMI) was 22.9. EILD occured in 42 (27%) patients, including one patient in whom eribulin treatment was stopped due to EILD. The patients with EILD had significantly higher BMI than the remaining 115 patients (25.4 vs. 22.1, p<0.0001), with no difference in the relative dose intensity of eribulin between the two groups (1.21 vs. 1.15 mg/body/week, p=0.36). Interestingly, the patients with EILD had significantly longer progression-free survival (PFS) than the other patients (p=0.018). Furthermore, among 78 patients without liver metastases, 18 with EILD showed significantly longer PFS than the other 60 patients (p=0.0035). During eribulin treatment, 17 (11%) patients developed fatty liver, and their mean BMI was 27.1. Eleven of 17 patients had EILD. **Conclusions:** Although EILD and fatty liver occurred with relatively higher frequency in clinical practice, most of the patients had no severe side effects. We found the paradoxical results showing positive correlation between EILD and PFS, especially in patients without liver metastases. Further studies are needed to confirm our findings in another cohort of patients.

**1044 General Poster Session (Board #137), Mon, 8:00 AM-11:45 AM**

**Three-arm randomized phase II study evaluating oral vinorelbine plus capecitabine versus paclitaxel plus gemcitabine versus docetaxel plus gemcitabine as first-line chemotherapy in patients with metastatic breast cancer: Final results (NorCap-CA223 trial).** *Presenting Author: Saverio Cinieri, Medical Oncology & Breast Unit, Senatore Antonio Perrino Hospital, Brindisi, Italy*

**Background:** Combination chemotherapy (CT) is among the standard treatment options in metastatic breast cancer (MBC), especially in patients (pts) with visceral metastases or need of rapid symptom or disease control. Full oral combination CT of Oral Vinorelbine (OV) + Capecitabine (C) is a convenient and effective alternative to taxane-based intravenous regimens. Aim of this study was to evaluate the efficacy of a full oral and two full intravenous combinations in MBC. **Methods:** Pts with HER2-negative taxane-naïve MBC, with an age ≥18 years were eligible. Pts were randomised to receive, as first-line CT, 3 weekly-cycles of either: ARM A: full oral combination of OV and C; ARM B: paclitaxel plus gemcitabine (G); ARM C: docetaxel plus G. Primary endpoint was disease control rate (DCR). Pts were stratified according to prior anthracycline CT and age < or ≥65 years. **Results:** 149 pts had been treated (ARM A 49; ARM B 50; ARM C 50). Baseline pt characteristics (Arms A/B/C): median age 58/56/57 years; prior (neo)adjuvant CT 49/46/58%; prior anthracycline 39/42/42%; visceral metastases 80/82/74%. Median number of cycles (range): 6(1-37)/6(1-12)/7(1-25). Safety: G3/4 adverse events per pt: neutropenia 50/46/86%, anemia 2/4/8%, infections 2/2/10%, diarrhoea 6/4/2%, vomiting 10/2/2%, fatigue 10/12/22%, alopecia (G2) 8/72/76%, febrile neutropenia (pts) 4/0/3, toxic deaths (pts) 2/1/0. Efficacy: DCR in the intent-to-treat population was [95%CI] 73.5 [59-85] /78 [64-88] /80 [66-90] %; progression-free survival: 7.6 /9.0/11.4 months; time to treatment failure: 4.6/4.8/5.2 months; overall survival: 30.2/29.6/31 months. **Conclusions:** The DCR as well the OS results reported in this trial confirm that the full oral combination of OV + C is an active combination which can be proposed as an alternative to taxane-based regimens as first-line CT in MBC, allowing to delay the constraints of an intravenous CT. As expected, each regimen presented a specific and particular tolerance profile, with, in particular, a low incidence of alopecia after full oral CT.

**1045 General Poster Session (Board #138), Mon, 8:00 AM-11:45 AM**

**Toxicity and prediction of survival benefit with metronomic chemotherapy in metastatic breast cancer.** *Presenting Author: Rabab Mohamed Gaafar, National Cancer Institute, Cairo University, Cairo, Egypt*

**Background:** Metronomic chemotherapy (MC) has shown efficacy in patients with metastatic breast cancer. We therefore tested the efficacy and toxicity of (MC) in pretreated metastatic breast cancer (MBC). **Methods:** This prospective phase II study was conducted in the period between July 2008 till July 2011. The study included 50 cases of heavily pretreated MBC who received (MC) (oral cyclophosphamide 50 mg/day & methotrexate 2.5 mg twice day1 and 2 every week). The primary end point was time to progression (TTP) while secondary end points were response rate, overall survival (OS), safety and impact of treatment on VEGF. **Results:** Forty eight patients were assessed. One case achieved complete response (CR) and 10 cases had partial response (PR) while 19 patients had stable disease with ORR of 22% while CBR was 45.5%. Median TTP was 5 months while median OS was 7 months with a median follow up period of 7 months (ranging from 1 to 33 months). Patients with negative progesterone receptors, ECOG PSI, achieving CR or PR and suffering from leucopenia, neutropenia and anemia due to treatment had significant prolonged TTP while patients with initial early stage at the time of diagnosis of breast cancer, receiving <5 previous treatment lines, achieving response and experienced anemia with (MC) had significant superior OS. In multivariate analysis, achieving response, PS I, time interval since initial diagnosis till starting (MC) and anemia were independent prognostic factors for longer TTP. Initial stage at presentation, number of previous treatment lines and response were independent prognostic factors for OS. No significant difference between the median level of VEGF at baseline and after 3 months. The median level of VEGF at baseline or after 3 months as well as the median percentage of reduction was not correlated with TTP or OS. **Conclusions:** MC is an attractive way of treatment being effective and less toxic. There is certain groups seem to benefit from this treatment especially those with good PS, achieved response and who experienced toxicity with treatment. Further trials are warranted to assess this approach early in the course of the disease and with other more active agents.

**1046 General Poster Session (Board #139), Mon, 8:00 AM-11:45 AM**

**HIP1 expression and response to chemotherapy in breast cancer.** *Presenting Author: Mireia Margeli, Institut Català d'Oncologia - Hospital Germans Trias i Pujol, Badalona, Spain*

**Background:** Huntingtin Interacting Protein 1 (HIP1) is a binding protein to inositol and clathrina that is related to neurodegeneration. Signaling of growth factors receptors trought clathrina is one of the mechanisms by which cells regulate the intracellular signaling. There have been observed high levels of HIP1 protein in breast, colon, kidney, lung, melanoma, ovarian and prostate cancer. Furthermore, HIP expression was negatively correlated with survival in prostate cancer. HIP1 overexpression has been shown to inhibit the degradation of EGFR and estrogen receptor. EGFR expression has been correlated with response to chemotherapy in triple negative breast cancer. **Methods:** Tumor biopsies were obtained from 83 breast cancer patients (p) treated with neoadjuvant chemotherapy, based on four cycles of fluorouracil, epirubicin and cyclophosphamide. Estrogen receptor, progesterone receptor, HER2, cytokeratin 5/6, vimentin and HIP1 were examined by tissue microarray. HER2 were also assessed by chromogenic in situ hybridization. We evaluated the prognostic and predictive value of HIP1 expression. **Results:** HIP1 was evaluated by immunohistochemistry in 83 p, being considered negative if the result was 0 or 1, and positive if it was 2 or 3. The result was 0 in 11 p (13.3%), 1 in 40 p (48.2%), 2 in 25 p (30.1%), and 3 in 7 p (8.4%). The value of huntingtin did not correlate with any of the clinical characteristics of the series, nor with ER, PR, vimentin, or HER2, nor subgroups. Negative HIP1 was correlated in the limit of significance to positive CK5 /6. Overexpression of HIP1 was correlated to higher pathologic response, as shown in table 1. HIP1 was not statistically correlated to DFS or OS, but p with overexpression of HIP1 had a median survival of 50 months whereas it was 67 months for p without overexpression of HIP1. **Conclusions:** HIP1 could be a prognostic and predictive factor in breast cancer. Showing that HIP1 is necessary for breast cancer progression and modulates key growth factor receptors involved in breast cancer, fuels the idea that HIP1 inhibition has therapeutic potential.

| | HIP1 | | |
|---|---|---|---|
| **Pathological response** | **Positive** | **Negative** | **P** |
| **Responder (CR+PR)** | 23 (71.9%) | 24 (47.1%) | .04 |
| **No responder (ED+PD)** | 9 (28.1%) | 27 (52.9%) | |

**1048 General Poster Session (Board #141), Mon, 8:00 AM-11:45 AM**

**First safety results of an international phase II study evaluating oral vinorelbine as a single agent as first-line chemotherapy for metastatic breast cancer patients with bone metastases (NorBreast-228 trial).** *Presenting Author: Guenther G. Steger, Department of Medicine I, Clinical Division of Medical Oncology, Medical University of Vienna, Vienna, Austria*

**Background:** Oral chemotherapy (CT) is an attractive treatment option for hormone receptor positive, metastatic breast cancer (MBC) patients (pts) pretreated by a hormone therapy. In our phase II study, we evaluated the role of single-agent Oral Vinorelbine (OV) as first-line CT in pts presenting bone metastases without visceral involvement. In this abstract, first safety results of this trial are presented. **Methods:** Main eligibility criteria included: age ≥18 years, documented bone involvement previously untreated by CT, hormone receptor positive disease previously treated by at least one hormone therapy, HER2-negative disease, Karnofsky PS ≥70 and absence of visceral metastases. Study treatment (until progression): OV 80 mg/m$^2$ weekly (following a first cycle at 60 mg/m$^2$ and dose escalation to 80 in the absence of grade 3 or 4 toxicity). One cycle was defined as four weeks of treatment. **Results:** Main pts characteristics in the full population were (n=70): median age: 60.6 years (34% ≥65 years); median Karnofsky PS 90%. Prior hormone therapy 100% (53% in advanced setting); prior (neo)adjuvant CT 63%; prior anthracyclines/taxanes 59/24%; prior palliative radiotherapy 41%. Bone involvement 100%; other metastatic sites: lymph nodes 14%, soft tissue 3%. Median duration of treatment 5.5 months (range 0.9-18.3), median number of cycles: 6 (range: 1-18);61% of pts received at least 6 cycles, 37% of ptsreceived more than 6 cycles and 29% received at least 9 cycles; median relative dose intensity: 83.5%; dose escalation was performed in 79% ofpts.Grade 3/4 adverse events per pt: neutropenia 37%, anemia 4%, diarrhoea 3%, nausea 3%, asthenia 1%, liver toxicity 1%, neutropenic infection 1%, non-neutropenic infection 1%. Grade 2 alopecia was reported in 6% of pts. **Conclusions:** In this particular population of metastatic pts, with hormone receptor positive disease and bone involvement, OV showed an optimal safety profile. These data shows that OV is a well tolerated first-line CT option in this setting, allowing prolonged active treatment in non-progressing pts.

**1049 General Poster Session (Board #142), Mon, 8:00 AM-11:45 AM**

**Survival with docetaxel plus capecitabine comparing with vinorelbine plus capecitabine followed by capecitabine maintenance treatment as first-line therapy in patients with advanced breast cancer: A phase III randomized clinical trial.** *Presenting Author: Binghe Xu, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China*

**Background:** Docetaxel/capecitabine (TX) is one of the standard regimens recommended by NCCN for metastatic breast cancer treatment. There are few clinical studies directly comparing TX and navelbine/capecitabine (NX), followed by capecitabine maintenance treatment, especially in advanced breast cancer patients previously treated with taxane in adjuvant setting. This study aimed to compare the efficacy and safety of TX and NX medications followed by capecitabine maintenance for patients with metastatic breast cancer. **Methods:** A total of 206 patients with advanced metastatic breast cancer were randomly assigned into TX (n=104) and NX (n=102) treatment groups, both with capecitabine maintenance medication. The primary endpoint was progression-free survival (PFS) and secondary endpoints included overall survival (OS), response rate (RR), duration of response (DOR) as well as safety. **Results:** The TX group achieved longer median PFS than the NX group (8.4 months vs. 7.1 months; $p = 0.0026$, HR = 1.65) and had better median DOR (7.8 months vs. 6.6 months, $p = 0.0451$). In the TX group 48 (46.2%) and in the NX group 42 (41.2%) patients attained maintenance medication. The OS period of the TX group was longer than in NX patients (35.3 months vs. 19.8 months), but without statistical significance. Patients ≥40 years of age, postmenopausal and with visceral metastases were more likely to benefit from a TX regimen in terms of PFS and OS, whereas hormone and positive HER2 receptor and history of taxane treatments did not affect PFS and OS differences between TX and NX patients. The tumor response rates were 55.3% in the TX vs. 54.9% in the NX group. In the TX group hand-foot syndrome occurred more frequently than in the NX group (47% vs. 16.7%, $p < 0.0001$), but frequencies of other minor adverse effects were similar in both groups. **Conclusions:** A TX regimen for advanced breast cancer followed by capecitabine maintenance medication led to longer PFS and DOR than a NX regimen even for patients who were previously treated with taxane in (neo) adjuvant settings. Clinical trial information: NCT01126138.

**1050 General Poster Session (Board #143), Mon, 8:00 AM-11:45 AM**

**Influence of pluripotent stem cell gene polymorphisms on breast cancer susceptibility and response to chemotherapy in a north Indian cohort.** *Presenting Author: Gaurav Agarwal, Department of Endocrine and Breast Surgery, SGPGIMS, Lucknow, India*

**Background:** OCT4, NANOG, LIN28 and SOX2 are the key transcription factors critical for the pluripotency and self-renewal of embryonic stem cells. Their dys-regulation leads to breast cancer cell growth, differentiation and tumor metastasis. We aimed to explore the role of pluripotent stem cell gene polymorphisms in breast cancer susceptibility and response to chemotherapy (CTx). **Methods:** This case-control study included 297 histologically proven female breast cancer patients and 273 healthy controls. Response to CTx was studied in 128 patients receiving neoadjuvant CTx and evaluated for response as per RECIST criteria. The association of tagger SNPs in *OCT4* (rs3130932), *NANOG* (rs11055786), *LIN28* (rs4274112) and *SOX2* (rs11915160) gene with breast cancer susceptibility and response to CTx were examined using Taqman allelic discrimination assays. Statistical analysis was done using SPSS ver 17. **Results:** Heterozygous genotype (P=0.019) and variant allele (P=0.003) of rs11915160 were found to be significantly associated with breast cancer susceptibility in premenopausal women. Similar association was found in dominant model (P=0.014). On univariate analysis of correlation of genotype with clinico-pathological characters, genotype (AG+GG) of rs4274112 polymorphism was found significantly associated with larger tumor size (P=0.040) and positive lymph node (P=0.002). However in multivariate analysis, larger tumor size was not significantly associated, but lymph node metastases was significantly associated with genotype (AG+GG) of rs4274112 polymorphism (P=0.007). Significant association was seen between hormone receptor positive tumors and rs3130932 polymorphism in multivariate analysis, both at the genotypic (AC+AA) (P=0.033) as well as the allelic (C) (P=0.023) levels. **Conclusions:** The *SOX2* rs11915160 variants may confer breast cancer risk in premenopausal women. *OCT4* rs3130932 and *LIN28* rs4274112 genetic variants may have significant effect in clinico-pathological characteristics of breast cancer patients. However, no association was found between any of the studied polymorphisms with response to CTx.

**1051 General Poster Session (Board #144), Mon, 8:00 AM-11:45 AM**

**Nabrax: Neoadjuvant therapy of breast cancer with weekly single-agent nab-paclitaxel—Final efficacy and biomarkers analysis of GEICAM 2011-02 trial.** *Presenting Author: Miguel Martin, Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain*

**Background:** Nanoparticle albumin bound paclitaxel (nab-P) administered weekly showed superior efficacy compared to every 3-weeks docetaxel in a randomized phase II study in first line metastatic breast cancer (Gradishar JCO 2009). We present a phase II trial designed to evaluate the activity and safety of weekly nab-P as neoadjuvant treatment of early stage breast cancer patients (pts) with positive estrogen receptors (ER) and negative HER2. **Methods**: Stage II-III breast cancer pts were included and treated with nab-P weekly (150 mg/m$^2$) on days 1, 8 and 15 every 4 weeks for 4 cycles. Following chemotherapy, pts underwent surgery and adjuvant therapy under the investigator criteria. The primary objective was to determine the percentage of pts with poor response (Symmans residual cancer burden –RCB– class III centrally determined). The study hypothesis was that the RCB III rate will drop from 33% (historical controls treated with docetaxel in the same population, Martin BCRT 2011) to 16% with nab-P. Secondary objectives included good pathological complete response (Symmans RCB class 0+I), objective response rate (ORR), breast conserving surgery (BCS) rate, safety and molecular subtypes and biomarkers (Ki-67, Cav-1, SPARC analyzed in a central lab) correlation with response. The safety and treatment administration analysis was reported previously (Martin SABCS 2013). We report here the efficacy and correlation between RCB 0+I and subtypes/biomarkers from the pre-treatment tumor samples. **Results**: 83 pts were recruited (81 evaluable). Median age was 47 years, 64.2% were premenopausal; most pts were stage II (35.9% IIa and 33.3% IIb). Central pathological response is currently available for 74 pts (7 pending). RCB III rate was 25.7% and RCB 0+I rate was 27%. The ORR by MRI was 76.5% and the rate of conversion to BCS was 40%. In the univariate analysis we found Ki67>20% and high expression of Cav1 in stroma to be correlated with RCB 0+I. **Conclusions:** Our study was unable to show the pre-specified efficacy hypothesis. However the RCB 0+I rate is encouraging taking into account docetaxel activity (13.3%) in this population; nab-P merits further evaluation in randomized trials. Clinical trial information: NCT01565499.

**1052 General Poster Session (Board #145), Mon, 8:00 AM-11:45 AM**

**Adding VEGFR-TKIs to chemotherapy and/or hormonal therapy in advanced breast cancer patients: Results of a meta-analysis.** *Presenting Author: Yucai Wang, Department of Medicine, Rutgers New Jersey Medical School, Newark, NJ*

**Background:** The addition of vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) to chemotherapy and/or hormonal therapy for advanced breast cancer management remains controversial. We reviewed data from RCTs and conducted a meta-analysis to systematically evaluate the benefits and risks of adding VEGFR-TKIs therapy to standard treatment for advanced breast cancer. **Methods:** PubMed, Web of Science and ASCO and ESMO databases were searched. Eligible studies were RCTs that compared treatment outcomes (OS, PFS and/or TTP) of standard therapy with or without addition of VEGFR-TKIs in advanced breast cancer. Study endpoints included OS, PFS, and grade 3 or above adverse events (AEs). Pooled HRs for survival outcomes and RRs for dichotomous data with 95% CI were calculated using comprehensive meta-analysis (v2). **Results:** Nine eligible trials comprising a total of 2,206 patients were identified. VEGFR-TKIs included sorafenib (3), sunitinib (2), vandetanib (2), axitinib (1), and motesanib (1), and standard therapies included paclitaxel (2), docetaxel (3), gemcitabine (2), capecitabine (2), and fulvestrant (1). The addition of VEGFR-TKIs did not improve OS (HR 1.01; 95% CI 0.88-1.16, $P = 0.889$) or PFS (HR 0.87; 95% CI 0.72-1.03, $P = 0.109$). However, adding VEGFR-TKIs increased the risk of hypertension (RR 3.38; 95% CI 1.37-8.30, $P = 0.008$), rash (RR 2.64; 95% CI 1.14-6.14, $P = 0.024$), hand-foot syndrome (RR 4.73; 95% CI 1.33-16.81, $P = 0.016$), and mucosal inflammation (RR 2.41, 95% CI 1.10-5.28, $P = 0.028$), but not the risk of vomiting, diarrhea or neutropenia. **Conclusions:** Our meta-analysis demonstrates that adding VEGFR-TKIs to standard treatment in advanced breast cancer did not improve treatment outcomes, and increased the risk of certain severe AEs, such as hypertension, rash, and hand-foot syndrome and mucosal inflammation. Because of patient and treatment heterogeneities among the trials, eg., ER/PR/HER2 status, locally advanced vs. metastatic, first vs. any line of therapy, additional studies are needed to further evaluate the efficacy of VEGFR-TKIs in advanced breast cancer.

**1053 General Poster Session (Board #146), Mon, 8:00 AM-11:45 AM**

**Phase II study of *pseudomonas aeruginosa*-mannose-sensitive hemagglutinin in combination with capecitabine for HER2-negative metastatic breast cancer pretreated with anthracycline and taxane.** *Presenting Author: Fangfang Lv, Fudan University Shanghai Cancer Center, Shanghai, China*

**Background:** Metastatic breast cancer (MBC) remains an incurable disease despite major therapeutic advances. *Pseudomonas aeruginosa*–mannose-sensitive hemagglutinin (PA-MSHA) has been established to have anti-proliferative effects against breast cancer cells in preclinical experiments, and is indicated for treatment of cancer in China. We performed a phase II trial combining PA-MSHA with capecitabine in patients with heavily pretreated MBC. **Methods:** Eligibility criteria included human epidermal growth factor receptor 2–negative MBC, prior therapy with anthracyclines and taxanes, at least one prior chemotherapy regimen for metastatic disease or early relapse after a taxane plus anthracycline adjuvant regimen, and adequate organ function and performance status. PA-MSHA 1 mg was administered subcutaneously every other day and capecitabine 2000 mg/m$^2$orally twice a day for 2 weeks on, 1 week off. The primary end point was progression-free survival. The trial was registered at www.ClinicalTrials-.gov (ID NCT01380808). **Results:** A total of 97 patients were enrolled. Median progression-free survival (PFS) was 4.0 months [95 % confidence interval (CI) 3.0–4.9), which was not significantly different from that in historical controls. However, median PFS was significantly longer (8.2 months; 95 % CI 6.7–9.7) in 24 patients with moderate immune-related adverse events (irAEs) such as fever or skin induration at the injection site than in those with no or mild irAEs (3.1 months, 95 % CI 2.5–3.6; $p = 0.003$). Overall survival was also improved in these patients (25.4 vs. 16.4 months; $p = 0.044$). PA-MSHA has a good safety profile, with only 6 patients (6.2 %) discontinuing treatment. PA-MSHA did not increase capecitabine-related toxicities such as hand-foot syndrome, nausea, and vomiting. **Conclusions:** Adding PA-MSHA to capecitabine has a good safety profile in patients with heavily pre-treated MBC, although benefit from this regimen might occur only in patients with moderate PA-MSHA–related adverse events. Clinical trial information: NCT01380808.

**1054 General Poster Session (Board #147), Mon, 8:00 AM-11:45 AM**

**Paclitaxel-induced severe sensory peripheral neuropathy is associated with NDRG-1 genetic variant and negative NDRG-1 expression in nerve tissue.** *Presenting Author: Raghav Sundar, National University Health System, Singapore, Singapore*

**Background:** N-myc downstream regulated gene (NDRG)-1 has been implicated in Charcot Marie Tooth disease, a peripheral nerve hereditary disorder and in the development and maintenance of the myelin sheath. We hypothesize that NDRG-1 may be implicated in paclitaxel-induced peripheral neuropathy. **Methods:** Breast cancer patients who received adjuvant weekly paclitaxel were genotyped for 10 single nucleotide polymorphisms (SNPs) in 9 genes, including rs2233335 in NDRG-1 using MassArray (Sequenom) technology. Immunohistochemical (IHC) staining of NDRG-1 was performed on normal nerve tissue in archival lumpectomy/mastectomy specimens. Clinical data including paclitaxel dose intensity and density, onset and severity of neuropathy was correlated with genetic and IHC data. **Results:** Of the 122 patients that were evaluated, 67% were Chinese, median age was 51 (26 – 79) years and 9% had diabetes. Mean total paclitaxel dose administered was 924 (240 – 960) mg/m$^2$. Median duration of treatment was 12 (3 – 18) weeks, with 36% completing full dose intensity (960mg/m$^2$ in 12 weeks). 57.4% developed all grade neuropathy, with 20.5% having ≥grade 2 severity. Severe neuropathy, defined as those requiring dose delay, dose reduction or early termination of chemotherapy, occurred in 9.8%. Expectedly, presence of diabetes correlated with severe neuropathy (36% vs 7%; p=0.01). Of the 10 SNPs evaluated, NDRG-1 (rs2233335) CC/CA genotype was significantly associated with severe neuropathy compared to the AA genotype (28% vs 7%, p=0.016). Of note, patients with the CC/CA genotype and who were younger than 50 years of age had a higher incidence of ≥grade 2 (80% vs 14%, p=0.005) and severe neuropathy (80% vs 6%, p=0.001) than those with the AA genotype. Patients with severe neuropathy were more likely to stain negative for NDRG-1 in nerve tissues compared to those who had no neuropathy (80% vs 0%, p=0.047). **Conclusions:** Absence of NDRG-1 expression on nerve tissue and NDRG-1 rs2233335 SNP is associated with paclitaxel-induced severe neuropathy, and may guide selection of patients who should avoid paclitaxel. Correlation of NDRG-1 SNP with expression and functionality requires further study.

**1055 General Poster Session (Board #148), Mon, 8:00 AM-11:45 AM**

**Clinical predictive models for chemotherapy-induced febrile neutropenia in breast cancer patients: A validation study.** *Presenting Author: Kai Chen, Breast Tumor Center, Sun Yat-sen Memorial Hospital, Guangzhou, China*

**Background:** This study aims to validate a predictive model (Jenkin's model) for febrile neutropenia (FN) during chemotherapy in early-stage breast cancer patients. **Methods:** A total of 428 breast cancer patients who received neoadjuvant/adjuvant chemotherapy (Anthracycline and/or taxane based) without any prophylactic use of colony-stimulating factor were included. Pretreatment absolute neutrophil counts (ANC) and absolute lymphocyte counts (ALC) were used by the Jenkin's model to assess the risk of FN. In addition, we modified the threshold of Jenkin's model and generated Model-A and B. We also developed Model-C by incorporating the absolute monocyte count (AMC) as a predictor into Model-A. The rates of FN in the 1st chemotherapy cycle were calculated. A valid model should be able to identify high-risk subgroup of patients with FN rate >20%. **Results:** Jenkin's model (Predicted as high-risk when ANC≦3.1*10^9/L; ALC≦1.5*10^9/L) did not identify any patient with a significantly high risk (>20%) of FN in our population, even if we used different thresholds in Model-A(ANC≦4.4*10^9/L;ALC≦2.1*10^9/L) or B(ANC≦3.8*10^9/L; ALC≦1.8*10^9/L) . However, with AMC added as an additional predictor, Model-C(ANC≦4.4*10^9/L;ALC≦2.1*10^9/L; AMC≦0.28*10^9/L) identified a subgroup of patients with a significantly high risk of FN (23.1%). **Conclusions:** In our population, the threshold of Jenkin's model should be changed and the AMC should be incorporated as a predictor, to have improved predictive ability.

| Model | Group | ANC (×10^9/L) | ALC (×10^9/L) | AMC (×10^9/L) | Total N | FN rate N(%) | P |
|---|---|---|---|---|---|---|---|
| Jenkin's | I | ≦5.2 | ≦2.4 | n/a | 155 | 15(9.7) | NS |
| | II | ≦5.2 | ≦2.4 | n/a | 93 | 9(9.7) | |
| | III | ≦4.4 | ≦2.1 | n/a | 72 | 14(19.4) | |
| | IV | ≦3.8 | ≦1.8 | n/a | 69 | 13(18.8) | |
| | V (high-risk) | ≦3.1 | ≦1.5 | n/a | 39 | 4(10.3) | |
| Model-A | Low-risk (group I and II) | ≦4.1 | ≦2.1 | n/a | 248 | 24(9.7) | <0.05 |
| | High-risk (group III, IV, and V) | ≦4.4 | ≦2.1 | n/a | 180 | 31(17.2) | |
| Model-B | Low-risk (group I, II, and III) | ≦3.8 | ≦1.8 | n/a | 320 | 38(11.9) | NS |
| | High-risk (group IV and V) | ≦3.8 | ≦1.8 | n/a | 108 | 17(15.7) | |
| Model-C | Low-risk | Not fulfil the | criteria of | high-risk group | 337 | 34(10.1) | <0.01 |
| | High-risk | ≦4.4 | ≦2.1 | ≦0.28 | 91 | 21(23.1) | |

**1056 General Poster Session (Board #149), Mon, 8:00 AM-11:45 AM**

**Bayesian network meta-analysis, comparison of cardiac events associated with liposomal doxorubicin, epirubicin, and doxorubicin in breast cancer.** *Presenting Author: Norihiro Yamaguchi, Mount Sinai Beth Israel, New York, NY*

**Background:** Anthracyclines have the potential for causing cardiac events (CE). Given minimal evidence based data predicting CE rates, a Bayesian network meta-analysis (NMA), a validated statistical methodology provides direct and indirect comparison among different regimens. **Methods:** We conducted a systematic review of prospective randomized controlled trials through MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Google Scholar comparing non-anthracycline based regimen (Non), doxorubicin (Dox), epirubicin (Epi), and liposomal doxorubicin (LD). We included studies published up to January 1, 2014, adjuvant and metastatic regimens, but not HER2/neu inhibitor containing regimens. Studies were included in the NMA with consensus of two authors. Our outcome measure was cardiac events greater than CTCAE grade 3. Bayesian NMA was conducted to estimate pooled Odds Ratio (OR). **Results:** Nineteen randomized controlled trials met criteria. We found a trend showing that LD is less cardiotoxic than Dox with an OR of 0.60 and 95% confidence interval (CI) [0.34-1.07]. There was no difference between Epi and LD with an OR of 0.95 and 95%CI [0.39-2.33]. Dox is more cardiotoxic than Non with an OR of 1.57 and 95%CI [0.90-2.72]. **Conclusions:** Our study showed that LD trended with a lower CE rate compared to Epi and Dox, but the difference did not reach statistical significance. One of the reasons is likely the small number of CE. Based on this analysis and given the low CE rate in the clinical context of the selected trials, the potential for cardiac toxicity need not be a major factor in clinical decision making.

| Comparison | Pooled OR | 95% CI |
|---|---|---|
| **LD vs Dox** | 0.60 | 0.34-1.07 |
| **LD vs Epi** | 0.95 | 0.39-2.33 |
| **Dox vs Non** | 1.57 | 0.90-2.72 |

**1057 General Poster Session (Board #150), Mon, 8:00 AM-11:45 AM**

**Assessing the value of weekly blood analysis in patients with localized breast cancer receiving adjuvant treatment with weekly paclitaxel.** *Presenting Author: Raul Diez-Fernandez, Hospital Universitario de Getafe, Getafe, Spain*

**Background:** Paclitaxel is one of the standard adjuvant treatments in localized breast cancer. Weekly paclitaxel has shown to improve disease-free and overall survival compared to every three weeks paclitaxel (Sparano JA et al, 2008). A retrospective analysis was conducted in our center in order to quantify the incidence of thrombocytopenia, neutropenia and impaired liver blood tests in patients with localized breast cancer receiving adjuvant treatment with weekly paclitaxel (80 mg/m$^2$). **Methods:** 163 patients over six years were identified from the chemotherapy prescription database. According to blood analysis results, patients were considered deemed well to receive treatment when neutrophils were $> 1.5$ x10$^9$/L, platelets were $> 100$ x10$^9$/L, ALT $< 10$xULN and bilirubin $< 1.25$xULN. **Results:** Patients received 1,862 infusions. 86 % of patients completed the 12 courses of chemotherapy previously planned and the mean number of weekly treatments was 11.42 per patient. Most patients had received previous treatment with anthracyclines (87.7%) and 46 patients (28.2%) received concurrent trastuzumab. Neutropenia (all grades CTC) occurred on 71 administrations (3.81 %) but was grade 3 in only 9 courses (0.48%); no grade 4 neutropenia was observed. Thrombocytopenia of any grade was not seen and only in two courses platelets were below 100 x 10$^9$/L. Increased blood bilirubin (any grade CTC) was seen in 25 courses of paclitaxel, but only in 9 of them they were above 1.25xULN (0.48%). No ALT results above 10xULN were observed. In 129 courses of chemotherapy the dose was reduced more than 5% (6.92%) but only in 25 courses this was due to neutropenia (1.34%) and in 3 courses due to increased bilirubin levels (0.16%). Treatment was hold 68 times (3.65%) and only in 16 courses this was because of neutrophil levels (0.86%). **Conclusions:** The incidence of neutropenia, thrombocytopenia and impaired liver blood tests is very low in patients with localized breast cancer receiving weekly paclitaxel as adjuvant treatment. Liver blood tests might be spared after the first course of chemotherapy and full blood count does not need to be checked on every course.

**1058 General Poster Session (Board #151), Mon, 8:00 AM-11:45 AM**

**Phase II randomized clinical trial evaluating neoadjuvant chemotherapy regimens with weekly paclitaxel (WP) or eribulin (E) followed by doxorubicin and cyclophosphamide (AC) in women with locally advanced HER2-negative breast cancer (LABC): NSABP FB-9.** *Presenting Author: Jame Abraham, Cleveland Clinic, Cleveland, OH*

**Background:** Eribulin (E) is a non-taxane, tubulin- and microtubule-targeting agent. In the randomized, phase III EMBRACE trial, disease-free survival and overall survival were prolonged in E versus physician's choice in heavily pretreated patients (pts). In this phase II randomized neo-adjuvant clinical trial, WP or E is followed by AC in patients with HER-2 negative LABC. The primary endpoint was pathologic complete response (pCR) in the breast and nodes. **Methods:** A total of 50 pts with LABC were accrued between January and August 2013. Median age was 50.5 years (range: 29-70 years). Twenty-three pts had stage IIB, 16 had stage IIIA, 9 had stage IIIB, and 2 had stage IIIC. Four pts had inflammatory breast cancer. Thirty-three were hormone-receptor positive and 17 were triple negative. Pts were randomly assigned (2:1) to receive either E (n= 31) (1.4 mg/m2 day 1 and day 8) every 3 weeks for 4 cycles, or WP (n= 19) (80 mg/m2) for 12 treatments. Both groups received AC (60 mg/m2 and 600 mg/m2) every 3 weeks for 4 cycles before surgery. Pts were evaluated by clinical examination and breast MRI at baseline and after completion of E or WP. MRI clinical partial response was defined as ≥30% decrease in tumor diameter. **Results:** Significant grade 3 toxicities included diarrhea (2%), febrile neutropenia (2%), mucositis (2%), and thromboembolic events (2%), 1 pt each. No pt experienced grade 3 or higher neuropathy. Baseline and follow-up MRI results are available on 44 pts. In the WP arm, 15/18 (83%) pts had a response (14 PR and 1 CR) and in the E arm, 15/26 (57%) had response (14 PR and 1 CR), either by investigator and/or central review. By central review WP pts had 50% response and E had 45%. Primary endpoint of pCR results will be reported. **Conclusions:** Both regimens are well tolerated with no unexpected toxicities. Both E and WP had moderate activity as per imaging in this LABC. A full analysis of complete pathological response data is pending. Clinical trial information: NCT01705691.

**1059 General Poster Session (Board #152), Mon, 8:00 AM-11:45 AM**

**Acute toxicity in African American and Caucasian patients with adjuvant/neoadjuvant chemotherapy for breast cancer.** *Presenting Author: Mansoor Ul Haq, University of Tennessee Health Sciences Center, Memphis, TN*

**Background:** The incidence of breast cancer is higher in Caucasian (C) compared to African American (AA) patients (pts), however the mortality is higher in AA. This disparity has been explained by a higher stage at diagnosis, triple negative tumors, high nuclear grade, and decreased access to health care among the AA women pts. This difference still persists when these factors are controlled. We hypothesized that AA pts have reduced dose intensity of chemotherapy due to treatment delays and dose reductions as a result of increased acute toxicity leading to inferior outcomes. **Methods:** Data was collected by retrospective chart review on 100 consecutive C and 100 AA pts with early stage breast cancer who received adjuvant or neoadjuvant chemotherapy during 2009 to 2011 at a community cancer center. Data collected included pt demographics, comorbidities, disease characteristics, treatment received, acute toxicities, and pt reported symptom burden as assessed by a validated electronic survey. **Results:** Mean age of C and AA pts was 56.1 vs. 51.5, respectively ($p = .0049$). All pts had ECOG performance status of 0-1, with no race differences. AA pts had higher rates of diabetes (17.0% vs. 11.9%) and hypertension (49.0% vs. 36.6%). The mean Charlson Comorbidity Index score was 3.1 for C and 3.4 for AA ($p = .064$). 44% of C presented at stage II and III as compared to 61% of AA patients ($p = .028$). AA had higher tumor grade ($p = .005$) . For chemotherapy AA got numerically more dose dense AC-paclitaxel, similar docetaxel-cyclophosphamide and less cyclophosphamide-methotrexate-5FU as compared to C. Most common side effects for C and AA respectively were, anemia: 50.5% vs. 68%, neutropenia: 14.9% vs. 12%, nausea: 27% vs. 15%, diarrhea: 13.9% vs. 11%, infection: 13.9% vs. 14% and neuropathy: 16.8% vs. 13%. Treatment delays and dose reductions did not differ between race groups. Patient reported symptom burden also did not differ among race groups. **Conclusions:** Despite difference in comorbidities and stage at presentation, no significant difference was observed in acute toxicities due to chemotherapy, in pt reported symptoms or the rates of chemotherapy delay and dose reduction between C and AA pts with early stage breast cancer.

**1060 General Poster Session (Board #153), Mon, 8:00 AM-11:45 AM**

**Effect of low-dose, short-course sunitinib (Su) on tumor vasculature and tumor blood flow for enhancement of chemotherapy efficacy in breast cancer.** *Presenting Author: Andrea Li Ann Wong, National University Health System, Singapore, Singapore*

**Background:** Continuous VEGFR-I use may ablate vasculature and impede chemotherapy delivery, failing to improve outcome; in contrast, low-dose, short-course VEGFR-I may normalize vasculature and enhance drug delivery. **Methods:** We conducted a phase Ib followed by phase II randomized study in chemonaive breast cancer patients to evaluate 1 week treatment with low-dose Su before each cycle of neoadjuvant doxorubicin/cyclophosphamide (AC) and measured tumor blood flow, vascular and lymphatic density with serial DCE-MRI and biopsy, at baseline, after 1 week Su, and after cycles 1 and 4 AC. **Results:** Phase Ib enrolled 9 patients: 25mg Su (n=3) reduced tumor blood flow; 12.5mg Su (n=6) increased tumor blood flow reflected by plasma volume (Vp) on DCE-MRI and increased SMA/CD31 staining indicating normal vessels, and was used in phase II. 47 patients were randomized in phase II: 24 AC, 23 Su+AC. 68%, 43%, 68%, 92% had T3-4, N+, ER+, HER2- tumor. No significant change in DCE-MRI parameters, SMA/CD31 and podoplanin staining was seen with AC alone. In contrast, Su+AC increased plasma volume and blood flow on DCE-MRI after 1 cycle (Vp 11.5 vs 8.4, p=0.047; F 104 vs 87, p=0.077), and SMA/CD31 double staining after 1 and 4 cycles (22.2 vs 48.9 vs 63.8, p=0.036) reflecting better tumor perfusion from normalized blood vessels. Su+AC also reduced lymphatic density after 1 and 4 cycles (podoplanin 3.3 vs 1.0 vs 0.7, p=0.039). Of note, SMA/CD31 change occurred in patients with good histological response after 1 AC (p=0.036), while podoplanin change occurred in ypN0-1 patients at surgery (p=0.038), and not those with less favorable response. Su+AC led to better histological response (grade 4-5) after 1 cycle (54% vs 25%) and more breast conservation (24% vs 10%), but pCR & node negativity rates (6 vs 5%; 35 vs 33%) were similar to AC alone, and may be due to more dose delay/reduction/omission from neutropenia (29% vs 5%, p=0.087). **Conclusions:** 1 week of 12.5mg Su prior to AC normalizes tumor vasculature to improve perfusion and reduces lymphatic density, which correlated with early histological response and less nodal involvement after chemotherapy, providing proof of concept of potential efficacy of this strategy. Clinical trial information: NCT01176799.

**1061 General Poster Session (Board #154), Mon, 8:00 AM-11:45 AM**

**Correlation between clinical tumor stiffness by elastography and response to neoadjuvant chemotherapy in patients with breast cancer.** *Presenting Author: Mitsuhiro Hayashi, Department of Breast and Endocrine Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto-city, Japan*

**Background:** Preclinical study has revealed that tumor stiffness can force tumor progression. Tumor stiffness appears to be caused by increased matrix cross-linking and changing in a number of stroma-related genes' expression, and seems to contribute to high malignant potential of tumor cells or disturb intestinal transportation of anti-tumor drugs in preclinical study. Now ultrasound elastography, can objectively evaluate tumor stiffness, has been clinically applied for differentiation of breast mass, therefore we explored novel clinical significance of tumor stiffness measured by elastography in breast cancer. **Methods:** We reviewed 432 patients with breast cancer who underwent ultrasound elastography before any treatments, including 79 patients who received neoadjuvant chemotherapy (NAC). We compared pre-NAC tumor stiffness with responses to NAC in patients treated by NAC, and investigated correlations between tumor stiffness and clinicopathological factors in all patients. The tumor stiffness was evaluated by fat lesion ratio (FLR) by strain elastography. **Results:** We categorized patients into two groups according to tumor stiffness with a cutoff value of FLR 10: 185 patients with high FLR (Hard tumor group) and 247 patients with low FLR (Soft tumor group). In patients treated by NAC, the hard tumor group had significantly lower pathological complete response (pCR) rate than the soft tumor group: 18% (8/44) vs. 63% (22/35), P<0.0001). There were also significant differences of pCR rate when we limited the analysis to triple negative cases (Hard 25% vs. Soft 88%, P=0.03) and HER2-positive cases (Hard 55% vs. Soft 93%, P=0.02). Multivariate analysis indicated that tumor stiffness was an independent predictive factor of pCR (hard tumor: odds ratio 0.04, 95%CI 0.004-0.226, P<0.0001) as well as HER2 status. In all patients, tumor stiffness was significantly correlated with tumor size, lymph node metastasis and fibrotic finding by conventional ultrasound. **Conclusions:** Pretreatment tumor stiffness evaluated by ultrasound elastography had a significant relationship with response to NAC in patients with breast cancer.

**1062 General Poster Session (Board #155), Mon, 8:00 AM-11:45 AM**

**A pilot study of dose-dense (biweekly) carboplatin plus paclitaxel with or without trastuzumab as neoadjuvant treatment for breast cancer.** *Presenting Author: Teng Zhu, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China*

**Background:** Dose-dense regimens have been shown to improve outcome when given as adjuvant therapy to patients with breast cancer compared with their three weekly counterparts. We investigated the efficacy and safety of dose-dense (biweekly) carboplatin and paclitaxel ± trastuzumab as neoadjuvant treatment in early breast cancer. **Methods:** Patients with tumor more than 2cm with or without node-positive breast cancer received treatment with 4 cycles of carboplatin area under the curve (AUC) 5 biweekly and paclitaxel 175mg/m$^2$ biweekly, and biweekly trastuzumab 4mg/kg was added for human epidermal growth factor receptor 2 (HER2) positive status. All patients received primary prophylaxis (PP) with recombinant human granulocyte colony-stimulating factors (G-CSF) from day 2 to 3. **Results:** Between 01/2009-12/2013, one hundred and twenty-two patients enrolled. The overall pathologic complete response (pCR) rate was 40.1 %( 49 out of 122). The pCR rate was 4.5%(1 out of 22) in patients of Luminal A Subtype; 13.8% in patients of Luminal B(HER2-) Subtype; 50.0% (9 out of 18)in patents of Triple Negative Subtype; 64.0%(16 out of 25) in patients of Luminal B(HER2+) Subtype; 85.0%(18 out of 21) in patients of HER2+ Subtype. 89 of 122 (73%) completed all chemotherapy as planned; the remaining patients (27%) had treatment modifications for toxicity. The dose limiting toxicities resulting in treatment discontinuation included: grade 3/4 neutropenia, grade 3/4 anemia, grade 3/4 thrombocytopenia, and other grade 3 nonhematologic toxicity including bone pain, neuropathy, mucocitis etc. There were 29(23.8%) episodes of grade 3/4 neutropenia, 4(3.27%) episodes of grade 3/4 anemia, and 2 (1.64%) episodes of grade 3/4 thrombocytopenia and there were 3(2.45%) episodes of grade 3 neuropathy. **Conclusions:** Dose-dense neoadjuvant carboplatin plus paclitaxel±trastuzumab is feasible and the regimen is more effective in Luminal B(HER2+) Subtype, HER2+ Subtype and Triple Negative Subtype. Additional study about the postoperative follow-up of this regimen is warranted.

**1063 General Poster Session (Board #156), Mon, 8:00 AM-11:45 AM**

**Is guideline-adherent adjuvant treatment an equivalent option for elderly patients who cannot participate in adjuvant clinical breast cancer trials? A retrospective multicenter cohort study of 4,142 patients.** *Presenting Author: Lukas Schwentner, Department of Gynecology and Obstetrics University Ulm, Ulm, Germany*

**Background:** It is well accepted that innovation in oncology is transported through randomized clinical trials (CT). However, elderly patients (>65) are usually excluded from CT. Therefore this study tries to answer the following questions: (1) Is there a difference in outcome parameters comparing study participants (PA) and elderly patients who are not able to participate? (2) Is guideline adherent treatment an equivalent option for elderly patients (>65)? **Methods:** This German multi-center [17 participating hospitals all are certified as breast cancer centers] retrospective cohort study called BRENDA included study participants <65 (PA) and elderly breast cancer patients >65 (E) obtained from 1992 until 2008. The definition of guideline adherence was based on internationally validated guidelines. **Results:** After adapting the exclusion criteria we included 960 (23.2%) PA and 3.182 (76.8%) E >65. E >65 demonstrate a significantly inferior RFS [RFS: p<0.001; HR=1.67 (95% CI: 1.32-2.11)] and OS [OS: p<0.001; HR=1.98 (95% CI: 1.50-2.62)] compared to PA <65. Within the E group 1.868 (58.7%) patients received guideline adherent adjuvant treatment. However when comparing PA <65 versus guideline conform E >65 we are not able to demonstrate a significant difference in RFS [RFS: p=0.218; HR=1.17 (95% CI: 0.91-1.50)] and OS [OS: p=0.054; HR=1.34 (95% CI: 1.00-1.81)]. However non-guideline adherent E >65 demonstrated significantly inferior survival parameters [RFS: p<0.001; HR=2.10 (95% CI: 1.61-2.62)] [OS: p<0.001; HR=2.50 (95% CI: 1.87-3.33)] compared to PA. **Conclusions:** Guideline adherent adjuvant treatment is an equivalent option for elderly patients who are excluded from participation in clinical trials. There is a strong association between guideline adherence and improved outcome parameters in elderly breast cancer patients.

**1064 General Poster Session (Board #157), Mon, 8:00 AM-11:45 AM**

**Stemness gene expression profile and correlation with clinicopathologic features (CPfs) in breast cancer (BC) patients (pts).** *Presenting Author: Giovanni Benedetti, Medical Oncology Macerata Hospital, Macerata, Italy*

**Background:** Cancer stem cells (CSC) identify a small pool of cells with self-renewal and pluripotency properties responsible of tumor initiation, maintenance and recurrence. The overexpression of genes maintaining pluripotency properties of CSC was described in poorly differentiated BC subtypes. We analyzed a panel of genes, responsible of CSC reprogramming and behaviour in a heterogenous group of BC tissues and correlated the gene expression profile with CPfs and prognosis. **Methods:** 140 primary invasive BC specimens (luminal A/B/Her2+/TN; n. 21/53/41/25) were collected from operated pts. mRNA expression for SOX2, SOX15, ERAS, SALL4, OCT4, NANOG, UTF1, DPPA2, BMI1, GDF3, ZFP42, KLF4 and TCL1 genes was assessed by RT-PCR. Correlations with molecular subtypes, menopausal status, grading, ER, PR, ki67 ($<$ or $>$ 20%), HER2, T-size and node status (N) were evaluated by Fisher's exact test and $\chi^2$ test. Association of stemness genes, CPfs and DFS was estimated by univariate and multivariate Cox-regression analysis ($p \leq 0.05$) . **Results:** In 117 samples assessable, 9 out of 13 stemness genes resulted variably expressed: GDF3 = 9, Sox2= 11, ERAS= 20, sox15 = 25, TCL1= 29, Nanog = 52, KLF4 = 67, SALL4 = 68, BMI1 = 97, without any correlation with molecular subtypes. NANOG, GDF3 and SOX2 significantly correlated with grade 2, N negative and higher KI67 respectively (p=0.019, p=0.029, p= 0.035). At univariate analysis SOX2 expression (HR= 2,357; p= 0.002), KI67 (HR= 2,187; p=0.028), N (HR=2,205; p=0.014); ER/PR (HR=0,582/HR=0,589; p0.065/0.068, respectively) resulted statistically significant. According to multivariate analysis, SOX2 (HR= 2,99; 95% CI 1,41-6,30; p=0.004), N (HR=2,44; 95%CI 1,25-4,76; p=0.009) and T-size >1 (HR=1,77; 95% CI=0,99-3,13; p=0.051) were independently associated with increased risk of recurrence, PR expression was associated with better prognosis (HR=0,57; 95% CI= 0,53-0,29; p=0.035). **Conclusions:** Our analysis confirm that stemness genes are variably expressed in a heterogenous group of BC pts, albeit only specific genes seem to correlate with any CPfs. Of note, SOX2 appeared to be a prognostic marker of recurrence irrespective of other variables.

**1065 General Poster Session (Board #158), Mon, 8:00 AM-11:45 AM**

**Application of a dynamic retraining for each patient using case-specific training cohorts to predict survival in breast cancer patients.** *Presenting Author: Balazs Gyorffy, Ist Department of Pediatrics, Semmelweis University, Budapest, Hungary*

**Background:** To exceed prediction accuracy of previous multigene prognostic classifiers, we propose a new dynamic predictor. Our classifier does not use a single universal training cohort and an identical list of informative genes to predict the prognosis of new cases but a case-specific predictor is developed for each test case. **Methods:** Gene expression data from 3,534 breast cancers with clinical annotation including survival was analyzed. For each test case we select a case-specific training subset including only molecularly similar cases and a case-specific predictor is generated. This method yields different training sets and different predictors for each new patient but preserves the independence of model building and validation. The model performance was assessed in leave-one-out validation and also in 325 independent cases. **Results:** Prognostic discrimination was high for all cases (n=3,534, HR=3.68, p=1.67E-56). The dynamic predictor showed higher overall accuracy (0.68) than the 21-gene predictor (0.64), the 97-gene genomic grade index (0.55) or the 70-gene prognostic signature (0.41). The dynamic predictor was also effective in triple-negative cancers (n=427, HR=3.08, p=0.0093) where the above classifiers all failed. Validation in independent patients yielded similar classification power (HR=3.57). The dynamic classifier is available online at http://www.recurrenceonline.com/?q=Re_training. **Conclusions:** In summary, we developed a new method to make personalized prognostic prediction using case-specific training cohorts. The dynamic predictors outperform static models developed from single historical training cohorts and they also predict well in triple-negative cancers.

**1066 General Poster Session (Board #159), Mon, 8:00 AM-11:45 AM**

**A phase II neoadjuvant trial of sequential triweekly nanoparticle albumin-bound paclitaxel and cyclophosphamide followed by 5-fluorouracil/ epirubicin/ cyclophosphamide in the treatment of operable breast cancer.** *Presenting Author: Norio Masumoto, Department of Surgical Oncology, Hiroshima University, Hiroshima, Japan*

**Background:** Nanoparticle albumin-bound (nab) Paclitaxel has shown favorable efficacy and toxicity profiles compared to other taxanes in the treatment of metastatic breast cancer. In this phase II trial, we evaluated a nab-paclitaxel-containing neoadjuvant regimen in patients with operable breast cancer. **Methods:** Fifty-five women with operable breast cancer without prior treatment were enrolled. All patients were to receive tri-weekly nab-paclitaxel and cyclophsphamide (TRI-ABC) followed by 5-fluorouracil/ epirubicin/cyclophosphamide (FEC) every 3 weeks for 4 cycles. Tri-weekly trastuzumab was administered concomitant with TRI-ABC in HER2-positive (HER2+ or 3+) patients. Primary endpoint was pathologic complete response (pCR; CR) rate in breast cancer tissue and lymph nodes. Secondary endpoints included clinical response, safety, rate of breast conserving surgery and disease-free survival. **Results:** Fifty-four patients received at least 1 dose of chemotherapy and were included in this analysis. All patients completed 4 cycles of TRI-ABC and 50 completed 4 cycles of FEC. The pCR rate was 36.5% (19/54). More patients with HER2-positive or triple-negative cancer experienced a pCR [59% (10/17) for HER2-positive, 57% (8/14) for triple-negative] compared with those of ER-positive/HER2-negative cancer [4% (1/23)]. The most significant toxicities were grade 2/3 neuropathy (16%) in TRI-ABC and grade 3/4 febrile neutropenia (7%) in FEC. **Conclusions:** TRI-ABC and FEC containing neoadjuvant regimen was well tolerated and showed favorable efficacy, especially in patients with chemo-sensitive breast cancer. These results suggest that albumin-bound paclitaxel based neoadjuvant regimen should be further evaluated in patients with ER-negative or HER2-positive breast cancer. Clinical trial information: 000007180.

**1067 General Poster Session (Board #160), Mon, 8:00 AM-11:45 AM**

**Impact of pharmacogenetics on docetaxel as neoadjuvant treatment of breast cancer.** *Presenting Author: Hanjing Xie, Karolinska Institutet, University Hospital, Stockholm, Sweden*

**Background:** Marked inter-individual variability of docetaxel has been reported previously. The pharmacogenetic contribution to variations of docetaxel-related toxicity and therapeutic response has not yet been thoroughly studied. The polymorphic cytochrome P450 (CYP) 3A4 plays en essential role in the metabolism of docetaxel. A comparatively frequent allele - CYP3A4*22, which was recently identified, has been shown to correlate with reduced enzyme activity. In this study, we aimed to investigate the effect of CYP3A4 as well as CYP3A5 genotype on docetaxel treatment in breast cancer patients. **Methods:** In the PROMIX trial, 151 patients with breast cancer received preoperatively six courses of docetaxel and epirubicin. In case of no change or partial response after the first two courses, bevacizumab was added for the remaining four courses. Grade 3 or 4 adverse events (AEs) and data on clinical/radiological and pathological response were addressed in relation to CYP3A4 genotype. Blood samples were used to extract DNA for genotyping analyses. **Results:** The allelic frequency of CYP3A4*22 and CYP3A5 *3 were 3 % and 8 %, respectively. Seven patients had decreased catabolic activity of docetaxel (PM), 22 patients had increased activity (EM), and 121 patients had normal activity (IM). Regarding the toxicity, a clear genetic influence was seen. The frequency of grade 3/4 AEs was significantly higher in the PM group, compared to that in the EM and IM group (P=0.02). 71.4 % of the patients in the PM group reported grade 3/4 AEs, while the frequency for the EM and IM groups were only 45.5 % and 44.6 %, respectively. One single patient was homozygote for both CYP3A4*22 and CYP3A5 *3, thus lacking enzyme activity, experienced a fatal colon necrosis shortly after the first course of treatment. After a median follow up of 25 months, there were in total 33 relapses, but none of them reported from PM group. **Conclusions:** The allelic variants CYP3A4*22 and CYP3A5 *3 contribute significantly to the inter-patient variations of docetaxel treatment. The impact of pharmacogenetics on a widely used drug as docetaxel must be considered in the era of individualized therapies. Genotyping should be considered as a valuable tool for dose optimization. Clinical trial information: NCT00957125.

**1068 General Poster Session (Board #161), Mon, 8:00 AM-11:45 AM**

**Cardiovascular magnetic resonance imaging compared to echocardiogram for detecting doxorubicin-induced cardiotoxicity.** *Presenting Author: Haleem J. Rasool, Mayo Clinic Health System, La Crosse, WI*

**Background:** Doxorubicin is a standard treatment for breast cancer, lymphoma, and leukemia. The benefits of doxorubicin are limited by its potential for cardiotoxicity. In this study we investigated whether MRI is superior to echocardiogram in detecting a reduction in cardiac systolic function indicative of doxorubicin toxicity. **Methods:** We studied all eligible prospective patients ages 18 years and above who presented to Mayo Clinic Health System, La Crosse WI, for the treatment of breast cancer or lymphoma and who were offered treatment with doxorubicin with curative intent dosing (240 - 300 mg/m2) between March 1, 2009 and October 2013. Patients received baseline cardiac MRI and echocardiogram. Both studies were repeated after 4 cycles of treatment. Ejection fraction calculated by both methods was compared and analyzed using the T-test. **Results:** We enrolled 28 eligible patients between the ages of 39 and 78 years. Twenty six patients received baseline echocardiogram and cardiac MRI. Eighteen patients completed the post treatment studies after 4 cycles of doxorubicin. Seven patients declined to undergo post treatment studies. The average baseline EF by echocardiogram was 61.5% and by MRI was 61.8%. Post treatment EF by echocardiogram was 60.9% and by MRI was 57.1%. There was no statistically significant drop in EF by echocardiogram while there was a statistically significant drop in EF using cardiac MRI ($p$ value $< 0.05$). Cardiac MRI findings alone did not lead to any doxorubicin dose reductions. **Conclusions:** Cardiac MRI is superior to echocardiogram in detecting doxorubicin induced reduction in cardiac systolic function. Echocardiogram is less expensive and more convenient for patients while MRI may be more sensitive in detecting doxorubicin cardiotoxicity. A larger study to confirm these findings is needed.

**1069 General Poster Session (Board #162), Mon, 8:00 AM-11:45 AM**

**The efficacy and safety of paclitaxel injection concentrate for nanodispersion (PICN) at two different doses versus paclitaxel albumin-stabilized nanoparticle formulation in subjects with metastatic breast cancer (MBC).** *Presenting Author: Minish Mahendra Jain, KEM Hospital and Research Center, Pune, India*

**Background:** PICN is a novel, solvent- and protein-free, 100-110 nm particle formulation of paclitaxel stabilized with polymer and lipids using Nanotecton Technology. We compared the safety and efficacy of PICN at two different doses versus paclitaxel albumin-stabilized nanoparticle formulation in a 3-weekly schedule in subjects with MBC. **Methods:** In this randomized, controlled non-inferiority trial,180 subjects aged18-65 years, with MBC, ECOG performance status $\leq 2$, estimated survival $\geq 12$ weeks and adequate organ function, were enrolled and randomly assigned to PICN 260 mg/m$^2$, PICN 295 mg/m$^2$, or paclitaxel albumin-stabilized nanoparticle formulation 260 mg/m$^2$. Both PICN and paclitaxel albumin-stabilized nanoparticle formulation were administered as a 30 min infusion in a 3-weekly dosing schedule. Treatment was continued until disease progression or the occurrence of unacceptable toxicity. Efficacy was evaluated according to RECIST 1.1 and safety was assessed using CTC-AE version 4.0. **Results:** A total of 180 subjects were enrolled in the study; 64 to PICN 260 mg/m$^2$ and 58 each to PICN 295 mg/m$^2$ and paclitaxel albumin-stabilized nanoparticle formulation 260 mg/m$^2$. Baseline demographic, medical and treatment history, and histologic criteria were well balanced. By independent blinded radiological assessment, no statistical difference was observed in ORR (Objective Response Rate) when PICN 260 mg/m$^2$ and paclitaxel albumin-stabilized nanoparticle formulation (35.4% v 42.5%, respectively; P=.76) or when PICN 295 mg/m$^2$ and paclitaxel albumin-stabilized nanoparticle formulation (48.8% v 42.5%, respectively; P=.62) were compared. No hypersensitivity reactions occurred with PICN despite the absence of premedication. The most frequently reported AEs were neutropenia, peripheral neuropathy and pain. The incidence of grade 3/4 neutropenia was 12.5, 24.1, and 20.6% in PICN 260 mg/m$^2$, PICN 295 mg/m$^2$, and paclitaxel albumin-stabilized nanoparticle formulation arm, respectively. Grade 3/4 peripheral neuropathy occurred in 7.8, 19, and 15.5% subjects with PICN 260 mg/m$^2$, PICN 295 mg/m$^2$and paclitaxel albumin-stabilized nanoparticle formulation arm, respectively. **Conclusions:** PICN when administered as 3-weekly dosing schedule demonstrated equal efficacy and a favorable safety profile compared to paclitaxel albumin-stabilized nanoparticle formulation in MBC. Clinical trial information: CTRI/2010/091/001116.

**1070 General Poster Session (Board #163), Mon, 8:00 AM-11:45 AM**

**Additional metabolic effects at the neoadjuvant chemotherapy (NCT) of locally advanced breast cancer (LABC).** *Presenting Author: Natalya A Abramova, Rostov Scientific Research Institute of Oncology, Rostov-on-Don, Russia*

**Background:** Dissociation of cellular respiration and oxidative phosphorylation (OF) in the mitochondria promotes activation of regulatory cascades of apoptosis and necrosis. Probably the local impact of drugs that block the various stages of the Krebs cycle - diphenhydramine (D) (NAD↔NADH transformations) or ATF (aerobic ATF resynthesis inhibition due to feedback)- may result in increased the damaging action of cytostatics. Coordination of key Krebs cycle enzymes activity when peritumoral injected D/ATF with clinical efficacy on LABC NCT was investigated. **Methods:** Elegibility criteria included measurable histologically verified LABC T3-4N0-3M0, ECOG$\leq$1. 2 cycles of NCT (FAC) were combined with injection of D/ATF in peritumoral zone 30 minutes before the start of NCT in the test group. Tumor response was assessed and compared to control group. OF processes activity was evaluated by the method of measuring of succinate dehydrogenase (SDH) and $\alpha$-glycerophosphate ($\alpha$-GPDH) in blood peritumoral lymphocytes before and 30 minutes after D/ATF injection, prior to administration of NCT (test group). **Results:** 60 pts were recruited (30- test and 30- control group). Test group tumor response was: CR 16,7%(5),PR 66,6%(20),SD16,7%(5). Control group tumor response was PR 66,6%(20),SD 30,0%(7),PD 3,4%(1). Differences are valid for CR ($p=0.014$) and SD($p=0.019$). Decrease in the activity of LDH after ATF was observed in 62.5% of the samples ($p=0.021$), after D- in 57.9% of the samples ($p=0.024$), the increase in $\alpha$-GPDH after D/ATF- in 41.6% of samples ($p=0.022$). The data showed a decrease in intensity of the OF in peritumoral area by injection of D/ATF. **Conclusions:** Changes in the activity of key Krebs cycle dehydrogenases in peritumoral lymphocytes with injections of D/ATF corresponds to clinical data on significant improvement in tumor response NCT LABC pts.

**1071 General Poster Session (Board #164), Mon, 8:00 AM-11:45 AM**

**Neoadjuvant chemotherapy for patients with breast cancer during pregnancy (BCP).** *Presenting Author: Sibylle Loibl, German Breast Group/Sana Klinikum Offenbach, Neu-Isenburg, Germany*

**Background:** Neoadjuvant therapy (NAT) is increasingly considered the treatment of choice for patients with HER2+ and triple-negative (TNBC) breast cancer. It is recommended to treat patients with breast cancer during pregnancy as closely as possible according to patients diagnosed outside pregnancy. Data on NAT during pregnancy are scarce. We compared patients with BCP who received NAT with pregnant patients who received NAT after delivery. **Methods:** Patients from the registry of the German Breast Group (GBG 29/BIG 02-03) and the international Cancer in Pregnancy initiative with BCP who received NAT were analyzed. A non-pregnant control cohort was matched using the Propensity Score based on age, cT Stage (cT 1-2 vs 3-4), cN Stage (cN0 vs cN+), grading (1 vs 2 vs 3), ER/PgR, HER2, neoadjuvant trastuzumab therapy. **Results:** 103/130 neoadjuvant treated BCP patients were identified with complete data who received NAT during pregnancy (n=62) or after delivery (n=41). Baseline characteristics were comparable. 42% HER2+ and 34% had TNBC. Median age was 34 years. BC was diagnosed in the first or second trimester in 63% of patients with NAT during pregnancy and in 19% of patients with NAT after delivery ($p<0.001$). Non-taxane containing regimen received 26% of patients with NAT during pregnancy compared to 5% of patients with NAT after delivery ($p<0.001$), taxane sequence received 73% and 69%, taxane combination received 0 vs 27%, and neoadjuvant trastuzumab received 64% vs. 77%, respectively. pCR (ypT0 ypN0) rate was 24% vs 23% ($p=1.0$). There was no difference in DFS and OS for patients with NAT during pregnancy vs thereafter (log rank $p=0.940$ and $p=0.653$). **Conclusions:** Based on this first analysis it seems that NAT during pregnancy is as effective as after delivery in patients with BCP. Results of the comparison with a non-pregnant control-cohort treated with NAT will be presented at the meeting.

**1072 General Poster Session (Board #165), Mon, 8:00 AM-11:45 AM**

**Sorafenib (SOR) plus docetaxel (DOC) as first-line therapy in patients with HER2-negative metastatic breast cancer (MBC): A randomized, placebo-controlled phase II trial.** *Presenting Author: Frederik Marme, National Center for Tumor Diseases, Gynecologic Oncology, Heidelberg, Germany*

**Background**: Anti-angiogenic therapy with the monoclonal anti-VEGF antibody Bevacizumab (Bev) in combination with chemotherapy increases overall response rates (ORR) and progression free survival (PFS) but without impact on overall survival. SOR, an anti-angiogenic multi-tyrosine kinase inhibitor (TKI) also targeting tumor growth directly, is approved for advanced renal cell and hepatocellular carcinoma. Three phase IIb trials (SOLTI-0701, NU07B1, AC01B07) have reported efficacy of SOR in combination with chemotherapy in MBC, even after prior Bev (AC01B07). As TKIs might have superior activity we conducted this trial in first-line MBC. **Methods**: Pts were randomized to DOC (75mg/m$^2$ q3w) + either SOR (400 p.o. twice daily (BID)) or placebo. Following an amendment after the inclusion of 63 pts, the SOR starting dose was reduced to 400 mg/d for cycle 1 and 600 mg/d for cycle 2 with the option to increase the dose to 800 mg/d after the second cycle in the absence of > grade 1 toxicities. The planned sample size was 288, but due to slow accrual the study was closed early after 102 patients. The primary end point was progression free survival (PFS). Important secondary endpoints were overall response rate (ORR), duration of response, time to progression (TTP), overall survival (OS) and safety/tolerability. Here we report the data after 78 PFS events in 95 evaluable patients. **Results**: Median age was 57 years with 71.6% of patients being post-menopausal. 74.5 of patients had a positive estrogen receptor (ER) status and 47.1% and 48.0% of patients had a tumor grading 2 and 3, respectively. Overall, as of December 13$^{th}$2013, the median PFS was 7.4 months with a median TTP of 7.9 months, a median duration of response of 8.9 months and an ORR of 47.1%. The corresponding median OS was 21.2 months. Grade 3 to 4 toxicities (> 5% of pts) included neutropenia (31%), lymphopenia (25%), leukopenia (25%), HFSR (19%), diarrhea (11%), febrile neutropenia (9%), and fatigue (8%). **Conclusions**: Final efficacy data including overall survival and detailed safety data will be presented by treatment arm. Comparative efficacy and safety data will also be presented by SOR dosing schedule. Clinical trial information: EUDRACT-Nr. 2008-001090-15.

**1073 General Poster Session (Board #166), Mon, 8:00 AM-11:45 AM**

**Response rates of taxane rechallenge in metastatic breast cancer patients, previously treated with adjuvant taxanes.** *Presenting Author: Arzu Oguz, Baskent University, Medical Oncology Department, Ankara, Turkey*

**Background:** This study was conducted to determine the efficacy of taxane-based regimens in metastatic breast cancer patients who have already taken taxanes in their adjuvant treatments and also to assess the response rates in each treatment line. **Methods:** The data of 938 metastatic breast cancer patients who had taken adjuvant taxane based chemotherapy, were reviewed retrospectively. Besides demographical variables, the treatments that were given when metastases occured, response rates (RR), clinical benefit rates (CBR: complete response (CR)+ partial response (PR) + stable disease (SD)) and progression free survival values were determined. For patient and tumor characteristics, descriptive statistical methods were used. Chi-Square test was used to compare differences between categorical variables. Kaplan-Meier curves were drawn to obtain survival probabilities and log rank test was used to compare these curves between groups. **Results:** Of 938 cases, metastases were detected in 189 (20.1%) during follow-up. The response rate in 45 patients receiving re-challenge with taxanes as first line treatment was 51.2% consisting of 4 (8.8%) complete and 19 (42.2%) partial remissions. The RR and CBR of taxane re-challenge in first line and later line therapies are summarized in the Table. When RR and progression free survivals were taken into account, there were no significant differences detected between patients receiving re-challenge with taxanes who had less than 2 years DFS until recurrence compared with those having DFS values more than 2 years (p values were 0.3 and 0.65 respectively). **Conclusions:** Re-challenge with taxanes both in the first line and later line trearments appear to be effecive and seems to be a reasonable option in taxane pre-treated patient group, due to the satisfactory response rates in all treatment lines. It was not possible to make a suggestion for those patients who had a DFS less than 1 year because of poor number of patients.

**Response rates of taxane rechallenge in treatment lines.**

| | First line | Second line | ≥ Third line |
|---|---|---|---|
| **Response rates** | 51% | 40% | 37% |
| **Clinical benefit rates** | 64% | 51% | 53% |

**1074 General Poster Session (Board #167), Mon, 8:00 AM-11:45 AM**

**Phase I trial of the PARP inhibitor veliparib (V) in combination with carboplatin (C) in metastatic breast cancer (MBC).** *Presenting Author: Robert Wesolowski, The Ohio State University, Columbus, OH*

**Background:** Poly(ADP-ribose) polymerase (PARPi) inhibitors have shown activity in BRCA mutant and triple negative breast cancers (TNBC). The ideal dose and schedule of C and oral PARPi V is not known. We used sequential fluoro-3'-deoxythymidine (FLT) PET imaging and correlated tumor uptake to C with varying doses/schedules of V. **Methods:** To identify the recommended phase 2 dose (RP2D) of V when combined with C in patients (pts) with MBC with either TNBC or HER2 negative/estrogen receptor positive tumors with defective Fanconi Anemia (FA) pathway (i.e. no FANCD2 foci in nuclei of proliferating tumor cells via FA Triple Stain Immunofluroscence test), we used a standard 3+3 phase I design. Escalating doses of V were evaluated on a 7, 14, or 21-day schedules (table). Response was based on RECIST criteria using FDG PET/CT scans. FLT PET was done at baseline, cycle 1 day 7 and 14 or 21 and after cycle 3. Lesions were track-matched with FDG PET/CT and semi-quantitatively assessed using 2D ROI placement in a matched, blinded fashion. **Results:** 44 pts with a median of 2 prior lines of chemotherapy (range 0-3), received a median of 5 cycles (range 1-36); 39 had TNBC. The table shows observed DLTs. Of 43 evaluable pts, 18.6% had a PR; 48.8% had SD. Of 16 pts with BRCA 1/2 mutation or defect in FA pathway, 25% had a PR and 62.5 % had SD. The change in SUV on FLT PET between baseline and follow up scans did not depend on dose or schedule of V (N=24). Pts with PR had significant drop in max SUV of target lesions between baseline and day 14 or 21 FLT PET compared to non-responders (p=0.046 - Wilcoxon Rank Sum test). **Conclusions:** Combination of V and C is active in MBC. Thrombocytopenia was the major toxicity observed. The RP2D is C: AUC 5 and V: 250 mg bid on days 1-21. We observed that early drop in SUV values on FLT PET was predictive of response. The study is supported by U01 CA076576. Clinical trial information: NCT01251874.

| Dose level | C dose (AUC) | V dose/schedule | N | DLT |
|---|---|---|---|---|
| **1** | 6 | 50 mg BID (D1-7) | 7 | G4 thrombocytopenia (N=2)<br>G4 neutropenia (N=1) |
| **1A** | 5 | 50 mg BID (D1-7) | 3 | None |
| **2** | 5 | 50 mg BID (D1-14) | 6 | Gr 4 thrombocytopenia (N=1) |
| **3** | 5 | 100 mg BID (D1-14) | 3 | None |
| **4** | 5 | 150 mg BID (D1-14) | 6 | G3 akathisia (N=1) |
| **5** | 5 | 200 mg BID (D1-14) | 6 | G4 thrombocytopenia (N=1) |
| **6** | 5 | 200 mg BID (D1-21) | 7 | G4 thrombocytopenia (N=1) |
| **7** | 5 | 250 mg BID (D1-21) | 6 | None |

**1075 General Poster Session (Board #168), Mon, 8:00 AM-11:45 AM**

**Safety and efficacy of *nab*-paclitaxel (*nab*-P) in patients (pts) with metastatic breast cancer (MBC): Real-world results from a U.S. health insurance database.** *Presenting Author: Debra A. Patt, McKesson Specialty Health, The Woodlands, TX*

**Background:** *nab*-P is an albumin-bound formulation of paclitaxel approved in 2005 for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy, based on an international phase 3 trial comparing *nab*-P with paclitaxel on an every 3 week (q3w) schedule. The objective of this study was to characterize safety and efficacy outcomes of *nab*-P in MBC in the United States using health insurance claims data. **Methods:** A retrospective claims analysis was conductedusing the Optum Research Database (United Health affiliate). The analysis included women aged ≥ 18 years diagnosed with MBC (≥ 2 claims of BC diagnosis separated by ≥ 30 days and ≥ 2 claims of metastatic spread) prior to *nab*-P initiation. Pts had ≥ 6 months of continuous enrollment in a US health insurance plan from January 2005 through September 2012, complete medical coverage and pharmacy benefits, no other primary malignancy, and no prior *nab*-P. Data were supplemented by Social Security Death Index sources. Cohorts were determined by line of therapy, *nab*-P regimen, and schedule. Descriptive statistics were used to characterize outcomes. Endpoints included treatment patterns, time to treatment discontinuation (TTD), overall survival (OS), and safety. **Results:** Of the 664 eligible pts, most were between 40-69 years of age (88%) and had received *nab*-P as ≥ second-line therapy (74%), monotherapy (61%), and weekly dosing (71%). Agents used in combination with *nab*-P included bevacizumab (22%) and HER2-targeted therapies (9%). Median TTD and OS were 6.1 and 17.4 months, respectively. By line of therapy (first, second, and ≥ third), TTD was 7.1, 6.6, and 5.3 months and OS was 22.7, 17.4, and 15.1 months. In a subgroup of pts with aggressive disease (≤ 50 years of age or having ≥ 3 metastases), median OS was 15.6 months, similar to the overall cohort. No new safety signals were observed. **Conclusions:** Consistent with clinical trial data, outcomes in this real-world population confirm the effectiveness and manageable safety profile of *nab*-P in pts with MBC. This analysis will also help evaluate the benefit of *nab*-P in pts aged ≥ 70 years.

**1076 General Poster Session (Board #169), Mon, 8:00 AM-11:45 AM**

**Does chemotherapy schedule matter when combining with bevacizumab? A stratified meta-analysis of randomized controlled trials.** *Presenting Author: Twan Ying Chang, National Taiwan University Hospital, Taipei, Taiwan*

**Background:** Adding bevacizumab (Bev) to chemotherapy (CT) improved the objective response rate and progression free survival (PFS) in many randomized controlled trials (RCTs), but the magnitude of benefit varied. For example, in advanced breast cancer, the magnitude of prolongation of PFS in weekly chemotherapy study (E2100) was more significant than that in non-weekly chemotherapy studies (AVADO and RIBBON-1). We conducted a meta-analysis to examine the association of chemotherapy schedules with Bev benefit in advanced cancers. **Methods:** Through literature search, we identified 26 RCTs which compared combination of Bev plus CT with CT alone for advanced cancers. Among them, 21 RCTs which contained different CT schedules within certain cancer type were enrolled. These included 5, 4, 5 and 7 RCTs for breast, ovary, lung and colorectal cancers. A meta-analysis with random effects model was conducted to generate summary estimates of Bev benefit in terms of the improvement of PFS. CT schedules were classified into weekly (w), non-weekly (non-w), and weekly + non-weekly (w/non-w). We performed the stratified analysis of CT schedules, CT drugs, and CT lines, cancer types, and Bev dosage/schedule. The Bucher's method was used to indirectly compare the PFS improvement from Bev. **Results:** Among the 21 RCTs, 7, 12, and 2 studies were with w, non-w, and w/non-w CT schedules, respectively. Overall, Bev in combination with CT was associated with a significant benefit of PFS (hazard ratio [HR], 0.66; 95% CI, 0.60-0.73). The HRs for w, non-w, and w/non-w CT schedules were 0.53 (95% CI: 0.45-0.63), 0.74 (95%CI: 0.68-0.81), and 0.61 (95% CI: 0.40-0.93), respectively. Using Bucher's method, the benefit of adding Bev was significantly greater in w CT schedule than that in the non-w CT schedule (HR: 0.71; 95% CI: 0.59-0.87). In contrast, the benefit of adding Bev did not statistically differ among various CT drugs, CT lines, cancer types, or Bev dosage/schedule. The overall heterogeneity ($I^2$=76.1% for 21 RCTs) was reduced after CT schedule stratification ($I^2$=36.7% for w and $I^2$=52.1% for non-w CT schedule). **Conclusions:** When combining Bev with CT, weekly CT schedule was associated with greater improvement of PFS.

**1077 General Poster Session (Board #170), Mon, 8:00 AM-11:45 AM**

**Comparison of the clinical treatment score with the adjuvant online score and the risk for recurrence score for estimating prognosis in early-stage high-risk breast cancer patients: A Hellenic Cooperative Oncology Group study.** *Presenting Author: Kyriaki Pliarchopoulou, Hellenic Cooperative Oncology Group (HeCOG), Athens, Greece*

**Background:** Early breast cancer is a heterogeneous disease, and, therefore, prognostic tools have been developed to evaluate the risk for distant recurrence. We compared the Clinical Treatment Score (CTS) with the Adjuvant Online Score (AOS) and the Risk for Recurrence Score (RRS) based on the expression of three proliferation markers (RACGAP1, Ki67 and TOP2A) in high-risk early breast cancer patients. **Methods:** A total of 1,681 patients, enrolled in two prospective phase III trials, were treated with anthracycline-based adjuvant chemotherapy. Formalin-fixed paraffin-embedded primary tumor tissue samples with adequate material were obtained from 898 patients. Sufficient RNA was extracted from 875 samples (52.1% of the randomized patients) followed by multiplex RT-PCR for assessing RACGAP1, Ki67, TOP2A and CALM2 mRNA expression. The CTS integrated the prognostic information from nodal status, tumor size, histological grade and age. **Results:** CTS was prognostic for disease-free survival (DFS, $p<0.0001$), while CTS, AOS and RRS were all prognostic for overall survival (OS, $p<0.0001$, $p<0.0001$, $p=0.036$, respectively). The use of AOS in addition to CTS added prognostic information regarding DFS (LR-$\Delta\chi^2$ 11.9592, $p<0.0001$). However, the use of RRS in addition to CTS was not proven to be a better prognostic tool in terms of DFS (LR-$\Delta\chi^2$ 0.8495; $p=0.357$). For estimating OS, the use of either AOS or RRS in addition to CTS added significant prognostic information. Specifically, the use of both CTS and AOS had significantly better prognostic value vs CTS alone (LR-$\Delta\chi^2$ 28.2266, $p<0.0001$), as well as the use of CTS and RRS vs CTS alone (LR-$\Delta\chi^2$4.2057; $p=0.040$). Additionally, more patients were scored as high-risk by AOS than CTS. **Conclusions:** Using CTS, AOS or RRS provides prognostic information in high-risk early breast cancer patients, with more patients determined as high-risk by AOS. The combination of CTS and AOS adds significant prognostic information compared to CTS alone for DFS, while the combination of CTS with either AOS or RRS are better prognostic tools than CTS alone for OS.

**1078 General Poster Session (Board #171), Mon, 8:00 AM-11:45 AM**

**Chemosensitivity and endocrine sensitivity predicted by mammaprint and blueprint in the Neoadjuvant Breast Registry Symphony Trial (NBRST).** *Presenting Author: Pat W. Whitworth, Nashville Breast Center, Nashville, TN*

**Background:** Classification into molecular subtypes is important for the selection of therapy for patients with breast cancer. Previous analyses demonstrated that breast cancer subtypes have distinct clinical outcome (Gluck, BCRT 2013). The aim of the prospective NBRST study is to measure chemosensitivity as defined by pathological Complete Response (pCR), or endocrine sensitivity as defined by partial response (PR) and metastasis-free survival in molecular subgroups. **Methods:** The study includes women aged 18-90 with histologically proven breast cancer, who are scheduled to start neo-adjuvant chemotherapy (NCT) or neo-adjuvant endocrine therapy (NET), and who provide written informed consent. Additional inclusion criteria include no excision biopsy or axillary dissection, no confirmed distant metastatic disease, and no prior therapy for breast cancer. Treatment is at the discretion of the physician adhering to NCCN approved regimens. **Results:** 336 Patients, T1-4 N0-3, had definitive surgery and the overall pCR rate was 24%. 32/167 (19%) IHC/FISH ERPR+/HER2- patients were re-classified by BluePrint (31 Basal). 43/95 (45%) IHC/FISH HER2+ patients were re-classified by BluePrint (25 Luminal and 18 Basal). 3/74 (3%) IHC/FISH triple negative patients were not Basal by BluePrint. Of 45 (13%) patients classified as Luminal A 32 received NCT; 1 patient (3%) had a pCR; 13 patients received NET and 9 (70%) had a PR. Of 116 (35%) patients classified as Luminal B 111 received NCT and 7 (6%) had a pCR. The pCR rate (17/149 (11%)) in IHC/FISH ERPR+/HER2- patients was higher. 55 (16%) are BluePrint HER2 and received NCT (51 plus trastuzumab); 27 (49%) had a pCR compared to 35/95 (37%) in IHC/FISH HER2+ patients. 120 (36%) are BluePrint Basal and received NCT; 46 (38%) had a pCR, similar to the pCR percentage seen in the 74 patients designated triple-negative by IHC/FISH. **Conclusions:** Molecular subtyping using MammaPrint and BluePrint leads to a reclassification of 23% (78/336) of tumors. BluePrint reclassification resulted in better grouping of patients into expected response groups compared to local surrogate subtyping with immunostains. Clinical trial information: NCT014799101.

**1079 General Poster Session (Board #172), Mon, 8:00 AM-11:45 AM**

**High-dose methotrexate for metastatic breast cancer to the central nervous system: A single-institution review of 46 patients.** *Presenting Author: Margaret A. Schwartz, Northwestern University, Chicago, IL*

**Background:** The prognosis for patients with metastatic breast cancer to the central nervous system (CNS) is poor. Methotrexate (MTX) is an active agent in the treatment of breast cancer and penetrates the CNS at high doses and rapid rate of infusion. **Methods:** We performed an IRB approved retrospective review of patients treated at Northwestern from 8/1/2003 to 12/31/2013. Demographic data collected included date of diagnosis, time to CNS metastases, Karnofsky Performance Status, HER-2 and hormone status, radiographic and/or cytologic response to MTX, progression-free survival (PFS) and overall survival (OS). **Results:** Forty-six patients met criteria for inclusion. All patients were women with a median age of 49 (range 28-80) and average KPS of 70 (range: 20-100). Median number of doses was 4 (range 1-22), dosed at 3.5 gm/m2. The median PFS and OS were 3.4 and 4.1 months (m). Patients with ER/PR- disease had median PFS/OS of 5.2m/8.7m (HER2-) and 1.2m/3.0m (HER2 +). Patients with ER/PR+ disease had median PFS/OS of 3.4m/4.1m (HER2 -) and 3.4m/3.8m (HER2 +). When response was evaluated based on KPS, PFS/OS rates are 6.8m/15.2m for patients with KPS≥70. Patients with KPS<70 had PFS/OS rates of 3.2m/4.0m. Six patients are alive after completing MTX treatment and continue systemic therapies. There were 34 patients with scans for treatment evaluation: 1 complete response, 3 partial responses, and 16 patients had stable disease. Most common toxicities were anemia, hypokalemia, mucositis, transient elevations in liver enzymes, and thrombocytopenia. **Conclusions:** High-dose intravenous methotrexate remains a treatment option for patients with CNS metastases of breast cancer. Patients with ER/PR negative disease trended toward better PFS and OS. Patients with KPS less than 70 may not warrant treatment given shorter survival.

**1080 General Poster Session (Board #173), Mon, 8:00 AM-11:45 AM**

**Effect of overexpression of human kinesin-14 family motor HSET on tumor progression and clinical outcomes in breast cancer patients.** *Presenting Author: Vaishali Pannu, Georgia State University, Atlanta, GA*

**Background:** Centrosomes are frequently amplified in human cancers. Breast cancers, in particular, display extra centrosomes in about 80% of tumor cells. Although amplified centrosomes could potentially compel cells to form multipolar spindles resulting in death-inducing aneuploidy, cancer cells cleverly turn things in their favor by suppressing multipolarity via centrosome clustering during mitosis. Thus cancer cells display bipolar spindles and derive the collateral benefit of maintaining low-level aneuploidy, an edge to their survival. HSET/KifC1, a kinesin-like minus-end directed microtubule motor, has recently found fame as a crucial centrosome clustering molecule. **Methods:** Samples from 193 breast carcinoma patients were immunohistochemically-stained for HSET, and its overexpression was correlated with progression-free survival (PFS) and overall survival (OS). FISH was performed on a subset of 30 samples using BAC probes from HSET locus on Chr. 6 and its centromere. Cell cycle profiling and immunoblot analysis of cell proliferation markers was done in HeLa and stably transfected HeLa-HSET-GFP cells; and in MDA-MB-231 breast cancer cells with or without transient HSET-GFP overexpression. **Results:** HSET was overexpressed in breast cancers and its nuclear accumulation correlates with histological grade. High HSET expression predicted poor PFS and OS. Further, deregulated HSET protein expression in breast cancers was associated with gene amplification and/or translocation. HSET overexpression promotes clonogenic survival and enhances kinetics of progression through G2 and M-phases of cell cycle at least in part, by disrupting spindle assembly checkpoint control. Importantly, HSET overexpression leads to upregulation of survivin, Aurora B, HIF1$\alpha$ and Bcl-2, thus delineating HSET-HIF1$\alpha$-Aurora B as a novel oncoprotein axis that spurs tumor progression. **Conclusions:** We offer first evidence of centrosome-clustering independent roles of HSET that fuel tumor progression and firmly establish HSET overexpression as a driver of tumor evolution. HSET may serve both as a potential prognostic biomarker and as a cancer-selective therapeutic target.

**1081 General Poster Session (Board #174), Mon, 8:00 AM-11:45 AM**

**Adjuvant taxane therapy for early-stage breast cancer: A real-world comparison of chemotherapy regimens in Ontario.** *Presenting Author: Sofia Torres, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*

**Background:** FEC-D (5-FU, epirubicin, cyclophosphamide - docetaxel) and dd (dose-dense) AC-P (doxorubicin-cyclophosphamide - paclitaxel) are considered equally effective regimens in the adjuvant treatment of breast cancer (BC), although never compared directly in a clinical trial. We compared the outcome of BC patients (pts) treated with FEC-D, dd AC-P and AC-P (q3 weekly). **Methods:** Retrospective study including all female BC pts diagnosed in 2003-2009 in Ontario, who received 1 of those regimens (ascertained from New Drug Funding Program and physician claims databases). Primary endpoint: overall survival (OS). Secondary endpoints: emergency room (ER) visits/admissions, risk of heart failure (HF). Analysis were conducted for OS and HF using Kaplan-Meier method and adjusted for confounders using proportional hazard models. Multivariable logistic regressions were performed for ER visits/admissions adjusting for confounders. FEC-D and ddAC-P were compared using propensity score (PS) matching. **Results:** 8,462 pts were identified, 4,710 (55.7%) received FEC-D, 2,065 (24.4%) AC-P and 1,687 (19.9%) dd AC-P. Patient characteristics were imbalanced between the arms. In unadjusted analyses, 5-year OS was 91.7% for FEC-D, 89.0% for dd AC-P and 87.4% for AC-P; after PS matching, it was 92% for FEC-D and 89% for ddAC-P. After adjusting for confounders, risk of death was lower for dd AC-P than AC-P (HR=0.76; 95% CI 0.61-0.96), and higher for dd AC-P than FEC-D (HR=1.24; 0.99-1.54) and for AC-P than FEC-D (HR=1.61; 1.26-2.06). ER visits / admissions during treatment, were higher for FEC-D (respectively, 50.5% and 23.7%), than AC-P (35.2% and 11.6%) and dd AC-P (30.5% and 8.4%); the differences persisted after PS matching (respectively, 48.2% and 23.5% for FEC-D, 31.1% and 8.7% for dd AC-P; p<0.0001). Risk of HF at 5 years for the PS matched groups was 1.37% for FEC-D and 1.49% for dd AC-P (p=0.71). **Conclusions:** OS was better for FEC-D and dd AC-P when compared with AC-P. This may be attributable to imbalances in patient characteristics. Propensity score matching for dd AC-P and FEC-D showed no difference in survival or HF risk between the arms but pts treated with FEC-D continued to have more ER visits/admissions.

**1082 General Poster Session (Board #175), Mon, 8:00 AM-11:45 AM**

**Nonmetastatic inflammatory breast cancer: Evolution of invasive disease-free (IDFS) and overall survival (OS) over a 21-year period.** *Presenting Author: Mahmoud Fekih, Department of Medical Oncology, Gustave Roussy, Villejuif, France*

**Background:** Inflammatory breast cancer (IBC) is a very aggressive type of locally advanced BC with a poor prognosis. Its management incorporating preoperative chemotherapy (CT), surgery, radiotherapy (RT), and hormone therapy (HT), when indicated, has become standard in the late 80s. Little is known regarding the evolution of its prognosis throughout the past 20 yrs. The objective of this single center study was to evaluate the evolution of IDFS and OS among patients (pts) with newly diagnosed, localized IBC. **Methods:** We retrospectively reviewed the records of all pts treated at Gustave Roussy for localized IBC between 01/01/1988 and 31/12/2008. 280 pts were eligible for the study. Pts were subdivided in 4 time groups: 1988 to 1992, 1993 to 1997, 1998 to 2002 and 2003 to 2008. We estimated IDFS and OS from the time of diagnosis using the Kaplan-Meier method. Log-rank tests were used to compare survival curves. **Results:** Median age was 51 yrs (22-91). 52 % of 231 cases tested for ER were positive and 33% of 78 cases tested for Her2 were positive. Pts received CT (98 %), surgery (55 %), RT (96 %) and HT (61%). Pts characteristics, median IDFS and OS across to 4 periods are all reported in Table 1. While IDFS and OS were mostly stable between 1988 and 2002, a significant improvement was noted thereafter (logrank p-value comparing 4$^{th}$period with the 3 other is 0.046 for IDFS and 0.056 for OS). During the 2 last time periods, median IDFS was 38 mo in Her2+ pts vs 46 mo in Her2- pts (p=0.27), while median OS was 96 mo in Her2+ vs 74 mo in Her2- pts (p=0.33). **Conclusions:** This study demonstrated a significant improvement in DFS and OS of IBC over the past two decades, especially since 2003.

| | 1988-92 | 1993-97 | 1998-02 | 2003-08 | p |
|---|---|---|---|---|---|
| n | 117 | 47 | 53 | 63 | - |
| Median age (yrs) | 52 | 50 | 52 | 52 | P=0.74 |
| ER + (%) | 37 | 45 | 42 | 54 | P=0.39 |
| HER-2+ (% of tested) | NA | NA | 11 | 32 | - |
| Surgery (%) | 21 | 40 | 93 | 97 | P<0.001 |
| Chimiotherapy (%) | 95 | 89 | 98 | 95 | P=0.81 |
| Median nb of CT cycles | 8 | 7 | 6 | 9 | P=0.001 |
| RT (%) | 97 | 98 | 93 | 97 | P=0.38 |
| Median IDFS (mo) | 32 | 30 | 39 | 63 | - |
| Median OS (m) | 53 | 66 | 63 | 91 | - |
| 5-years IDFS (%) | 39 | 36 | 45 | 56 | - |
| 5-years OS (%) | 48 | 55 | 55 | 71 | - |

**1083 General Poster Session (Board #176), Mon, 8:00 AM-11:45 AM**

**Developing and evaluation of a new clinicopathologic response index after neoadjuvant chemotherapy as a predictor of clinical outcomes in locally advanced breast cancers.** *Presenting Author: Tarek M. A. Abdel-Fatah, Nottingham University City Hospital NHS Trust, Nottingham, United Kingdom*

**Background:** There is an urgent need to identify a set of clinico-pathological criteria which is more sensitive than pathological complete response (pCR) to assess the response to neo-adjuvant chemotherapy (Neo-ACT) and to guide the subsequent adjuvant therapy (AT). **Methods:** We performed a clinico-pathological assessment of 427 patients who had completed Neo-ACT with a median follow-up of 5-years. The patients were divided into: 1) Training set (n=172) treated with anthracycline combination (AC); 2) Internal validation set (n=130) treated with AC+Taxane; and 3) external validation set (n=125) treated with AC-/+Taxane. **Results:** Among the clinico-pathological factors associated with higher risk of relapse and death after Neo-ACT in univariate analysis: absence of fibrosis in both primary tumour site and lymph node (LN), presence of lymphovascular invasion, and increasing number of LN metastases, maintained significance as independent predictors for both disease free survival (DFS) and breast cancer specific survival (BCSS) after controlling for AT and other covariates by using multivariate Cox proportional hazards models with backward stepwise exclusion (p<0.01); whilst the percentage of reduction in primary tumour size was associated with DFS only (p=0.022). New pathological response indecies (NPRIs) for DFS and BCSS were calculated and four prognostic-groups (NPRI-PGs) were identified. Patients with NPRI-PG2 for DFS (n=63/172; 36.6%) and BCSS (66/172; 38.4%) has the same prognosis as those who achieved pCR (NPRI-PG1; 15%). The receiver operating characteristic (ROC) curves indicated that the NPRI outperformed the currently used prognostic factors [area under the curve (AUC) >0.85] and adding NPRI has improved their performance as a predictor for DSF (AUC>0.87) and BCSS (AUC> 0.88). **Conclusions:** The NPRI accurately predicts DFS and BCSS, with a higher sensitivity than pCR . The NPRI can improve the sensitivity and specificity of clinico-pathological response as a study end-point, for assessing response to a Neo-ACT regimen, and can serve as a valuable tool for the discovery of future predictive molecular markers.

**1084 General Poster Session (Board #177), Mon, 8:00 AM-11:45 AM**

**Predicting chemotherapy response in invasive breast cancer.** *Presenting Author: David Harrison, School of Medicine, University of St Andrews, Fife, United Kingdom*

**Background:** The care of patients with estrogen receptor positive (ER+), node negative early breast cancer has been revolutionized by first generation mRNA signatures that have improved the identification of patients with low risk of recurrence following adjuvant hormone therapy who may be spared chemotherapy. Additionally, a signature may be of value in predicting response to chemotherapy in high-risk individuals. We developed a second generation prognostic signature in ER+ breast cancer consisting of a weighted combination of cell division (CCP), immune and receptor genes (molecular score) and clinical parameters (combined score). Here, we aimed to understand the capacity our signature to predict chemotherapy effectiveness regardless of ER status. **Methods:** The first cohort consisted of 247 ER+ patients treated pre-operatively with TFEC or TFAC. Association of the signature with complete pathological response (pCR) was evaluated by logistic regression. The second data set was a population cohort of 431 adjuvant chemotherapy treated and 599 untreated invasive breast cancer patients. The interaction between chemotherapy treatment and CCP, molecular and combined scores was individually tested in a Cox proportional hazards model with distant metastasis free survival as outcome. **Results:** CCP and molecular scores were predictive of pCR in the pre-operatively treated cohort (CCP score p=0.015; molecular score p=0.029). In the population cohort, the test for interaction with adjuvant treatment was highly significant with p-values of 0.000016, 0.000020 and 0.00012 for CCP, molecular score, and combined score, respectively. In all cases higher scores were associated with response or improved outcome. **Conclusions:** A second generation prognostic tool for ER+ invasive breast cancer predicts pre-operative chemotherapy response in an ER+ breast cancer cohort. Molecular and clinical combined components predict outcome in adjuvant chemotherapy treated cohort regardless of ER status. After further studies to validate prognostic and predictive efficacy, the second generation prognostic signature may offer enhanced discrimination for the care of breast cancer patients.

**1085 General Poster Session (Board #178), Mon, 8:00 AM-11:45 AM**

**Amilorides: Familiar antihypertensive medications with a novel potential against breast cancer.** *Presenting Author: Jean Paul Atallah, Staten Island University Hospital-North Shore LIJ Health System, Sanford R. Nalitt Institute for Cancer & Blood-Related Diseases, Staten Island, NY*

**Background:** When compared to normal breast epithelial cells, breast cancer cells exhibit increased metabolic activity, which produces excessive intracellular hydrogen ions (H+). This increase in intracellular acidity (decrease in pH) is ameliorated by increasing the activity of the hydrogen pump, NHE1, which exchanges one intracellular H+ with an extracellular Na+. Therefore, breast cancer cells require the constant activity of NHE1, whereas normal cells do not. **Methods:** The objective of this project is to:1) Test the anti-cancer effects of two different NHE1 inhibitors (5-methyl-N-isobutyl Amiloride (MIA) and the well know antihypertensive Amiloride Hydrochloric Acid (A-HCl) ) on three human breast cancer cell lines (MCF-7, SKBR3, and MDAMB468); 2) Determine whether MIA can potentiate the effects of Cyclophosphamide (CPA) or Doxorubicin (Dox); 3) Assess the relationship between MIA treatment and the pro-survival transcription factor NF-kappa-B. **Results:** Treatment of all of three breast cancer cell lines with either MIA or A-HCl induced a dose-dependent cytotoxic response, with MIA being ~10-times more effective than A-HCl. The cancer cells MDAMB468, which models triple negative breast cancer, were the most sensitive to amiloride treatment. MIA when delivered in combination with CPA, increased the latter's cytotoxic effect, however, this was not seen when breast cancer cells were exposed to a combination of MIA and DOX. In response to MIA treatment alone, breast cancer cells exhibit an immediate increase in nuclear localization of NF-kappaB. **Conclusions:** Our results suggest that amilorides can be used alone or in combination with existing chemotherapies to effectively kill breast cancer cells. Cyclophosphamide with MIA combination demonstrated enhanced antitumor activity. The molecular response of amiloride treatment, involves at least in part, nuclear localization of the transcription factor NF-kappaB. Amilorides as antihypertensives have a very good safety profile. We show that inhibiting NHE1 activity with amilorides offers a novel approach to treating breast cancer.

**1086 General Poster Session (Board #179), Mon, 8:00 AM-11:45 AM**

**Centrosome declustering agents: Potential interphase-targeting antimetastatic chemotherapeutics.** *Presenting Author: Vaishali Pannu, Georgia State University, Atlanta, GA*

**Background:** The recent clinical failure of mitosis-targeted drugs has proven that cells in patient tumors divide infrequently, unlike cancer cells in cultures and xenograft models. Given the preponderance of interphase cells in clinical tumors, we asked whether targeting amplified centrosomes, held in tight clusters throughout interphase, presents a superior chemotherapeutic strategy that sabotages interphase-specific cellular activities such as directional migration. We utilized supercentrosomal N1E-115 murine neuroblastoma cells as a test-bed to study interphase centrosome declustering. **Methods:** We immunostained centrosomes and mitotic spindles in (i) paraffin-embedded clinical tumor samples of high-grade carcinomas of breast, prostate, bladder, head and neck, pancreas and colon, and (ii) cancer cell lines derived from a variety of tumor types, to determine the percentage of cells with amplified centrosomes and mitotic spindles. We analyzed how putative centrosome declustering agents [CDAs, *viz.*, reduced 9-Bromonoscapine (RBN), Griseofulvin (GF) and PJ-34] disperse interphase centrosome clusters and compared them with Paclitaxel, a tubulin polymerizing drug currently in clinical use. Declustering potency of these drugs was ranked using a quantifiable declustering index (DI). **Results:** About 80% of patient tumor cells bear "supercentrosomal" clusters in interphase and mitosis; by contrast, cancer cells in culture exhibit a higher proportion of mitotic cells and lower levels of centrosome amplification. In cultured N1E-115 cells, RBN was the strongest declustering agent (DI=0.36), followed by GF (DI=0.28) and PJ-34 (DI=0.14). Dispersal of interphase centrosome clusters caused Golgi scattering, disrupted focal adhesion contacts, inhibited neurite formation by 70-80% and caused spindle multipolarity. **Conclusions:** CDAs (i) inhibit cell-substrate adhesion and polarized protrusion development, which are essential for directional migration in interphase cells, and (ii) induce catastrophic mitoses, suggesting that (a) disbanding the centrosome-Golgi axis is a potential anti-metastasis strategy and (b) interphase is a clinically important chemotherapeutic target.

**1087 General Poster Session (Board #180), Mon, 8:00 AM-11:45 AM**

**Treatment and prognosis of breast cancer patients with brain metastases according to intrinsic subtype.** *Presenting Author: Sayaka Kuba, Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan*

**Background:** It is still unclear how breast cancer (BC) subtype should affect treatment decisions for BC patients with brain metastases (BRM). This study analyzed extent and type of local BRM treatments and their outcomes according to BC subtype in patients with BC and BRM. **Methods:** We reviewed records and database information for women who were treated at the National Kyushu Cancer Center between 2001 and 2010. Patients' BC was divided into three subtypes: luminal (ER+ and/or PgR+, but HER2−); HER2 (HER2+) and TNBC (ER−, PgR− and HER2−). **Results:** Of 524 patients with advanced BC, we reviewed the 65 patients who had BRM and whose records showed ER, PgR and HER2 status, and outcome dates. Of these 65 patients, there were 26 (40%) with luminal BC, 26 (40%) with HER2 BC, and 13 (20%) with TNBC. Symptomatic BRM rates were similar across subtypes (HER2: 81%; luminal: 85%; TNBC: 77%). Percentages of patients with ≤ 4 BRMs did not significantly differ by subtype (HER2: 73%; luminal: 54%; TNBC: 46%; *P*=0.22). For local BRM treatments, 40 underwent stereotactic radiosurgery (SRS) or surgery, 21 received whole brain radiation therapy, and 4 had no local brain treatment. Rates of SRS or surgery for BRMs significantly differed among BC subtypes (HER2: 81%; luminal: 42%; TNBC: 47%; *P*=0.03). Median survival after BRMs also varied significantly by subtype (HER2: 22 months; luminal: 10 months; TNBC: 6 months; *P*=0.02). Having the HER2 subtype, performance status ≤ 1, ≤ 4 BRMs, undergoing systemic therapy after brain metastasis and undergoing SRS or surgery predicted longer overall survival after BRMs appeared. Multivariate analysis demonstrated that without systemic therapy and without having the HER2 subtype were independent factors associated with increased risk of death (HR 2.4, 95 % CI 1.01-5.6; p = 0.05 and HR 2.9, 95 % CI 1.5-5.8; p = 0.003 and respectively). **Discussion:** The number of BRMs is an important prognostic factor, as local brain treatment can be given for patients with BRMs. Patients with HER2 BC had more chance to receive SRS or surgery and better prognosis, as anti-HER2 treatment might be able to control systemic disease. **Conclusions:** Local brain treatments and prognosis differed with subtype in patients with BRM.

**1088 General Poster Session (Board #181), Mon, 8:00 AM-11:45 AM**

**Cosmetic outcome within one year of breast-conserving surgery, after external beam or intraoperative radiotherapy for early breast cancer: Objective assessment of patients from a randomized controlled trial.** *Presenting Author: Norman R. Williams, Clinical Trials Group, Division of Surgery and Interventional Science, University College London, London, United Kingdom*

**Background:** The international randomised controlled TARGeted Intraoperative radioTherapy (TARGIT) trial demonstrated non-inferiority between the technique of TARGIT (Intra-Operative RadioTherapy (IORT) with Intrabeam) and whole-breast external beam radiotherapy (EBRT) in women with early breast cancer. We have shown in a sub study of 342 patients that cosmesis at one year or later is better after TARGIT than EBRT; a significant component was cX2b ("redness", a surrogate for radiation induced erythema grade I or II). The aim of this study was to determine if the single high dose of TARGIT leads to impaired cosmesis within the first year after surgery. **Methods:** Frontal digital photographs were taken of women participating in the TARGIT Trial at a single centre and analysed, blinded to treatment received, by BCCT.core software which produced Harris scores for symmetry, colour and scar; scores for cX2b were also recorded, a high score indicating "redness." **Results:** 17 women (9 EBRT, 8 IORT), median age 65 years (range 50 to 79) had photographs taken at baseline (up to 5 days prior to surgery), then at one month (median 31d), at 6m if given EBRT (median 87d from first fraction), and at 12m (median 332d). All images scored Excellent, Good or Fair with no differences apparent over time or between treatment groups. At 6m there was a significant change from baseline in cX2b in the women given EBRT (see Table); this change persisted to 12m. No change was seen after IORT. **Conclusions:** This objective assessment of aesthetic outcome in patients from a randomised trial demonstrates that "redness" associated with EBRT is significantly worse within 90d of commencement; this change was not seen in women treated with IORT. This study provides further evidence that the objective scoring of cosmesis using BCCT.core is feasible and may be an approach for standardisation, and shows an early beneficial effect of TARGIT on cosmesis.

**Increase in cX2b from baseline mean (SEM).**

| | 1 month | 6 months | 12 months |
|---|---|---|---|
| **EBRT** | -0.04(0.09) | +0.18(0.06)* | +0.18(0.17) |
| **IORT** | +0.02(0.03) | | +0.04(0.10) |

* Significant increase from baseline P = 0.0247, paired t-test.

**1089 General Poster Session (Board #182), Mon, 8:00 AM-11:45 AM**

**Accuracy of ultrasound during neoadjuvant therapy for breast cancer to predict pathologic response.** *Presenting Author: Michael Luke Marinovich, Screening and Test Evaluation Program (STEP), The University of Sydney, Australia*

**Background:** Early assessment of response to neoadjuvant chemotherapy (NAC) for breast cancer may allow therapy to be tailored; however the optimal method for response assessment has not been established. We estimated the accuracy of ultrasound (US) to predict pathologic response (pCR) after NAC using common response criteria and pCR definitions, and estimated incremental accuracy of US over known prognostic variables. **Methods:** Participants in the GeparTrio trial with US tumor measurements at baseline and after two (of six) NAC cycles, and randomised to no change in NAC, were eligible. US partial response in two dimensions was assessed by World Health Organisation (WHO 2D) criteria; Response Evaluation Criteria In Solid Tumors (RECIST) and WHO criteria were also applied to the longest diameter (1D). Four pCR definitions were applied. Sensitivity (correct prediction of pCR), specificity (correct prediction of no-pCR), and diagnostic odds ratios (DORs) were calculated. Areas under the curve (AUCs) were derived from logistic regression models of the probability of pCR, including patient variables with and without US. **Results:** In 832 patients, there was a significant trend for decreasing DORs as the pCR definition became less stringent (p=0.01). For WHO 2D, DORs for the pCR definitions were 4.07 (ypT0 ypN0), 3.75 (ypT0/is ypN0), 3.14 (ypT0/is ypN+/-), and 2.65 (ypT0/is/1a ypN+/-). DORs did not differ between US criteria (p=0.60). Comparable high sensitivity and lower specificity within pCR definitions were found for WHO 2D and RECIST; WHO 1D was highly specific with low sensitivity. Sensitivity was highest for prediction of ypT0 ypN0 by WHO 2D (sensitivity=81.7% specificity=47.6% vs. 42.3% and 80.4% for WHO 1D). Adding US to models including patient variables (age, T stage, histology, subtype) improved the AUC for predicting pCR by 2-3%, regardless of US criterion or pCR definition. **Conclusions:** US accuracy is highest for the prediction of pCR defined as ypT0 ypN0, shown by previous studies to be most predictive of long term survival. WHO 2D and RECIST criteria maximise sensitivity, while specificity is maximised by WHO 1D. Knowledge of the US result modestly improves the prediction of pCR by patient characteristics.

**1090 General Poster Session (Board #183), Mon, 8:00 AM-11:45 AM**

**Local therapy and overall survival for stage IV breast cancer: SEER 1988-2010.** *Presenting Author: Alexandra Thomas, University of Iowa Carver College of Medicine, Iowa City, IA*

**Background:** There is still discussion regarding the role of surgery and radiation therapy (RT), for women who present with metastatic breast cancer. **Methods:** We included women who presented with Stage IV breast cancer from 1988-2010, reported to the Surveillance, Epidemiology, and End Results (SEER) program. Microscopically confirmed, first malignant cancers were included. Treatments were categorized: surgery only, RT only, surgery and RT, and no surgery or RT. Kaplan-Meier survival curves were created. Cox models controlled for age, treatment, hormone receptor (HR) status, marital status, year of diagnosis, and tumor size. Surgery and RT were part of the initial therapy. Surgery was to the primary tumor. RT site was not specified. **Results:** This series included 31,044 women with Stage IV breast cancer. Of these 25% received surgery, 19% received RT, 19% received both surgery and RT and 37% received no surgery or RT. The mean age of women who received surgery and RT was younger than those who received no surgery or RT (59 vs 64, p<0.001). Those who received surgery and/or RT were more likely to be married than those did not (p<0.001). Kaplan-Meier curves revealed that those who received surgery or surgery with RT had better overall survival than those who did not receive either or had RT alone (p<0.001). Age < 45 (HR=0.85), being diagnosed 2006-2010 (HR=0.72), surgery alone (HR=0.70), surgery with RT (HR=0.61), HR positive (HR=0.51), and being married (HR=0.79), conferred survival advantage in our Cox model (all p<0.001). Breast Tumor size ≥ 5 cm increased risk of death (HR 1.35, p<0.001). RT only women tended to have larger breast tumors (p<0.001). Median survival increased overtime, for all treatment groups. **Conclusions:** In this population-based series, local treatment was associated with longer survival. Median survival, by year of diagnosis, has improved markedly.

| | Total | No surgery or RT | Surgery | RT | Surgery and RT |
|---|---|---|---|---|---|
| | 31,044 | 11,436 | 7,681 | 5,808 | 5,819 |
| **Mean age** | 62 | 64 | 62 | 62 | 59 |
| **Married** | 43% | 39% | 45% | 41% | 49% |
| **Mean survival (mo)*** | 22 | 16 | 28 | 19 | 31 |
| **Median survival (mo)*** | 13 | 7 | 19 | 11 | 22 |
| **Age** | | | | | |
| **<45** | 18 | 13 | 22 | 13 | 27 |
| **45-64** | 16 | 10 | 22 | 13 | 23 |
| **65+** | 10 | 5 | 15 | 9 | 18 |
| **Diagnosis yr** | | | | | |
| **1988-1995** | 17 | 8 | 22 | 12 | 23 |
| **1996-2000** | 18 | 10 | 24 | 14 | 30 |
| **2001-2005** | 20 | 13 | 27 | 15 | 35 |

* Conditional on having died: 91% of women diagnosed 1988-2005 are deceased.

**1091 General Poster Session (Board #184), Mon, 8:00 AM-11:45 AM**

**Indocyanine green fluorescence imaging system as an alternative to the conventional sentinel lymph node mapping using a radiotracer in breast cancer.** *Presenting Author: Tomoharu Sugie, Kansai Medical University, Hirakata, Japan*

**Background**: Near-infrared fluorescence signal of indocyanien green (ICG) can visualize subcutaneous lymphatic flows and draining (sentinel) lymph nodes (SLNs). In fluorescence ICG Breast Study Group 01 study (fICG BR01), this ICG fluorescence mapping was superior to the dye method in early stage breast cancer (Sugie T, et al. Ann Surg Oncol 2013). The following fICG BR02 study evaluates clinical usefulness of this ICG fluorescence method in comparison to the conventional radioisotope (RI) method. **Methods:** On the day before or on the day of SLN biopsy, $^{99m}$Tc-labelled colloid was injected into the subareolar region of each patient. Before the start of operation, ICG was injected into the subareolar region and lymphatic flows bound for the axilla were traced with PDE camera (Hamamatsu Photonics Co, Japan). A real-time navigation surgery by ICG florescence imaging enabled to identify SLNs to be excised. A gamma probe was used to verify no residual radioactivity in the axilla after SLN removal. **Results:** A total of 847 women with T1-2 breast cancer were enrolled and 821 pts. were included in the per-protocol final analysis. The median pts. age was 55 (range, 22-80) years and the median BMI was 22.1 (range, 14.9-38.8) kg/m$^2$. There was no significant difference in the detection rate between the ICG and RI method (97.2% vs 97.0%). However, a combination of ICG and RI achieved a significant higher detection rate than RI alone (99.8% vs 97%, p<0.001). The involvement of SLNs was found in 180 pts. and a detection rate of positive SLN using ICG fluorescence and RI was 93.3% and 90%, respectively. The detection rate of SLNs with a combination of ICG and RI was improved significantly compared with RI alone (97% vs 90%, p<0.001). There is no serious adverse event due to hypersensitivity to ICG. **Conclusions:** The ICG fluorescence method has a high detection rate of SLN comparable with that of the RI method. A combination of these two methods yield a significant improvement of SLN detection compared with RI alone. The results of this study confirm that ICG fluorescence imaging system is an alternative and/or additive to the conventional SLN mapping using a radioactive tracer in breast cancer. Clinical trial information: UMIN000005167.

**1092 General Poster Session (Board #185), Mon, 8:00 AM-11:45 AM**

**The influence of radiotherapy on sleep disturbances in breast cancer patients.** *Presenting Author: Sheela Hanasoge, Department of Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, GA*

**Background:** Sleep disturbances are distressing and common among breast cancer patients during treatment. However, few studies have examined the impact of radiotherapy (RT) on sleep quality. The goal of this study was to prospectively assess breast cancer patients before, during, and after RT to determine the impact of RT on sleep. **Methods:** Following breast conserving surgery, 80 breast cancer patients were enrolled on a prospective, longitudinal study of sleep before, during, and after whole breast RT. All patients received a dose of 50 Gy followed by a 10 Gy boost. Subjects completed the Pittsburgh Sleep Quality Index (PSQI) before (i.e., baseline), at week 6 of RT, and 6 weeks after RT completion. Demographic, patient- and treatment-related factors were also recorded. Paired t tests were used to test longitudinal differences in PSQI between time points. Linear mixed models were used to identify predictors of higher PSQI scores and poor sleep (i.e., PSQI score >5). **Results:** Before, during, and after RT, 61%, 56%, and 59% of subjects were poor sleepers, respectively. PSQI scores did not significantly change during or after RT compared with baseline measures. On univariate analysis, significant predictors of higher PSQI scores were prior chemotherapy treatment, African American race, and having less than a college education (all $p<0.01$). Tumor stage, axillary lymph node dissection (vs. sentinel lymph node biopsy only), patient age, marital status, and income were not significant predictors of poor sleep. On multivariate analysis, African American race ($p<0.006$) and having less than a college education ($p<0.004$) remained significant predictors of higher PSQI scores at each time point. **Conclusions:** Our findings indicate that sleep disturbances are prevalent during breast cancer treatment. Nevertheless, it appears that RT does not contribute to poor sleep while patient baseline characteristics including African American race and low educational level are associated with higher PSQI scores throughout and after RT. Studies aimed at developing interventions for these patients at risk for sleep disturbances during breast cancer treatment are warranted.

**1093 General Poster Session (Board #186), Mon, 8:00 AM-11:45 AM**

**Do hospitals in a large metropolitan area utilize published breast cancer care practices and guidelines?** *Presenting Author: Christine B. Weldon, Center for Business Models in Healthcare, Chicago, IL*

**Background:** Insufficient utilization of guideline and evidence based care practices contribute to the cancer crisis (IOM 2013). We examined utilization of published breast cancer (BC) care practices and guidelines at hospitals in a large metropolitan area. **Methods:** IRB approved web survey of all 35 hospitals in a large metro area that provide BC treatment. Using guidelines/recommendations (NCCN, NAPBC, ADA, IOM) and peer-reviewed literature (62 studies) we developed a survey on BC care practices. Results analyzed by simple frequencies and Fisher's exact test. **Results:** Response rate: 91% (32/35 sites). Care practices, included in the table, are utilized by < 50% of sites. Radiation oncologist preoperative consults (53%, 8/15) and offering indicated pre-operative chemo* (67%, 10/15) are associated with 15 sites that have high volume (67+/year, Chen CS 2008) BC surgeons, compared to 17 sites without high volume BC surgeons (12%, 2/17) and (24%, 4/17) respectively, $p=0.02$, $p=0.03$. Indicated supportive services, such as a dental checkups (ADA 2008), are more likely at sites with patient-centered written treatment plans (IOM 2011) (58%, 7/12) than at sites without written treatment plans (10%, 2/20), $p=0.006$. **Conclusions:** Low utilization of published care practices and guidelines is concerning and requires attention. Other metro areas and regions should be examined as our findings indicate that patients may have limited local choices of care that is up-to-date on published guidelines and practices.

| Practices | Site utilization n=32 |
|---|---|
| Radiation oncologist consult prior to BC conserving surgery BCS (Jagsi R 2012) | 33% |
| *Offer pre-operative chemotherapy to patients with large tumors-IIA, IIB and T3N1MO considering BCS (NCCN BINV 10) | 48% |
| Reconstructive surgeon consult prior to mastectomy decision (NAPBC 2.18) | 33% |
| Fertility/reproductive health assessment (NCCN BINVC AYAO 6) | 32% |
| Indicated patients referred for dental checkup (ADA 2008) | 28% |
| Patients screened for distress at initial visit, at intervals and at changes in disease status (NCCN DIS A for tool) | 29% |
| Patients are screened for pain at each contact (NCCN PAIN A,C) | 45% |
| Palliative care screening at care initiation and/or regularly during care (NCCN PAL 1 2) | 25% |

**1094 General Poster Session (Board #187), Mon, 8:00 AM-11:45 AM**

**Why women are choosing mastectomy: Influences beyond the surgeon.** *Presenting Author: Andrea Marie Covelli, University of Toronto, Toronto, ON, Canada*

**Background:** Rates of unilateral (UM) and contralateral prophylactic mastectomy (CPM) for early stage breast cancer (ESBC) have been increasing. Surgical decision making is comprised of the surgeon, the patient and the external environment. We sought the perspectives of patients who chose UM +/- CPM and treating surgeons to understand why mastectomy rates have been increasing. **Methods:** We completed a grounded theory qualitative study to examine the surgeon's practice and the patient's decision making that resulted in the choice for UM +/- CPM. Purposive sampling identified women across Toronto, Canada who were suitable candidates for breast conserving therapy (BCT) but underwent UM +/- CPM. Academic and community breast surgeons from across Ontario, Canada and the United States were also recruited. Data were collected through semi-structured interviews, this continued until data saturation was reached. Constant comparative analysis identified key ideas. **Results:** 29 patients and 45 surgeons completed interviews. The dominant theme was 'Desire for control', women strived to improve their cancer outcomes by undergoing more extensive surgery. Surgeons described BCT and UM as equivalent treatment options for ESBC and frequently recommended BCT. Despite this, surgeons described women initiating the request for UM+CPM. In this average risk population CPM was discouraged by the surgeons, describing no survival advantage. The most influential factor in a woman's request for CPM was their personal cancer experiences with family and friends and not the surgical consultation. A previous negative experience with breast cancer translated into an overestimated risk of recurrence, contralateral cancerand subsequent mortality. Women chose UM+CPM to ensure they would 'never go through this again.' Despite feeling confident in their choice most women had ongoing issues with disturbed skin sensation, cosmesis and body image. **Conclusions:** Factors, especially a previous cancer experience, are extremely influential when women choose UM+/- CPM. As many women had long term pain and issues with cosmesis after UM +/- CPM, we suggest women may benefit from education including exposure to other patients' post-operative concerns to aid in their decision making.

**1095 General Poster Session (Board #188), Mon, 8:00 AM-11:45 AM**

**Postoperative complications in nipple-sparing mastectomy.** *Presenting Author: Erin M Garvey, Mayo Clinic Arizona, Phoenix, AZ*

**Background:** Nipple-sparing mastectomy (NSM) has been accepted as a risk reducing procedure and for treatment of select breast cancers. The purpose of this study was to detail the types of postoperative complications experienced at a single center. **Methods:** A prospective breast cancer database was reviewed from June 2006 to November 2013. Patients who underwent NSM were identified and analyzed for postoperative complications. **Results:** Over the 7.5 year study period, a total of 1,630 breast cancer procedures were performed for 1,540 patients. 701 procedures were mastectomies, 392 of which included reconstruction. 160/392 procedures (41%) were attempted NSM and 147/160 (92%) were successful NSM. Most NSMs (87.8%) were followed by implant based reconstruction. The majority of patients were Caucasian (83.7%), average age was 51 years, average BMI was 25.5 and 50.3% were pre-menopausal. 5.4% were current and 30.6% were former smokers. 2.7% were prediabetic and 3.4% were diabetic. The average tumor size was 2 cm and the majority of patients either had DCIS (23.8%) or stage I cancer (40.8%). 29.9% underwent hormonal treatment, 17.7% cytotoxic treatment, 6.8% neoadjuvant treatment and 4.8% radiation treatment. 58.5% of procedures were associated with postoperative complications including a 1.4% rate of autogenous flap loss, 6.1% wound breakdown, 6.8% hematoma, 6.8% flap ischemia, 11.6% infection rate resulting in 12.4% expander/implant loss, 21.8% seroma and 33.3% nipple related complications. Repeat operative intervention was required for 7/9 wound breakdowns, 9/10 flap ischemia cases and 13/49 nipple related complications. No patient, disease or treatment characteristics were statistically associated with an increased risk of postoperative complications on univariate analysis; however, older age ($p=0.09$) and current or former tobacco use ($p=0.08$) trended toward an increase in postoperative complications. **Conclusions:** Nipple-related complications were the most common postoperative complications seen in NSM. Increased age and current or former tobacco use trended toward an increase in postoperative complications.

**1096 General Poster Session (Board #189), Mon, 8:00 AM-11:45 AM**

**Evaluation of cardiac dose reduction with deep inspiration breath hold in patients with left-sided breast cancer receiving adjuvant radiotherapy.** *Presenting Author: Rosanna Yeung, Department of Radiation Oncology, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada*

**Background:** Studies have suggested increased cardiac morbidity from radiation exposure to the heart and left anterior descending artery (LAD) in breast cancer patients receiving adjuvant radiotherapy (RT). Deep inspiration breath hold (DIBH) techniques have demonstrated reduction to heart, LAD and lung dose in left-sided breast cancers. There is, however, limited data on which patients derive most benefit from DIBH technique. **Objective:** To compare reduction in cardiac and LAD doses using a DIBH technique in left-sided breast cancer patients treated with adjuvant RT to the breast alone versus those also receiving regional nodal RT **Methods:** Twenty consecutive patients with left-sided breast cancer underwent CT simulation in free breathing (FB) and DIBH. Patients were grouped into two cohorts: those receiving whole breast RT alone +/- boost (WBRT) versus whole breast/chest wall RT with regional nodal irradiation (WBRT + RNI). 3D conformal plans were devised, and dosimetric comparisons were made between the two techniques for each cohort. **Results:** Eleven patients received WBRT while nine patients received WBRT + RNI. All patients had comparable CTV coverage on both DIBH and FB treatment plans. Mean heart and LAD doses were lower in all DIBH versus FB plans in both groups, but the benefit was larger in the group receiving RNI compared to those receiving WBRT alone (average relative reduction in mean heart and LAD dose: 55.9% and 71.9% vs 34.2% and 45.1%, respectively). All patients met a mean heart dose of $<$4Gy on DIBH. On FB, only one patient in the WBRT group did not meet this constraint, compared to five patients in the WBRT +RNI group. **Conclusions:** Patients receiving WBRT+RNI had a greater reduction in heart and LAD dose from DIBH than patients receiving WBRT alone. The majority of patients receiving WBRT met a mean heart dose of $<$4Gy on FB planning, while less than half of patients receiving WBRT + RNI were able to meet this constraint. These findings suggest a greater benefit from DIBH treatment in patients receiving RNI, while patients receiving WBRT alone may be safely treated with a FB technique. Ongoing prospective cohorts are being evaluated to ensure validity of these findings.

**1097 General Poster Session (Board #190), Mon, 8:00 AM-11:45 AM**

**The role of surgery in patients with primary metastatic breast cancer (PMBC) receiving monoclonal antibody treatment.** *Presenting Author: Jana Barinoff, Clinic of Gynecology and Obstetrics, Agaplesion Markus Hospital, Frankfurt, Germany*

**Background:** Apart from the individual palliative need, the beneficial effect of surgically removing the primary tumor in PMBC on long-term outcomes, as suggested by retrospective series and meta-analyses, remains controversial. A cohort of 2,401 patients (pts) with metastatic breast cancer from two prospective non-interventional studies (NIS), enrolled between 2000 and 2011, was screened with respect to this question. **Methods:** One study investigated trastuzumab therapy for HER2+ metastatic breast cancer in addition to mainly 1st line chemotherapy. The second NIS observed bevacizumab therapy for mostly HER2– disease additional to chemotherapy as 1st line treatment. Progression-free survival (PFS) was defined as the time from start of antibody therapy to disease progression or death; overall survival (OS) was defined as the time from start of targeted therapy to death of any cause. **Results:** 570 (24%) pts had PMBC, and valid information on primary tumor surgery was available for 568. Out of these, 426 (75%) underwent local surgery (LS). The LS group was characterized by less overall metastatic burden (20% vs. 39% with $\geq$3 sites involved) and a lower proportion of T4 tumors (26% vs. 52%). No major differences were observed with respect to age, hormone receptor and HER2 status, visceral disease, prior palliative treatment and performance status. Numerically, the LS group showed a slightly favorable PFS (medians: 13.6 vs. 11.8 months; p=0.18) and OS (34.1 vs. 31.7; p=0.23). However, in multivariate analysis including all other univariately significant parameters (age, hormone receptor status, visceral disease, number of involved sites, performance status), no trend for better outcome after surgery remained observable, neither for PFS (hazard ratio 0.99; p=0.92) nor OS (0.95; p=0.71). **Conclusions:** In PMBC pts treated with modern targeted therapies, our findings confirm the recent preliminary results from two randomized studies with no survival advantage for LS shown in the overall pt population. However, further analyses are warranted to define specific risk groups, which may benefit from surgical removal of the primaries.

**1098 Poster Highlights Session (Board #12), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**A pilot study of preoperative (Pre-op), single-dose ipilimumab (Ipi) and/or cryoablation (Cryo) in women (pts) with early-stage/resectable breast cancer (ESBC).** *Presenting Author: Adi Diab, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Because intratumoral cryo with immune modulation generates a potent systemic anti-tumor immune response in murine models, this strategy may improve outcomes for women with ESBC. In this study, we evaluated the safety of pre-op cryo and/or ipi (10mg/kg) in ESBC pts and explored immune correlates including tumor infiltrating lymphocytes (TILs). **Methods:** Eligibility: age $\geq$18y with operable $\geq$1.5 cm invasive ESBC planning mastectomy (TM). Pts were sequentially assigned to receive pre-op: cryo alone (group A), ipi alone (B), or ipi and cryo (C). Tissue biopsies and/or cryo were performed 7-10d prior to TM. Ipi was administered 8-15d prior to TM (1-5d prior to cryo). The regimen was to be considered safe/tolerable if at least 5/6 pts in each group proceed to TM without delay. Toxicity evaluation continued for 30d after TM for group A and 12wks after ipi administration for groups B&C. Research peripheral bloods for immune correlates were obtained at baseline, biopsy, TM and 2-3 wks thereafter. Blood, biopsy and TM samples were evaluated by flow-cytometry. **Results:** The study is complete. Pre-op cryo-alone, ipi-alone and the combination were well tolerated and the primary safety endpoint was achieved with all 19 enrolled pts undergoing TM without delay. Group A was expanded to 7 pts after a possible technical failure in 1 pt, 6 pts enrolled to group B and 6 pts enrolled to group C. Median age was 48y (range 34-72y). Tumor necrosis/infarction was observed in 9/12 pts who underwent cryo. A trend toward an increased frequency of blood CD4+ICOS+, CD8+ICOS+, CD4+Ki67+ and CD8+Ki67+ T-cells was observed at TM compared with baseline in the ipi treated groups only. Analysis of TILs in the TM specimens suggested a higher ratio of CD8+Ki67+ T-cells to CD4+CD25+FOXP3+ (T-regulatory) cells in group C when compared with A&B. **Conclusions:** Pre-op cryo and ipi, alone or in combination, are safe/tolerable in pts with ESBC. Immune correlates revealed activation of T-cells in the blood in single-dose ipi treated pts and a modest increase in the ratio of tumor CD8+Ki67+ T-cells to T-regulatory cells after combination therapy only. A Phase II study of pre-op ipi and cryo in ESBC is planned. Clinical trial information: NCT01502592.

**1099 General Poster Session (Board #192), Mon, 8:00 AM-11:45 AM**

**A multicenter prospective study of image-guided radiofrequency ablation for small breast carcinomas.** *Presenting Author: Takayuki Kinoshita, National Cancer Center Hospital, Tokyo, Japan*

**Background:** As the management of breast carcinoma evolves toward less invasive treatments, the next step is the possibility of removing the primary tumor without surgery. The most promising noninvasive ablation technique is radiofrequency ablation (RFA), which can effectively kill tumor cells with a low complication rate. **Methods:** To determine if RFA is oncologically and cosmetically appropriate for the local treatment of primary breast carcinoma, this multicenter prospective study used RFA as the sole local treatment of breast tumors $\leq$ 1.5cm in size on ultrasound and MRI. After confirmation that the standard baseline core biopsy for diagnosis and measurement of tumors markers (ER, PgR, HER-2/neu expression and the presence of the Ki-67 proliferative marker) have been obtained, consent will be obtained and the patient scheduled RFA. All patients received adjuvant radiation therapy. The first primary endpoints of this study is successful tumor ablation, as evidenced by negative findings on vacuum-assisted or core biopsies and imaging studies after RFA. The second primary endpoints is the incidence of procedure related adverse events. The response to ablation was evaluated with both vacuum-assisted or core biopsies and imaging studies every 3 months during the first year. The long-term outcomes were assessed using quality of life measurement scales and imaging studies every 6 months thereafter through year 5. **Results:** Of the 58 patients who participated in this study, 55 completed the protocol. In 50 of the 55 (91%) treated patients, successful tumor ablation, as determined by negative findings on vacuum-assisted or core biopsies and imaging studies, was confirmed. In these 50 patients, there were no local or distant recurrences after 1 year. The remaining 5 patients with biopsies positive for residual tumor underwent surgical resection. In 46 of the 50 patients with successful ablation, cosmetic outcomes were excellent after 1 year and only 2 patients experienced minor skin burns during the tumor ablation. **Conclusions:** RFA in patients with early breast carcinoma can achieve local control rates similar to those with wide local excision, but with improved cosmetic results. Clinical trial information: 000008675.

**1100 General Poster Session (Board #193), Mon, 8:00 AM-11:45 AM**

**Development of a novel nomogram predicting nonsentinel lymph node metastases among patients with breast cancer after neoadjuvant chemotherapy (NACT): A transSENTINA substudy.** *Presenting Author: Cornelia Liedtke, University of Schleswig-Holstein, Campus Luebeck, Luebeck, Germany*

**Background:** The optimal timing for sentinel lymph node biopsy (SLNB) in the setting of NACT is still unclear. Recent studies such as SENTINA suggest that performing SLNB in patients with a cN+ status before, converting to cN0 after NACT (arm C) results in a non-acceptable false-negative rate. Therefore, there is a need to predict non-SLN status and tailor axillary surgery after NACT. The goal of this study was to develop an optimized nomogram based on data from SENTINA trial patients. **Methods:** The SENTINA trial with 1,737 patients from 104 institutions was previously described in detail. 181 patients in arm C were analyzed as a development set. Risk factors for non-sentinel node involvement have been selected based on prior univariate logistic regression analysis using a threshold of p<=0.2 and subsequent multivariable logistic regression using a backward selection procedure applying the likelihood ratio test. Validation of the model was carried out using a leave-one-out-validation (LOOV). The performance of the nomograms was evaluated by the area under the receiver operator curve (AUC). **Results:** Selected variables of the final prediction model comprised number of positive resected lymph nodes (OR=1.656, CI: 1.025-2.677, p=0.039), sonographic diameter of largest lymph node (OR=1.126, CI: 1.037-1.223, p=0.005) and tumor diameter after NACT (OR=1.180, CI: 0.962-1.447, p=0.112). A preliminary nomogram was built and yielded a mean AUC of 0.75252 (SD=0.004576, min=0.748, max=0.766) in LOO-validation. Selecting a cutpont of 36%, a sensitivity of 82% and a specificity of 49% may be reached. Additional analyses are ongoing and results will be presented. **Conclusions:** We developed a nomogram for prediction of non-sentinel lymph node metastases following NACT using the SENTINA patient database. The nomogram yielded AUC values comparable to previously presented nomograms. A provisional cutpoint for clinical decision making is described. External validation is planned.

**1102 General Poster Session (Board #195), Mon, 8:00 AM-11:45 AM**

**Mapping of the axilla: Lymph node involvement in level 1, 2, and 3 of the axilla and in the interpectoral region in early breast cancer.** *Presenting Author: Andreas Jakob, Ortenau Klinikum Offenburg, Offenburg, Germany*

**Background**: Axillary clearance provides important information for prognosis and staging. The aim of this study was to determine the involvement of the different regions of the axilla in node positve primary breast cancer (PBC). **Methods**: We conducted a retrospective analysis of data from a single-center, unselected cohort of women with PBC. Between 1997 and 2001 axillary lymph node (LN) dissection comprised of clearance of level 1, 2, and 3 and since 2002 the interpectoral region was also routinely dissected. In all patients level 1 was dissected, level 2 in 98,8%, level 3 in 94,9% and the interpectoral (ip) region in 63,9% of the women. **Results**: We analysed data of 1,868 women with PBC treated at our institution between 1997 and 2009. 740 (39,6%) of the patients had node pos. disease. Out of these patients 267 (36,1%) had only one LN involved. The other patients (63,9%) had more than one pos. LN. The involvement of the different axilla regions dependent on the number of positive LN referring to the dissection frequency was: 1 pos LN: level 1 96,6%; level 2 0,8%; level 3 1,6% ip 1,7%. 3 pos LN: level 1 100%; level 2 8,9%; level 3 7,9%; ip 7,4%; ≥ 1 pos LN: level 198,8%; level 2 29,4%; level 3 18,9%; ip 9,2%. The involvement of level 2,3 and ip region in relation to the number of pos. LN in level 1:1 pos LN: level2 6,4%; level 3 3,3%; ip 2,6%. 3 pos LN: level 2 19,5%; level 3 10,3%; ip 8,9%. 4-9 pos LN: level 2 52%, level 3 27,8%; ip 12,9%. The frequency of stage pN0 was dependent on the number of removed lymph nodes: in patients with less than 10 LN removed, stage pN0 was diagnosed in 77,5% and in patients with more than 23 resected LNs in only 56% **Conclusions**: In 64% of patients with node positive PBC, there are more than one LNs involved. Patients with one positive LN in level 1 will have positive nodes in the other regions in over 10%; with two positive nodes in level 1 in 20%; and with three positive nodes in level 1 in 40%, respectively. In patients with 4-9 positive LNs in level 1, level 3 will be involved in 28%. There is an increased risk of metstatic spread to regions, which are not routinely dissected, dependent on the number of positive LNs in level 1. This could have implications on accurate staging and surgical procedures.

**1103 General Poster Session (Board #196), Mon, 8:00 AM-11:45 AM**

**The prognostic B2-Score for metastatic breast cancer: An external evaluation of 852 patients.** *Presenting Author: Achim Wöckel, Department of Gynecology and Obstetrics University Ulm, Ulm, Germany*

**Background:** The B2-Score is an individual, quantitative assessment of the likelihood of overall survival for advanced breast cancer patients based on routine parameters easily accessible in daily clinical care. Although major progress has been made, the optimal therapeutic management of the individual patient is still unknown. Besides elaborative molecular classification of tumors simple clinical measures such a prognostic score may be helpful to further individualize optimal breast cancer care. This study is a further external evaluation of this score. **Methods:** This German multicenter [17 certified breast cancer centers] retrospective cohort study called BRENDA (Quality of breast cancer care under evidence-based guidelines) included 10.119 advanced breast cancer patients. In the Cox regression model, hormone receptor (HR) status, the specific site of metastasis, and metastatic-free interval (MFI) were associated with survival from first relapse. **Results:** Medianage at primary diagnosis was 63 yrs (range 22-96), median MFI was 17 mths (range 0-200). 78.2% were HR-positive. 88.8% were M0 at primary diagnosis. 73.6% of the M0- patients were treated non-guideline adherent with respect to primary adjuvant therapy. 18% had 2 or more guideline violations. Median [mean] of $B^2$Score was 11 (range 3-38) [12.1; STD 6.4]. 40.0% were low risk, 27.3% intermediate risk and 32.7% high risk. 5 years cumulative survival was 37% (95% CI 31%-44%) for low risk, 25% (95% CI 18%-31%) for intermediate risk and 11% (95% CI 7%-16%) for high risk. Cox-Mantel Hazard Ratio for intermediate risk was 1.34 (p=0.007; 95% CI 1.08-1.66) and for high risk 2.30 (p=<0.001; 95% CI 1.89-2.81) compared to low risk. **Conclusions:** The B2-Score classified these patients into 3 risk groups with highly significant different overall survival, confirming the prognostic value of this score. More than 70% of the advanced breast patients in this study—originally M0—were treated nonguideline adherent with respect to adjuvant therapy.

**1104 General Poster Session (Board #197), Mon, 8:00 AM-11:45 AM**

**Investigating the regulation of e-cadherin mRNA and protein expression by integrin $\alpha 3\beta 1$ in breast cancer cells.** *Presenting Author: Anupam Batra, Albany Medical College, Albany, NY*

**Background:** E-cadherin is an adhesion glycoprotein in epithelial tissues and reduced expression is associated breast cancer metastasis. The cell surface integrin $\alpha 3\beta 1$ is also associated with malignant progression of breast tumors. Our genome-wide microarrays identified that E-cadherin mRNA levels are modulated by $\alpha 3\beta 1$ in MDA-MB-231 breast cancer cells. The current study investigates the association between these two important structural genes in breast cancer progression. **Methods:** MDA-MB-231 cells were stably transduced with lentivirus expressing short hairpin RNA (shRNA) targeting the $\alpha 3$ integrin subunit or with control shRNA. Total RNA was isolated for qPCR with primers specific for integrin $\alpha 3$, E-cadherin, and GAPDH. Immunoblot was performed using mouse anti-serum against E-cadherin or rabbit anti-serum against ERK, followed by secondary horse-radish peroxidase-congugated antibody. Immunohistochemistry (IHC) was then performed using rabbit anti-serum against either $\alpha 3$ or E-cadherin. **Results:** Our experimental model consisted of human breast cancer MDA-MB-231 cells with $\alpha 3\beta 1$-expressing or $\alpha 3\beta 1$-deficient populations. qPCR revealed a 24-fold ($p < 0.05$) increase in E-cadherin mRNA in $\alpha 3\beta 1$-deficient cells relative to controls. These findings confirmed our earlier microarray data, which indicated that $\alpha 3\beta 1$ suppresses the expression of E-cadherin mRNA. However, immunoblot of lysates from the same cells showed increased levels of E-cadherin protein in $\alpha 3\beta 1$-expressing controls relative to $\alpha 3\beta 1$-deficient cells. IHC showed increased staining in $\alpha 3$-expressing cells corroborating immunoblot results. **Conclusions:** E-cadherin mRNA levels were found to be increased in $\alpha 3$-deficient breast cancer cells whereas E-cadherin protein expression was down-regulated in the same cells as detected by immunoblot and IHC. We suggest that E-cadherin may be part of a group of genes up-regulated in the absence of $\alpha 3\beta 1$, but that this regulation is counter-balanced by translational or post-translational down-regulation of E-cadherin protein. Further studies are needed to understand the complex regulatory networks that control E-cadherin expression in response to $\alpha 3\beta 1$ in breast cancer progression.

**1105 General Poster Session (Board #198), Mon, 8:00 AM-11:45 AM**

**Differential response of neoadjuvant chemotherapy with taxane-carboplatin versus taxane-epirubicin in patients with locally advanced triple-negative breast cancer.** *Presenting Author: Jiayu Wang, Department of Medical Oncology, Cancer Institute and Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

**Background:** Triple-negative breast cancer (TNBC) may be more sensitive to platinum. The aim of this study was to compare the different pathologic complete response (pCR) in patients with locally advanced TNBC treated with platinum-based neoadjuvant chemotherapy with nonplatinum regimen. **Methods:** Eligible locally advanced TNBC women received either paclitaxel (or docetaxel)- carboplatin (TC) or paclitaxel (or docetaxel)-epirubicin (TE) q3w for up to 4-6 cycles. The primary end point was the rate of pathological complete response (pCR), defined as the absence of invasive cancer in the breast and axilla at the time of surgery. The second end point was the clinical response rate and recurrence free survival (RFS). **Results:** In total, 92 patients were enrolled between January 2009 and December 2012. Of these, 43 patients were assigned to TC group, and 49 to TE group. The pCR rate was higher in TC group than in TE group (37.2% versus 16.1%, p=0.032). The clinical response rates were similar in TC and TE group (83.7% versus 87.8%, p=0.500). The incidence of grade 3–4 neutropenia (TC: 39.5% versus TE: 46.9%, p=0.399) and febrile neutropenia, were not significantly different between two groups. Peripheral neuropathy was frequent but never severe. G3 alopecia was more frequent in TE group than in TC group. RFS has not been evaluated yet because of limited follow-up time. **Conclusions:** This study suggested that platinum-based chemotherapy was superior to nonplatinum regimen in the neoadjuvant treatment of locally advanced TNBC, as measured by pCR. Further large-scale prospective randomized trials are warranted.

**1106 General Poster Session (Board #199), Mon, 8:00 AM-11:45 AM**

**A phase II study of tivantinib (ARQ-197) for metastatic triple-negative breast cancer.** *Presenting Author: Sara M. Tolaney, Dana-Farber Cancer Institute, Boston, MA*

**Background**: Data suggests that MET expression and activation is important for initiation and progression of triple-negative breast cancer. Tivantinib (ARQ 197) is an orally administered agent that was originally presumed to target MET, though recent preclinical data suggests it may inhibit microtubule polymerization. **Methods**: We conducted a two-stage, single arm study of tivantinib in patients (pts) with metastatic triple-negative breast cancer. Pts could receive 1 to 3 prior lines of chemotherapy in the metastatic setting and were required to have measurable disease. Treatment consisted of twice daily oral dosing of tivantinib (360 mg po bid), on a 21 day cycle. Pts underwent restaging scans at 6 weeks, and then every 9 weeks. Response was evaluated using RECIST 1.1, and the primary endpoint was progression-free interval of 6 months (PFS≥6). The target samples size was 26 pts, and if ≥5 pts had PFS≥6 the null rate (10%) would be rejected in favor of a 31% rate of activity. Tumor biomarkers that may predict response to tivantinib were explored. **Results**: The study closed for futility after 22 pts were enrolled; pts had received a median of 2 prior lines of chemotherapy for metastatic disease. Only 1 pt had PFS≥6 (4.5%, 95% CI 0.2%-24.7%). One pt achieved a partial response (PR) for a 4.5% overall response rate, and 6 pts (27%) had stable disease as the best response. The median PFS was 1.2 month (95% CI 1.0-1.4). There were few grade 3+ adverse events (1 grade 3 anemia, 1 grade 3 fatigue, and 3 pts with grade 3/4 neutropenia). Whole exome sequencing of archival tumor tissue and tissue from time of progression in the pt who experienced a PR was also performed. Somatic alterations identified in the post-progression biopsy include mutations in known breast cancer genes MAP2K4 and TP53, as well as a mutation of unknown significance in the kinase domain of JAK2. Biomarker studies of MET expression and amplification in archival tumor tissue are ongoing. **Conclusions**: This represents the first study of tivantinib for the treatment of metastatic triple-negative breast cancer. These results suggest that tivantinib is well tolerated, but is largely inactive when used as monotherapy to treat metastatic triple-negative breast cancer. Clinical trial information: NCT01542996.

**1107 General Poster Session (Board #200), Mon, 8:00 AM-11:45 AM**

**Frequent *BRCA1/2* and *BARD1* germline mutations in triple-negative breast cancer patients.** *Presenting Author: Jacques De Greve, Familial Cancer Clinic and Medical Oncology, University Hospital Brussels, UZ Brussel, Brussels, Belgium*

**Background:** Triple negative breast cancer (TNBC) accounts for 10-20% of all breast cancers and conventional chemotherapy is the only effective systemic treatment. Germline *BRCA1/2* mutations are found in approximately 15% of TNBC patients. PARP inhibitors are being investigated in this subset of patients. In the past we have documented pathogenic mutations in BARD1, a BRCA1 interacting protein, in families at high risk for breast cancer. In the current study we have analyzed the germline DNA from 61 estrogen receptor negative patients included in the TOP trial for the presence of mutations in the *BRCA1, BRCA2* and *BARD1* gene. **Methods:** Patients signed a separate informed consent for the current retrospective genetic analysis and were offered oncogenetic counseling. Genetic variants were detected by High Resolution Melting curve Analysis (HRMA) and confirmed by Sanger sequencing. In Silico tools were used to further characterize these variants. **Results:** Of the 61 ER- patients 42 were TNBC and 19 were HER2-positive. *BRCA1/2* mutations were found in 8/42 (19%) TNBC, but none in the ER-/HER2 cohort. We also found four (10%) strong candidate pathogenic mutations in the *BARD1* gene, including two protein truncating mutations (p.Gln564X and p.Arg641X), while no such mutations were found in 245 control samples. Only two *BARD1* truncating mutations have been reported worldwide earlier in germline DNA from breast cancer patients, including a case we identified in one out of 196 high risk breast cancer families. Our data suggest that TNBC patients are enriched for pathogenic *BARD1* mutations as compared to the incidence in control samples and in high breast cancer risk families. Additional clinical-genomic correlations are being investigated. **Conclusions:** Almost one third of TNBC (29%) have a BRCA pathway mutation. These patients should become eligible for exploring the efficacy of PARP inhibitors.

**1108 General Poster Session (Board #201), Mon, 8:00 AM-11:45 AM**

**The relationship between body mass index, diabetes, and triple-negative breast cancer prognosis.** *Presenting Author: Jose M Pacheco, John Cochran Veterans Affairs Medical Center, Washington University School of Medicine, Saint Louis, MO*

**Background:** Higher body mass index (BMI) and diabetes are associated with worse breast cancer prognosis. However, information on how these variables relate to survival in triple-negative breast cancer (TNBC) is limited. **Methods:** We retrospectively reviewed 501 patients with TNBC first seen at the Washington University Breast Oncology Clinic between January 2006 and December 2010. Cox proportional hazards models were used to determine the relationship between BMI at diagnosis and diabetes with overall survival (OS) and disease free survival (DFS). **Results:** 448 patients had BMI recorded and 71 had diabetes. Of these, 4.50% with BMI available and 2.82% with diabetes presented with stage IV disease. The median age at diagnosis was 53 (23-98) years and follow-up was 40.1 months. There was no significant difference between groups in time from imaging to biopsy, time from biopsy to surgery, receipt of neoadjuvant or adjuvant chemotherapy, pathologic complete response to neoadjuvant chemotherapy, grade, pathological stage or duration of follow-up. Additionally, for BMI groups, there were also no differences in age or menopausal status. Interestingly, baseline BMI and diabetes were not associated with OS or DFS. OS hazard ratios (HRs) for overweight patients (BMI 25.1 to 29.99), those with class I obesity (BMI 30 to 34.99) or BMI ≥ 35 were 0.82 (CI 0.53 – 1.25, p = 0.35), 0.86 (CI 0.56 – 1.33, p = 0.50) and 0.87 (CI 0.54 – 1.40, p = 0.57), respectively. While the HRs for DFS in overweight patients, those with class I obesity or BMI ≥ 35 were 0.83 (CI 0.54 – 1.27, p = 0.39), 0.93 (CI 0.60 – 1.44, p = 0.74) and 0.96 (CI 0.61 – 1.52, p = 0.87), respectively. Similarly, the HRs for diabetics were 1.14 (CI 0.75 – 1.75, p = 0.55) for OS and 0.90 (CI 0.59 – 1.39, p = 0.63) for DFS. **Conclusions:** We conclude that obesity and diabetes did not significantly affect survival for TNBC patients in this single center cohort study.

**1109 General Poster Session (Board #202), Mon, 8:00 AM-11:45 AM**

**Histopathologic and immunohistochemical findings in triple-negative breast cancers showing clinical progressive disease during neoadjuvant chemotherapy.** *Presenting Author: Yuko Tanabe, Department of Breast and Medical Oncology, National Cancer Center Hospital, Tokyo, Japan*

**Background:** Clinical progressive disease (cPD) occurs during neoadjuvant therapy (NAC)in 3–5% of triple negative breast cancer (TNBC) patients. Predictive biomarkers are required for subtype specific characterization given the heterogeneous response to NAC in TNBC. This case-control study retrospectively analyzed histopathological and immunohistochemical data with the aim of detecting potential predictors of cPD. **Methods:** Using a pathology database of patients who had undergone surgical resection, 102 patients with TNBC were identified: 22 with cPD during NAC (PD group) and 80 controls (C group). Formalin-fixed paraffin-embedded tumor tissue sections were immunohistochemically examined for expression of 14 molecules, including ABCB1, which is a member of the ABC transporter family, and the following epithelial-to-mesenchymal transition (EMT) markers: vimentin, Twist NB, E-cadherin, ZEB1, and Snail2. Chi-square tests were conducted to compare differences between the groups. **Results:** Histologically, the PD group included 14 (64%) invasive ductal carcinomas (IDCs) and 8 (36%) metaplastic carcinomas (MPCs). In the C group, 59 (74%) were IDCs, 20 (25%) were types other than IDC or MPC, and only 1 was an MPC (1%) ($p<0.001$). The positive expressions of cytoplasmic vimentin (77%), nuclear Twist NB (27%), nuclear ZEB1 (36%), and nuclear Snail2 (59%) in the PD group were higher than those in the C group (54%, $p=0.049$; 3%, $p=0.0011$; 13%, $p=0.0093$; 48%, $p=0.049$, respectively). Nuclear ABCB1 expression was higher in the PD group (64%) than in the C group (6%) ($p<0.001$); conversely, cytoplasmic ABCB1 was present more frequently in the C group (96%) than in the PD group (77%) ($p=0.011$). The positive expression of nuclear ABCB1, nuclear ZEB1, or cytoplasmic vimentin occurred in 95% of the PD group compared to 61% in the C group ($p= 0.002$). **Conclusions:** A metaplastic phenotype, cytoplasmic vimentin or nuclear ZEB1 expression, and increased nuclear localization of ABCB1 could be predictors for cPD during NAC in TNBC patients.

**1110 General Poster Session (Board #203), Mon, 8:00 AM-11:45 AM**

**Expression of PD-L1 and NY-ESO-1 in early and advanced triple-negative breast cancer.** *Presenting Author: Anna Tessari, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy*

**Background:** Advanced triple negative breast cancer (TNBC) is a poor prognosis disease to which no targeted therapies are available. PD-L1 is a key player in tumor immune escape, and significant responses have been obtained inhibiting this pathway in various malignancies. NY-ESO-1 is a tumor-specific antigen and represents a possible target for vaccine therapy. Here we evaluate PD-L1 and NY-ESO-1 expression in early and advanced TNBC patients. **Methods:** 26 metastatic TNBC patients who underwent both primary surgery and distant lesion biopsy were selected. From representative paraffin-embedded block, we obtained 3 tissue-cores of 1.5 mm diameter for the construction of a tissue microarray, which was evaluated by immunohistochemistry. **Results:** In primary and metastatic lesions NY-ESO-1 was expressed in 12% and 24% of the samples respectively (30.8% overall positivity). PD-L1 was expressed in 100% of early TNBC and in 92% of corresponding metastatic lesions. Two patients lost PD-L1 expression in the distant lesion: one patient received anthracyclines, taxanes and CMF as adjuvant treatment and one received also paclitaxel and carboplatin as first line therapy before the distant lesion biopsy. All but one patient maintaining the PD-L1 expression in the advanced disease received anthracycline for early breast cancer, 52% and 91% adjuvant taxanes and CMF respectively, 26% various first line treatments before the biopsy. This observation is apparently in conflict with the hypothesis that doxorubicin inhibits PD-L1 expression. No correlation between NY-ESO-1 expression and age, time to relapse, presence of metastasis and cytotoxic treatments were observed. **Conclusions:** This study first investigates PD-L1 expression in TNBC patients and reports 100% positivity in the early stage, mostly maintained in the advanced disease. No clear correlation with PD-L1 loss and chemotherapy could be identified. This study reports that NY-ESO-1 is expressed in a subpopulation of TNBC, also in the metastatic setting, that could benefit from an anti-NY-ESO-1 vaccine, and indicates that TNBC is an ideal subgroup for anti-PD-L1 therapies. Patients positive on the early breast cancer specimen could then avoid a further biopsy of the metastatic site.

**1111 General Poster Session (Board #204), Mon, 8:00 AM-11:45 AM**

**Pretreatment neutrophil to lymphocyte ratio may be an useful tool in predicting survival in early triple-negative breast cancer patients.** *Presenting Author: Mirco Pistelli, Department of Medical Oncology, AOU Ospedali Riuniti, Ancona, Italy*

**Background:** There is a growing body of evidence that immune response plays a large role in cancer outcome. The neutrophil to lymphocyte ratio has been used as a simple parameter of systemic inflammation in several tumors. The purpose was to investigate the association between pre-treatment NLR, disease-free survival and overall survival in patients with early triple negative breast cancer (TNBC). **Methods:** We reviewed the records of patients with stage I-III TNBC at our Institution from 2006 to 2011. Patients were divided into two groups, according to a pre-treatment NLR cut off value was 3. The difference among variables was calculated by chi-square test. DFS and OS were estimated using Kaplan-Meier method. Cox analysis was performed to analyze clinical parameters for their prognostic relevance. **Results:** A total of 90 patients were eligible for analysis: 18,7% of patients showed higher pre-treatment NLR (group B). Median age at diagnosis was 53 years (range 28-79). The median follow-up time was 53.8 months (13.1-195.2). There was no significant correlation among pre-treatment NLR and various clinical pathological factors, including age, menopausal status, tumor size, lymph nodes status, grading, Ki-67, necrosis, lympho-vascular invasion. At univariate analysis patients with higher pre-treatment NLR (group B) showed significantly lower DFS ($p<0.01$; HR=0.21, 95% CI 0.01-0.39) and OS ($p<0.01$; HR=0.16, 95% CI 0.007-0.37). Multivariate analysis revealed that pre-treatment NLR was an independent prognostic factors influencing DFS ($p=0.006$; HR=5.12, 95% CI 1.6-16.38) and OS ($p=0.008$; HR=6.84, CI 1.6-28.5). **Conclusions:** Our study suggests that pre-treatment NLR may be associated with DFS and OS of patients with early TNBC and can be easily introduced in clinical practice in order to identify TNBC patients with poor prognosis. Prospective studies are needed to assess the potential role of NLR in guiding treatment decisions, patient selection, and clinical trials design.

**1112 General Poster Session (Board #205), Mon, 8:00 AM-11:45 AM**

**The role of CHFR as a predictive marker of response to taxane-based preoperative chemotherapy in triple-negative breast cancer.** *Presenting Author: Elisavet Paplomata, Department of Hematology and Oncology, Winship Cancer Institute of Emory University, Atlanta, GA*

**Background:** Taxanes are frequently used in the treatment of breast cancer. CHFR (checkpoint with forkhead and ringfinger domains) is a novel biomarker of resistance to microtubule targeting agents that can help individualize care and identify targets for overcoming this resistance. Our institution showed that high CHFR is associated with decreased response to taxanes and worse overall survival in patients with lung cancer. The current work evaluated the translational significance of CHFR in breast cancer. **Methods:** We studied a cohort of patients with triple negative breast cancer (TNBC), who were treated with pre-operative taxane-based chemotherapy followed by surgery. Archived paraffin-embedded tissue was stained for CHFR using immunohistochemistry. The level of protein expression was assessed by light microscopy and scored for intensity of staining and percentage of staining cells. CHFR expression was associated with pathologic complete response (pCR) and progression free survival (PFS). Covariates included age, race, stage, grade, tumor size, lymph node involvement, and type of chemotherapy. The univariate association with pCR was assessed using the chi-square test or Fisher's exact test, where appropriate for categorical covariates; and ANOVA for numerical covariates. The univariate and multivariate association with PFS was assessed using the Cox proportional hazard model. **Results:** We analyzed tumor samples from 43 eligible patients, with median age of 57 years. 27.9% of patients achieved a pCR. 88.4% of patients had high CHFR expression. The expression of CHFR was not associated with clinical outcomes: pCR rate or PFS. All analyses were repeated on 30 patients treated with doxorubicin/cyclophosphamide and paclitaxel; the high expression of CHFR still did not have a statistically significant association with pCR or PFS though there was a marginal trend towards better PFS. **Conclusions:** In this cohort of TNBC patients, the majority of tumors had high CHFR expression. This did not associate with clinical outcomes: pCR and PFS. We hypothesize that TNBC may be characterized by high CHFR; evaluation of hormone receptor positive and HER2 positive tumors may be worth exploring.

**1113 General Poster Session (Board #206), Mon, 8:00 AM-11:45 AM**

**Survival outcomes across ethnicities in triple-negative breast cancer.** *Presenting Author: Moira Katherine Rushton, University of Ottawa, Ottawa, ON, Canada*

**Background:** Triple negative breast cancer (TNBC) is a heterogeneous disease characterized by the lack of receptor expression (ER, PR, and HER2/neu negative). Amongst breast cancer types TNBC has a less favourable prognosis. There is a higher incidence of TNBC in African-American women than Caucasian women. What has not been clearly elucidated is whether survival outcomes are different among women with TNBC from different ethnic background. **Methods:** The objective of our study was to determine if significant differences exist in overall survival (OS) of TNBC patients across various ethnicities, including but not limited to Caucasian, African-American, and Asian. Using population data a multivariate analysis was done to take into account age, stage, and treatments received. **Results:** Using data from SEER database 6,227 cases of TNBC across all ethnicities were reported in 2010. At year one of follow-up, mortality rate was 2.6% (n=162) Race was found to be a potential predictor of breast cancer mortality with a mortality rate of 3.13% in American Indian/Alaskan Native and Pacific Islander patients; 2.75% in black patients; 2.6% in white patients. When adjusted for age and stage at time of diagnosis in multivariate analysis, there was no significant difference in OS for any ethnicity when compared to Caucasian patients. Specifically black TNBC patients had an OR 1.089 (p=0.69) and Asian patients OR 1.084 (p=0.87). **Conclusions:** While there was some suggestion that there was a higher one year breast cancer mortality rate in some populations, in multivariate analysis this was not a significant finding. Longer follow-up is needed before conclusions can be made about differences between ethnic groups. We are planning to review other large population databases to gather a greater pool of data to answer this question. Determining if there are certain populations do worse will inform the medical oncology community of an area to focus greater study to determine how to optimize therapies for that patient group.

**1114 General Poster Session (Board #207), Mon, 8:00 AM-11:45 AM**

**The impact of TSG101 in triple-negative breast cancers.** *Presenting Author: Shiva D.J. Sharma, University College Dublin, Belfield, Ireland*

**Background:** TSG101 is an essential protein and constituent of cellular function involved in the sorting and trafficking of cell components destined for processing or degradation and is also integral to exosome production and release. Limited information is known about TSG101 and exosomes in the field of breast cancer and even less in the difficult to treat subset of triple-negative breast cancer (TNBC). We propose that TNBC tumours demonstrating high levels of TSG101 are more likely to recur locally and at distant sites due to enhanced exosome mediated communication in the tumour microenvironment through the propagation of chemoresistance. **Methods:** Cellular viability of our TNBC cell lines (BT-549 and MDA-MB-231) after incremental Paclitaxel treatments were assessed by MTT viability assay. Using an siRNA knockdown we were able to selectively target and reduce the intracellular levels of TSG101 protein. TNBC cell lines were treated with Paclitaxel at 24 and 48 hours. Immunohistochemical staining for TSG101 was performed to evaluate the expression of TSG101 in breast cancer clinical cases. **Results:** Using an MTT viability assay, BT-549 TNBC cells were found to be more sensitive to the chemotherapeutic drug Paclitaxel compared to the MDA-MB-231 TNBC cells which were shown to be more chemoresistant. Following 24 and 48hours of treatment with Paclitaxel the levels of TSG101 in the MDA-MB-231 cells remained level, while the levels of TSG101 were lower in the more Paclitaxel sensitive BT-549 cells. Subsequent exosome profiling of media collected from TSG101 protein knockdown cells showed differential size and number of exosomes released from BT-549 and MDA-MB-231 cells after Paclitaxel treatment. Immunohistochemical analysis of 85 breast cancer cases on TissueMicroArray established strong cytoplasmic staining of TSG101 in 20% of cases, while 53% of tumours demonstrated none/weak staining of TSG101. **Conclusions:** We conclude that TSG101 is differentially expressed in the TNBC in vitro and that expression levels are influenced by Paclitaxel treatment. We also conclude that siRNA knockdown of TSG101 impedes the release of exosomes. We suggest that TNBC tumours that clinically express high levels of TSG101 may express a more aggressive phenotype.

**1115 General Poster Session (Board #208), Mon, 8:00 AM-11:45 AM**

**Pretreatment platelets count levels as a prognostic factor in triple-negative breast cancer in a Hispanic cohort.** *Presenting Author: Saul Campos Gomez, Centro Oncológico Estatal ISSEMYM, Toluca, Mexico*

**Background:** Platelet count has been reported to have predictive value in various cancer entities. Several studies suggest a negative impact of thrombocytosis for patient's survival in different types of cancer. In the case of breast cancer, evidence about involvement of platelets is still inconclusive. Therefore, the aim of our study was to assess the influence of pretreatment platelet count levels on survival and establish its prognostic relevance for breast cancer patients in a large cohort of triple negative breast cancer patients. **Methods:** We retrospectively studied patients diagnosed with primary triple negative breast cancer that had completed all phases of primary treatment from 2005 to 2012, finding 118 patients with platelet counts prior to therapy and clinical follow-up. Baseline platelet numbers were evaluated at diagnosis (before the start of any therapy for disease). Platelet levels were categorized into the following three groups: normal low (< 200 g/L), normal high (200-400 g/L) and thrombocytosis (> 400 g/L). Overall survival (OS) was assessed using the Kaplan-Meier method and were compared using the LogRank test. To evaluate the independent prognostic significance of NLR, multivariate Cox regression models were used. **Results:** Patients with lower platelets count (< 200 g/L) showed significantly lower median overall survival than those with normal high (200-300 g/L) and thrombocytosis (> 400 g/L) (33 months vs. 71 months, log Rank p=0.024). Pretreatment thrombocytosis was observed only in 9 patients (7.6%). Low platelets counts along with advanced stage were independently correlated with poor prognosis, with hazard ratio 1.2 (p 0.02), and 2.1 (p 0.001), respectively. Estimated media OS, for patients with low platelets count, normal high count and thrombocytosis were 56, 38 and 36 months respectively. **Conclusions:** In our retrospective study, normal low platelet counts at time of diagnosis were associated with poor prognosis in triple negative breast cancer. We hypothesize that platelets in normal high levels as scavenger of VEGF and therefore as a potent antiangiogenic cellular component of the tumor microvasculature in triple negative breast cancer can also be considered.

**1116 General Poster Session (Board #209), Mon, 8:00 AM-11:45 AM**

**Antitumoral activity of EC70124, a novel multitarget kinase inhibitor, in triple-negative breast cancer.** *Presenting Author: Maria D. Cuenca-Lopez, Translational Research Unit, Albacete University Hospital, Albacete, Spain, Albacete, Spain*

**Background:** Receptor tyrosine kinases (RTK) and downstream signaling routes play a central role in the genesis and/or promotion of different breast cancer tumors including the triple negative subtype. Kinase inhibitors designed to neutralize their function are in clinical development. We describe the preclinical evaluation of EC-70124, a novel, unique profile, multi-target kinase inhibitor, in triple negative breast cancer. **Methods:** Cell proliferation and growth was measured by MTT uptake and matrigel in a representative panel of triple negative cell lines. Evaluation of apoptosis and cell cycle was performed by flow cytometry. Western-blot and phospho-array kits were used for evaluation of signaling intermediates. To evaluate if EC-70124 combined with other chemotherapy drugs was synergistic we used the CalcuSyn v2.0 software. Gene-set enrichment analyses were performed to identify relevant functions affected by the drug and the identified genes were confirmed by RT-PCR. In vivo anti-tumor effect was evaluated using xenografted animals. **Results:** EC-70124 is a hybrid indolocarbazole analog obtained by combinatorial biosynthesis of Rebeccamycin and Staurosporine pathways and produced by fermentation. Doses of EC-70124 in the nanomolar ranged reduced proliferation in a panel of triple negative cell lines including HS578T, BT549, MDA-MB231 and HCC3153. Treatment with EC-70124 at 500 nM led to an induction of DNA damage measured by γH2AX. Cell cycle analyses showed an arrest at the G2/M phase in HS578T and BT549; that was confirmed by the biochemical evaluation of cell cycle mediators. Gene expression analyses showed different cellular functions induced by EC70124 being up regulation of DNA repair genes one of them. The up-regulation of these genes was confirmed by RT-PCR. EC70124 produced tumor regression of MDA-MD231 tumors in xenografted animals. No major toxicities were observed. Studies in combination with standard of care chemotherapy showed enhanced activity. **Conclusions:** EC-70124 is a novel multi-target kinase inhibitor with anti-tumoral activity in triple negative breast cancer. Its mechanism of action is mediated through an induction of DNA damage and cell cycle arrest at G2/M.

**1117 General Poster Session (Board #210), Mon, 8:00 AM-11:45 AM**

**Similarities between the biology of breast cancer in Kenya among blacks and that seen among whites elsewhere.** *Presenting Author: Nicolas Anthony Othieno-Abinya, University of Nairobi, Nairobi, Kenya*

**Background:** Breast cancer is the commonest type of cancer among women worldwide, and the number one cause of cancer deaths among women. Its incidence increases with age, and the commonest pathological subtype is invasive ductal carcinoma. Hormone receptors (ER/PR) are expressed in about 70% of the cases and are associated with favourable outcome. HERr2/Neu is overexpressed in 20-30% of breast cancers and is associated with aggressive disease with poor outcomes. Tumours not expressing any of these biological features (triple negative) are commonly associated with dire outcome. Reports so far indicate racial differences with triple negative disease being more common among Blacks than other races. **Methods:** A prospective breast cancer care (BRECC) registry at the Kenyatta National Hospital, Nairobi. Details taken included biodata, symptoms, pathology, hormone receptors, HER2 overexpression, mode of diagnosis, stage at diagnosis, intervention and outcome. **Results:** A total of 269 patients - 268 were females, 1 male, all black. Median age was 48 years. Of 260 cases evaluable, 148 (56.9%) were aged $<$ 50 years and 112 (43.1%) $\geq$ 50. The commonest modes of presentation were breast lump in 149 out of 228 cases evaluable (65.4%), breast pain in 70 (30.7%) and nipple changes in 65 (28.5%). Of 181 cases evaluable, 146 (80.7%) were invasive ductal carcinoma. Two out of 113 were grade 1, 48 (42.5%) grade 2, 63 (55.8%) grade 3. Of 62 cases evaluable, 38 (61.3%) were oestrogen receptor positive, 40 (64.5%) progesterone receptor positive and 11 (17.7%) Her2 positive. Hormone receptor positive, HER2 negative cases were 40 (64.5%); hormone receptor negative, HER2 positive were 6 (9.7%); hormone receptor negative, HER2-negative (triple negative) were 10 (16.1%); hormone receptor positive, HER2-positive were 6 (9.7%). **Conclusions:** The median age for breast cancer in Kenya is young, though increasingly approaching that seen in whites. Hormone receptor and HER2 expression levels don't differ significantly from what is reported among whites.

**1118 General Poster Session (Board #211), Mon, 8:00 AM-11:45 AM**

**Mutant p53: A therapeutic target for the treatment of triple-negative breast cancer?** *Presenting Author: Naoise C. Synnott, Education and Research Centre, St.Vincent's University Hospital and School of Medicine and Medical Science, University College Dublin, Dublin, Ireland*

**Background:** Despite intensive efforts, a validated targeted therapy for triple-negative breast cancer (TNBC) remains elusive. One of the most frequent genetic alterations identified to date in TNBC is mutation in the p53 gene, which has been found in $>$ 80% of these samples. The aim of this study was therefore to investigate mutant p53 as a potential target for the treatment of TNBC. **Methods:** Two compounds, PRIMA-1 and PRIMA-$1^{MET}$which have previously been shown to reactivate mutant p53 and convert it to a form with wild-type properties were investigated in a panel of 18 p53 mutant breast cancer cell lines (TNBC = 12; non-TNBC = 6). Cytoxicity was determined using the MTT assay, while induction of apoptosis was measured using both the Cell Death ELISA kit and flow cytometry. **Results:** Using the MTT assay, $IC_{50}$ concentrations across 12 p53 mutant TNBC cell lines ranged from 1.4 to 15.1$\mu$M for PRIMA-1 and from 0.9 to 11.9 $\mu$M for PRIMA-$1^{MET}$. Response to PRIMA-1 correlated significantly with that to PRIMA-$1^{MET}$ ($p<0.0001$). Inhibition of cell growth varied from 4.1 to 90.8% for PRIMA-1 and from 3.1 to 96.6% for PRIMA-$1_{MET}$ using concentration of inhibitor at 6.25 $\mu$M. PRIMA-1 and PRIMA-$1^{MET}$ also reduced the ability of the mutant p53 cells to form colonies with $IC_{50}$ values ranging from 0.16 to 10.7 $\mu$M for PRIMA-1 and from 0.02 to 9.6 $\mu$M for PRIMA-$1^{MET}$. No significant difference in sensitivity for either inhibitor was observed between ER-positive and ER-negative cell lines, HER2-positive and HER2-negative cell lines or between TN and non-TN cell lines. In addition to inhibiting cell proliferation, both PRIMA-1 and PRIMA-$1^{MET}$also induced apoptosis in MDA-MB-453 cells. **Conclusions:** Our preclinical results suggest that targeting mutant p53 with either PRIMA-1 or PRIMA-$1^{MET}$is a potential new approach for treating p53-mutated breast cancer including the subgroup with triple-negative disease.

**1119 General Poster Session (Board #212), Mon, 8:00 AM-11:45 AM**

**Evaluation of *BRCA1*/2 mutation status among women with triple-negative breast cancer.** *Presenting Author: Axel Muendlein, Vorarlberg Institute for Vascular Investigation and Treatment, Feldkirch, Austria*

**Background:** Testing for BRCA1 and BRCA2 mutations in breast cancer patients is used to identify risk of second primary cancers and risk of cancer in the patients' family. A high proportion of BRCA1 mutation positive patients have triple-negative breast cancer (TNBC). TNBC shows a poor prognosis and no effective treatment strategies against TNBC are available to date. However, BRCA-related cancers are sensitive to platinum chemotherapy as well as to drugs targeting poly (ADP-ribose) polymerase enzymes, which are under development so far. Women with TNBC are thought to be more likely to be BRCA mutation carriers, but there have only been limited numbers of studies investigating BRCA1- and BRCA2-mutation status among Caucasian patients with TNBC. **Methods:** We determined the prevalence of BRCA1 and BRCA2 mutations within a cohort of 88 unselected TNBC cases including patients from Germany and Austria. Double-stranded Sanger sequencing of all exons of BRCA1 and BRCA2, respectively, was performed. **Results:** We identified a total of 14 deleterious mutations in BRCA1 and of 4 deleterious mutations in BRCA2, including 10 frame shift, five missense and two nonsense mutations as well as one splice mutation. One of our patients carried two deleterious BRCA1 mutations. The total rate of deleterious BRCA1/2 mutation carriers was 19.3% in our cohort. Furthermore, six mutations with biological significance, but unclear clinical impact, have been found. In total, 15 novel mutations have been identified, which have not been described in public BRCA mutation databases (NCBI, BIC, LOVD, and UMD, respectively) so far. **Conclusions:** We conclude that women with TNBC frequently show BRCA1 as well as BRCA2 mutations. TNBC patients may therefore benefit from BRCA genetic testing to identify those with a masked family history of breast cancer or to indentify candidates who may profit from BRCA-related therapies.

**1121 General Poster Session (Board #214), Mon, 8:00 AM-11:45 AM**

**Classification of molecular subtypes of triple-negative breast cancer using reverse phase protein arrays (RPPAs).** *Presenting Author: Hiroko Masuda, Morgan Welch Inflammatory Breast Cancer Program and Clinic, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Gene expression analyses have identified molecular subtypes of triple-negative breast cancer (TNBC), such as the basal-like subtype and the 7 molecular subtypes that are refining our understanding of breast cancer biology. However, these subtypes are not well defined enough to enable development of targeted therapy or prediction of prognosis in a clinical setting. Reverse phase protein array (RPPA) analysis could be easily adapted to a clinical setting for this purpose because it allows investigation of potential targets at the protein level and can lead to the development of immunohistochemical assays. **Methods:** We used 80 TNBC RPPAs obtained from patients at The MD Anderson Cancer Center between 03/87 and 04/06. RPPA analysis showed 154 breast cancer related proteins, including both total and phosphorylated proteins. We classified the TNBC samples using 2 types of clustering analysis, k-means and hierarchical, and silhouette width analysis. To assess the biological features of each TNBC subtype, we mapped antibody names from the RPPA dataset to HGNC gene symbols and fit a Gene Set Enrichment Analysis. We also performed correlation analysis between each TNBC subtype and recurrence-free survival (RFS) and overall survival (OS). **Results:** Results of both clustering showed that the optimal number of subtypes in the TNBC RPPA dataset was 2-3. Clusters of $k = 2$ from the k-means and hierarchical clustering methods showed the same, indicating that these 2 clusters were stable and sufficiently different and therefore could be reproduced using different methods. The top canonical pathways, which were associated with 2 clusters, were the DNA repair and replication pathway (cluster 1) and the immune response and adipocytokine signaling pathways (cluster 2). OS and DFS rates were different between the 2 clusters, but the differences were not significant (DFS: $p = 0.3$; OS: $p = 0.1$), probably owing to small sample size. **Conclusions:** Two types of clustering analysis showed that we identified 2 stable TNBC subtypes at the protein level. These results indicate that distinguishing between basal and stromal subtypes is a useful first step in identifying TNBC heterogeneity in the clinical setting.

**1122 General Poster Session (Board #215), Mon, 8:00 AM-11:45 AM**

**The outcome of special histologic types of triple-negative breast cancer (TNBC).** *Presenting Author: Katarzyna Pogoda, Department of Breast Cancer and Reconstructive Surgery, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland*

**Background:** Triple-negative breast cancer (TNBC) is a heterogeneous disease. Knowledge of the outcome of special histological subtypesof TNBC can facilitate tailored adjuvant treatment. The aim of the study was to determine recurrence rate and overall survival of special histological subtypes of TNBC in order to select those with excellent and the worst prognosis. **Methods:** Of 4,563 consecutive breast cancer patients diagnosed in Cancer Center and Institute of Oncology in Warsaw, Poland, between the years 2005 and 2008, 502 patients (9%) were TNBC (ER-/PR-/HER2-negative). Median follow-up was 7 years (range 5–9 years). 426 cases with known histological types were selected and analyzed in terms of the disease free and overall survival using the Kaplan-Meier method. Competing risk analysis was performed in order to assess the risk of recurrence and the comparison between types. **Results:** From 426 TNBC subtypes, 352 (82%) cases were classified as ductal not otherwise specified (NOS), 21 (5%) were classified as lobular, 17 (4%) were classified as metaplastic, 10 (2.3%) were classified as medullary, 7 (1.6%) as apocrine, 6 (1.4%) as papillary, 4 (0.9%) as neuroendocrine, 2 (0.5%) as cribriform and 2 (0.5%) were classified as mucinous. 5-year DFS and OS of ductal NOS type was 73% and 62%, respectively. 5-year DFS was the best for patients with apocrine (100%), medullary (100%) and neuroendocrine (100%) types while it was the worst in papillary (50%) and lobular (68%) TNBC. 5-year OS was the best in apocrine (90%) and medullar (100%) types and was the worst in papillary (17%) and lobular (61%) types. In metaplastic TNBC 5-year DFS and OS was 79% and 65%, respectively. Taking into account competing risk of death and different clinical stages of the disease, the risk of recurrence was the highest in patients with lobular TNBC (HR=2.83, p=0.04). **Conclusions:** The diagnosis of special types of TNBC is associated with different outcome if compared with ductal NOS type. Medullary and apocrine types had excellent prognosis while lobular TNBC seems to be the most aggressive and requires intensive treatment. Histological special type of TNBC should be taking into consideration when choosing adjuvant treatment, apart from specified other prognostic factors.

**1123 General Poster Session (Board #216), Mon, 8:00 AM-11:45 AM**

**Outcomes of patients with triple-negative breast cancer compared to non-triple negative breast cancer: A single-center study.** *Presenting Author: Caroline M. Hamm, Windsor Regional Caner Centre, Windsor, ON, Canada*

**Background:** Triple negative breast cancer is defined as estrogen receptor negative, progesterone receptor negative, Her-2-neu negative breast cancer. The lack of targeted therapies for this patient group has been considered to be a negative prognostic factor. **Methods:** Twelve hundred thirty four non-triple negative (n-TNBC) breast cancer patients and 167 triple negative (TNBC) patients were reviewed retrospectively. All patients were treated in a single centre in Ontario, and all received standard of care in Ontario, Canada. Hormone receptor positive patients received anti-estrogen therapy, and Her-2 positive patients received chemotherapy and trastuzumab. **Results:** Although overall progression free survival was statistically inferior for the TNBC group ( $p < 0.001$), important information is found when analyzed by stage at presentation. Median progression free survival (PFS) was not reached for any stage I, nor stage II patient group. There was no difference in overall survival for stage one between the n-TNBC and the TNBC groups, but was inferior for the TNBC group for Stage II and III. Few relapses were seen in the stage 1 TNBC group, and none were identified after 40 months (median follow-up 40 months). All analyses are as of yet unadjusted. **Conclusions:** Although the overall outcome of TNBC patients is inferior to their n-TNBC counterparts, their presenting stage is still vitally important in predicting outcome. Stage 1 TNBC carries a good prognosis, possibly better than the NTN counterpart. Ongoing research to identify these TNBC patients at an earlier stage is vital to improving outcomes in this patient population.

| | | OS in years | | | | PFS in years | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **N (%)** | **Mean** | **Median** | **Log Rank** | **p** | **Mean** | **Median** | **Log Rank** | **P** |
| **n-TNBC across stages** | | | | 284 | <0.001 | | | 130 | <0.001 |
| **Stage 1** | 511 (41) | 8.4 | --- | | | 7.7 | --- | | |
| **Stage 2** | 508 (41) | 7.3 | 9.0 | | | 7.1 | --- | | |
| **Stage 3** | 164 (13) | 5.9 | 6.0 | | | 5.1 | 7.0 | | |
| **Stage 4** | 51 (4) | 2.7 | 2.0 | | | n.r. | --- | | |
| **Overall n-TNBC** | 1234 (100) | 7.3 | 9.0 | | | 7.1 | | | |
| **TNBC across stages** | | | | 31.6 | <0.001 | | | 17.7 | 0.001 |
| **Stage 1** | 40 (24) | 7.7 | --- | | | 7.3 | --- | | |
| **Stage 2** | 92 (55) | 6.0 | --- | | | 6.3 | --- | | |
| **Stage 3** | 33 (20) | 4.3 | 5.0 | | | 4.0 | --- | | |
| **Stage 4** | 2 (1) | 1.0 | 0.0 | | | 1.0 | 1.0 | | |
| **Overall TNBC** | 167 (100) | 6.1 | --- | | | 6.2 | --- | | |
| **n-TNBC versus TNBC** | | | | 314 | < 0.001 | | | 145 | < 0.001 |

**1124 General Poster Session (Board #217), Mon, 8:00 AM-11:45 AM**

**Surgical removal of primary tumor in metastatic breast cancer: Impact on health-related quality of life (HR-QOL) in a randomized controlled trial (RCT).** *Presenting Author: Rajendra A. Badwe, Tata Memorial Center, Mumbai, India*

**Background:** We have previously reported in a RCT that surgical removal of the primary tumor (versus not) did not significantly improve median overall survival (18.8 Vs 20.5 months) in women with MBC[1]. This procedure would still be worthwhile if it improved the quality of life in these women. We report here HR-QOL analysis of this RCT. [NCT: 00193778]. **Methods:** HR-QOL was assessed in these women using the EORTC QLQC30 and BR23 (English or validated local language versions). The questionnaires were completed by these women at baseline (at randomization) and at protocol defined follow-up time points thereafter. **Results:** Of the 350 women randomized to surgical removal of the primary Vs not, HR-QOL assessment was available at baseline for 178 (surgery=84, no surgery=94), 3-6 months for 139(surgery=74, no surgery=65), 6-9 months for 122 (surgery=65, no surgery=57) and 18-24 months for 94(surgery=45, no surgery=49). The groups were balanced and representative of patients in the main study (N=350) with respect to age, hormone receptor status, site of metastasis, no of metastatic lesions. The mean BR23 arm score was worse in the surgical arm at 3-6 month evaluation (18.9 Vs 10.4, p=0.003) but not at subsequent evaluations whereas mean BR23 breast symptom score was worse in no-surgery arm at 18-24 month evaluation (18.7 Vs 10.0, p=0.009), which corresponds to median OS in these women. There was no significant difference in mean global QOL score between the 2 arms at baseline (64.2 Vs 65.8, p=0.5), 6-9 months (69.9 Vs 67.7, p=0.5), 18-24 months (64.7 Vs 60.0, p=0.3) and all other time points. There was no significant difference between the 2 arms in all other domains of HR-QOL at any time point. **Conclusions:** Surgical removal of the primary tumor did not significantly improve the HR-QOL in women with MBC. Taken together with survival results our data provides strong evidence that surgery for primary should not be routinely performed in women with metastatic breast cancer. Clinical trial information: 00193778.

**1125 General Poster Session (Board #218), Mon, 8:00 AM-11:45 AM**

**Prognostic value of routinely determined tumor infiltrating lymphocytes in triple-negative breast cancer.** *Presenting Author: Jana Pahole Golicnik, Institute of Oncology, Ljubljana, Slovenia*

**Background:** Tumor infiltrating lymphocytes (TIL) was suggested to influence disease outcome in triple negative breast cancer (TNBC). Our hypothesis was that TIL determined by routine histopathological examination (RHE) is a prognostic and predictive factor in TNBC. **Methods:** Clinical and pathological data from 267 consecutively diagnosed and treated patients (pts) with TNBC from the year 2000 to 2006 was retrospectively collected. On RHE, lymphocytic infiltration was evaluated morphologically on H and E slides. Lymphocytic infiltration of the stroma surrounding the tumor or the tumor nests inside the tumor mass was scored as mild, moderate or intensive. The prognostic and predictive impact of TIL was calculated using Cox model. **Results:** The median age of pts was 56 years, 38.6% being premenopausal, 57.3% had tumors >2cm, 80.5% grade 3, 46.1% nodal involvement, and in 23.2% of pts lymphovascular invasion (LVI) was present. TIL was determined in 240 tumors; in 187 (78%) mild or moderate and in 53 (22%) intensive TIL was described. In the whole group of pts 79.8% received chemotherapy, among them 56.5% anthracycline based (A) only, 14.5% A and taxane (AT), 23.8% cyclophosphamide-methotrexate-fluorouracil (CMF) and 5.1 % other schemes. At a median follow-up of 10 years 93 pts progressed. Ten-year disease free survival (DFS) of pts with intensive TIL was 80.8 %, comparing with 60.5% in other pts (p=0.02). The differences in 10-year DFS for pts with intensive TIL was almost significantly better when treated with A (intensive TIL vs other 82.4% vs 62.7%, p=0.06), however this difference was not significant in the CMF group (85.7% vs 66.5%, p=0.16) while the opposite was noted in the AT group (62.5% and 68.8%, p= 0.69). **Conclusions:** In pts with TNBC intensive TIL determined on RHE predicts better disease outcome. In addition, pts with intensive TIL may benefit more from adjuvant A compared with AT.

**Estimated DFS hazard ratios, 95% CI and p-values for the Cox multivariate model.**

| **Variable** | **HR (95%CI)** | **p** |
|---|---|---|
| **TIL (intensive vs other)** | 0.45 (0.22-0.93) | 0.03 |
| **Grade (1+2 vs 3)** | 0.88 (0.67-1.15) | 0.34 |
| **Size (>20 mm vs <20 mm)** | 1.63 (0.98-2.72) | 0.06 |
| **Lymph nodes (positive vs negative)** | 2.39 (1.45-3.92) | <0.01 |
| **LVI (yes vs no)** | 1.17 (0.70-1.96) | 0.54 |

**1126 General Poster Session (Board #219), Mon, 8:00 AM-11:45 AM**

**CK14, FOXA1, and androgen receptor (AR) expression in patients (pts) with triple-negative breast cancer (TNBC).** *Presenting Author: Ayca Gucalp, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** TNBC is recognized to be heterogeneous based on gene expression profiling. An AR+, androgen-dependent subset of TNBC benefits from antiAR drugs. FOXA1, a nuclear mediator of steroid receptor signaling is involved in the regulation of ER and AR. FOXA1 expression in ER+ BC correlates with better prognosis; the significance of FOXA1 in TNBC is not established. We report the rates of FOXA1 expression in relationship to AR, basal markers and outcome in a retrospective cohort of pts with TNBC. **Methods:** We identified 1,032 pts with resectable, TNBC (ER/PR<1%; HER2 0-2+/FISH <2) who had surgery at MSK (1998-2006). Exclusion criteria: neoadjuvant chemotherapy, radiation, inflammatory/metastatic BC. We constructed tissue microarrays from 311 primary tumors (>1cm, post 2002) with three 0.6mm cores per tumor. Standard IHC methods were used. Scored positive: FOXA1 >3 per Badve CCR 2007; AR and EGFR paralleled the ASCO/CAP criteria for ER and HER2 respectively; CK5/6 and CK14 any cytoplasmic stain. Associations were analyzed with Fischer Exact/Spearman correlation tests. Log Rank test was used for survival analysis. **Results:** 303 pts met eligibility criteria. # of positive/evaluable cases: AR 16/283 (6%), FOXA1 79/273 (29%), CK5/6 185/290 (64%), CK14 128/278 (46%) and EGFR 234/289 (81%). There was a significant correlation between FOXA1 and AR (p=1.19E-10). There were inverse correlations between FOXA1 and CK14 (p=0.003), AR and CK14 (p=0.004) and AR and EGFR (p=0.018). 264/291 (91%) pts met Nielsen criteria (NC) for basal-like BC (BLBC). 94% (15/16) of AR+ tumors and 98% (121/124) of CK14+ tumors co-expressed NC. 46% of BLBC by NC expressed CK14. CK14 expression was associated with worse DFS (p=0.003, 5-year DFS 69% vs. 83%) and OS (p=0.01, 5-year OS 71% vs. 85%). FOXA1 expression was not associated with a significant difference in DFS (HR 0.98, p=0.26) or OS (HR 0.99, p=0.52). **Conclusions:** CK14 expression was the only prognostic marker for survival in our cohort. A high proportion of the AR+ tumors are BL according to NC, which is contradictory to gene expression data. There may be differences between these subsets or discordance between protein expression of AR and molecular subtype of TNBC (luminal AR vs. BL).

**1127 General Poster Session (Board #220), Mon, 8:00 AM-11:45 AM**

**The yield of staging investigations in triple-negative breast cancer patients.** *Presenting Author: Renee Elizabeth Lester, Tom Baker Cancer Centre, Calgary, AB, Canada*

**Background:** Current guidelines suggest that asymptomatic Stage I and II node negative patients do not require staging investigations to rule out metastatic disease. Our provincial cancer centre's guidelines released last year recommends blood work (CBC, kidney and liver function), CT scan of chest and abdomen, and bone scan for node positive breast cancer patients. **Methods:** We conducted a retrospective chart review of all triple-negative breast cancer patients diagnosed from January 2008 to December 2010. Triple negative is defined as <1% staining on immunohistochemistry (IHC) for both estrogen receptor (ER) and progestin receptor (PR) as well as the absence of HER2 overexpression on IHC or negative for gene amplification by FISH. The collected data included patients age, date of diagnosis, tumor size, grade, number of lymph nodes, presence/absence of lymphovascular invasion, and whether or not staging investigations were performed and their results. **Results:** One hundred and twelve patients were diagnosed with triple negative breast cancer in our centre between January 2008 and December 2010. Ninety five (86%) underwent staging investigations, 43 (45%) ordered by the medical oncologist and the remainder arranged by the referring physician. Twenty out of thirty stage I patients had some form of imaging (either bone scan, liver ultrasound, or CT). This did not yield any positive studies for metastatic disease. Similarly 25 out of 29 stage IIA patients were staged. Of those 25 patients, 12% had evidence of metastatic spread diagnosed on imaging. All 19 stage IIB patients were staged; of which 10.5% were also found to have metastatic disease. **Conclusions:** Stage I asymptomatic TNBC patients do not require routine staging investigations as the yield is quite low. However this study suggests that newly diagnosed triple negative patients that are stage II (either node negative or node positive) should undergo routine imaging to rule out any metastatic spread as this changes the intent of therapy. Further data collection is warranted.

| Stage | # of pts | # staged | # by MO | # positive | Yield |
|---|---|---|---|---|---|
| 1 | 30 | 20 | 6 | 0 | 0% |
| 2A | 29 | 25 | 14 | 3 | 12% |
| 2B | 19 | 19 | 9 | 2 | 10.5% |
| 3A | 15 | 14 | 7 | 1 | 7% |
| 3B | 6 | 6 | 3 | 0 | |
| 3C | 1 | 1 | 1 | 0 | |
| 4 | 10 | 10 | 3 | 6 | |
| Total | 110 | 86% | 39% | 12 | |

**1128 General Poster Session (Board #221), Mon, 8:00 AM-11:45 AM**

**Effect of afatinib alone and in combination with dasatinib in triple-negative breast cancer cell lines.** *Presenting Author: Mohamed F.K. Ibrahim, Molecular Therapeutics for Cancer Ireland, National Institute for Cellular Biotechnology, Dublin, Ireland*

**Background:** TNBC is a subtype of breast cancer negative for expression of estrogen and progesterone receptors and lack of HER2 gene amplification. It is associated with poor prognosis and lack of targeted therapies. Therefore, there is a need for identification of new therapies. EGFR, a member of the ErbB family, is frequently overexpressed in TNBC. Furthermore, crosstalk between EGFR and Src kinase signaling has been observed in breast cancer. The aim of this study is to assess the activity of afatinib, an irreversible pan-HER tyrosine kinase inhibitor alone and in combination with dasatinib, a Src inhibitor, in TNBC. **Methods:** Using proliferation assays, the effect of afatinib was assessed alone and in combination with dasatinib in TNBC cell lines. Combination indexes (CI) at $ED_{50}$, effective dose of combination that inhibits 50% of growth, were determined using the Chou and Talalay equation. CI < 1 implies synergy and CI > 1 implies antagonism. **Results:** The 6 TNBC cell lines tested responded to afatinib with $IC_{50}$ values ranging from 0.02 to 2.44 $\mu$M. As previously shown, the TNBC cell lines showed sensitivity to dasatinib with $IC_{50}$ values ranging from 9.6 nM to 3.1 $\mu$M. The HDQ-P1 cell line, classified as belonging to the basal-like 2 subtype of TNBC, showed significant sensitivity to both afatinib ($IC_{50}$ = 17.5 ± 2.1 nM) and dasatinib ($IC_{50}$= 16.6 ± 5.3 nM). The combination of afatinib and dasatinib was synergistic in 5 of the 6 TNBC cell lines tested (Table). **Conclusions:** Our results suggest that afatinib may have activity in TNBC. We also demonstrate that afatinib in combination with dasatinib may be more effective than either agent alone.

**Effect of afatinib in combination with dasatinib in TNBC cell lines.**

| | | % growth inhibition | | | |
|---|---|---|---|---|---|
| Cell lines | Subtype | Afatinib | Dasatinib | Afatinib + Dasatinib | CI ($ED_{50}$) |
| HCC1143 | Basal-Like 1 | 1 $\mu$M - 30.9 ± 5.6 | 200 nM - 52.6 ± 3.2 | 61.9 ± 3.7 | N/A |
| HCC1937 | Basal-Like 1 | 1 $\mu$M - 53.8 ± 3.1 | 50 nM - 43.1 ± 1.5 | 70.0 ± 2.2 | 0.39 ± 0.09 |
| HDQP1 | Basal-Like 2 | 100 nM - 66.5 ± 2.4 | 200 nM - 87.1 ± 2.5 | 91 ± 0.8 | 0.26 ± 0.05 |
| MDA-MB-231 | Mesenchymal stem-like | 1 $\mu$M - 60.9 ± 10.7 | 200 nM - 87.6 ± 2.2 | 89.5 ± 3.0 | 1.05 ± 0.09 |
| Hs578T | Mesenchymal stem-like | 1 $\mu$M - 15.7 ± 1.9 | 50 nM - 53.8 ± 1.5 | 65.5 ± 2.7 | 0.22 ± 0.04 |
| BT20 | Unclassified | 1 $\mu$M - 36.9 ± 4.1 | 625 nM - 39.7 ± 1.5 | 76.9 ± 1.4 | 0.00 ± 0.00 |

**1129 General Poster Session (Board #222), Mon, 8:00 AM-11:45 AM**

**Correlation of Notch1 expression with clinical characteristics, signaling biomarkers, and survival in breast cancer patients.** *Presenting Author: Aleksandra Filipovic, Imperial College London, London, United Kingdom*

**Background:** Notch1 signalling plays an important oncogenic role in breast cancer and represents a therapeutic target amenable to targeting with small-molecule gamma secretase inhibitors and specific anti-Notch1 monoclonal antibodies. Canonical Notch1 signaling is mediated by nuclear Notch1 cleaved fragment. Some evidence suggests non-nuclear, non-canonical signalling from cytoplasmic or membrane Notch1. Current study aims to investigate the clinical relevance of Notch1 expression in invasive breast cancer. **Methods:** A well-characterised Nottingham Tenovus cohort of invasive breast cancers (n = 1078), with long-term follow up data, was analysed using immunohistochemistry for Notch1 (Santa Cruz, C-20). X-tile software was used to generate cut-off values for further correlation of the Notch1: nuclear (≥ 20% positive cells) and membrane/juxtamembrane staining (≥ 50% cells). **Results:** High Notch1 membrane staining was correlated with high grade (p = 0.001), size > 2cm (p = 0.001), ductal histotype, advanced disease stage (p = 0.044), triple negative phenotype (p = 0.001), HER2 positive status (p = 0.02), HER3 positivity (p = 0.019), basal cytokeratin CK5 expression (p = 0.001) and PI3K activity (p = 0.008). High membrane Notch1 predicted worse breast cancer specific overall survival at 25 years of follow up (p = 0.017). Conversely, nuclear Notch1 was predominantly present in lobular carcinomas and correlated inversely with the triple negative subtype ( p = 0.019) as well as PI3K (p = 0.014), thereby its higher expression was predictive of favourable survival outcome (p = 0.008). **Conclusions:** Different subtypes of breast cancer may rely on different Notch1 signaling pathways, including nuclear and non-nuclear signalling. For the first time, we emphasize the clinical relevance of Notch membrane expression in highly aggressive disease. Therefore, our findings bear significant translational relevance, as we propose that Notch1 membrane expression assessment may be used for stratification of patients who may derive particular benefit from anti-Notch1 monoclonal antibody therapy or other Notch inhibitors in the clinic.

**1130 General Poster Session (Board #223), Mon, 8:00 AM-11:45 AM**

**Association of *TP53* codon 72 polymorphism with *TP53* mutation in triple-negative breast cancer (TNBC) patients.** *Presenting Author: Mathilde Födermayr, Hospital Elisabethinen Linz, Linz, Austria*

**Background:** A high rate of *TP53* mutations was observed in TNBC, suggesting a role in TNBC carcinogenesis. Missense mutations cause single amino acid substitutions with altered protein function. Non-missense (nonsense, frameshift, splice site) mutations lead to functional loss or complete deletion of protein p53. Other reports have focused on *TP53* polymorphisms. Codon 72 polymorphism (SNP rs1042522) is found in a proline-rich region of exon 4, encoding alleles Pro72 (ancestral form; CCC) or Arg72 (CGC) and varies with geographical latitude, accumulating towards the south; it is also common in African-Americans, where a high incidence of TNBC is evident. Effect of anticancer therapy may be influenced, as Pro72 is apparently less effective in apoptosis induction. Here, we investigated the incidence of Arg72 and Pro72 and the association of this polymorphism with *TP53* mutations in a Caucasian population of TNBC patients (pts). **Methods:** DNA was extracted from formalin-fixed paraffin-embedded tissue of operation specimen. For investigating *TP53* mutation status (exons 4-9) DNA was PCR amplified and sequenced. For correlation of two parameters, the Fisher's exact test was used. **Results:** In a cohort of 35 consecutive TNBC pts, 25 *TP53* mutations in 23 pts (65.7%) were observed: 13 missense (52%), 5 nonsense (20%), 4 frame shift (16%), 2 splice site (8%), 1 silent mutation (4%). Distribution of codon 72 polymorphism was 60% Arg/Arg, 11.4% Pro/Pro ($p<0.001$), 28.6% Pro/Arg ($p=0.016$). Non-missense mutations occurred mostly in pts carrying the hetero- or homozygous allele Pro72: Nonsense mutations showed a significant association with Pro/Arg (4/5; $p=0.03$), frameshift mutations with Pro/Pro (2/4; $p=0.02$) compared to Arg/Arg carriers. No correlation of *TP53* mutation status or codon 72 polymorphism with clinical outcome was observed. **Conclusions:** Non-missense *TP53* mutations leading to functional loss or deletion of protein p53 were significantly associated with homo- or heterozygous Pro72 carriers, despite the high rate of homozygous Arg72 carriers in our Caucasian TNBC pts cohort. Further studies elucidating a potential association of Pro72 with TNBC carcinogenesis and treatment response are warranted.

**1131 General Poster Session (Board #224), Mon, 8:00 AM-11:45 AM**

**Evaluation of lymphocyte infiltrate composition in triple-negative mammary carcinomas and its association with clinical-pathologic and demographic data.** *Presenting Author: Geraldine Eltz Lima, Hospital A.C. Camargo, São Paulo, Brazil*

**Background:** Triple-negative breast cancer corresponds to 15-20% of cases. Despite the advances in development of therapies for breast cancer treatment, this subtype still have a dismal prognosis. Chronic inflammation is involved in cancer development. However, the regulatory mechanisms underlying the recruitment and functioning of inflammatory cells in tumors are not completely clarified. The role of tumor lymphocytic inflammatory infiltrate in predicting survival of breast cancer patients is controversial. Our objective was to evaluate the lymphocyte inflammatory infiltrate and its association with clinical, pathological and demographic characteristics in triple-negative mammary carcinomas patients **Methods:** We studied a retrospective cohort of51 stage I to III, operated triple-negative breast cancer patients. Clinical data was recovered from electronic medical charts. Pathological samples were arranged in duplicate in a TMA, with tissue blocks from core biopsies or surgical specimens. Slides were stained with antibodies against CD4 and CD8, FOXP3. The number of positive staining cells for each antibody in each core was counted. The mean value of duplicates was used in all calculations. Fisher's exact and Mann-Whitney tests were used to verify the association between clinical-pathological and demographic data and the number lymphocytes. Overall (OS) and disease free survival (DFS) curves were calculated using Kaplan-Meier method and comparisons between curves was done by log-rank test. **Results:** Median age was 43 years-old. Mean OS was 101 months (87-115) and mean DFS was 87,35 months (71,84-102). There was no association between CD4+ cell counts and any other variable. CD8+ cell counts were associated with tumor size, and larger tumors presented with more intense CD8+ infiltrate. Higher FOXP3+ cell counts were associated with high histological and nuclear grade. There was no statistically significant association between any lymphocyte subset and OS or DFS. **Conclusions:** CD8+ and FOXP3+ lymphocyte infiltration are associated with pathological tumor characteristics and may play a role in tumor development, progression and prognosis.

**1132 General Poster Session (Board #225), Mon, 8:00 AM-11:45 AM**

***BRCA*-mutation status combined with BCL2 protein in prediction of relapse in triple-negative breast cancer (TNBC) treated with adjuvant anthracycline-based chemotherapy.** *Presenting Author: Katerina Bouchalova, Laboratory of Experimental Medicine, Institute of Molecular and Translational Medicine, Palacky University, Olomouc, Czech Republic*

**Background:** The role of BRCA mutation status as a predictor in TNBC is unclear. Data show an association of high BCL2 expression and resistance to anthracyclines. BCL2, size and nodal status are independent predictors for both relaps and death in TNBC treated with adjuvant anthracyclines (Bouchalova et al. ASCO 2012). The objective of this study was to determine whether combination of BCL2 and BRCA1 status predicts outcome in TNBC patients treated with adjuvant anthracycline-based therapy. **Methods:** The study included 187 patients with TNBC, 178 of whom were treated with adjuvant chemotherapy (164 had anthracyclines). BCL2 analysis was performed using IHC. BRCA1 was obtained from patients records: mutation (mut), wildtype (wt) and unknown status were present in 21.39, 19.25, and 59.36 %, respectively. The data were analysed with software Statistica and R. **Results:** Among six BCL2/BRCA1 TNBC subtypes, BCL2high/BRCA1wt predicts the worst, while BCL2low/BRCA1mut the best RFS (logrank $p<0.05$). BCL2high protein expression predicts poor relapse free survival (RFS) in BRCA1wt TNBC patients treated with adjuvant anthracycline-based regimens (logrank $p=0.007$, hazard ratio, HR 13.24, 95%CI 1.19-147.93). Interestingly, there was no significant difference in RFS between BCL2low/BRCA1mut and BCL2high/BRCA1mut, but between BCL2low/BRCA1mut and BCL2high/BRCA1wt (logrank $p=0.009$) TNBC patients treated with adjuvant anthracycline-based therapy. BCL2high/BRCA1wt predicts trend to the worst overall survival (OS) analyzed together with other subtypes treated with adjuvant anthracycline-based regimens (logrank $p=0.065$). **Conclusions:** Dividing TNBC into subtypes according BCL2 protein expression and BRCA1 mutation status predicts good, vs. poor outcome in patients treated with adjuvant anthracycline-based chemotherapy. BCL2 expression together with BRCA1 status could facilitate decision making on adjuvant therapy. Underlying mechanisms could be revealed by further research. In patients with BCL2high/BRCA1wt other types of adjuvant therapy should be considered.

**1133 General Poster Session (Board #226), Mon, 8:00 AM-11:45 AM**

**A randomized, parallel-arm, phase II trial to assess the efficacy of preoperative ixabepilone with or without cetuximab in patients with triple-negative breast cancer (TNBC).** *Presenting Author: Angel Augusto Rodriguez, Houston Methodist Research Institue, Houston, TX*

**Background:** Epithelial growth factor receptor pathway (EGFR) is expressed in TNBC and may be important in a subset of this heterogeneous disease. We evaluated the efficacy and toxicity of an anti-EGFR antibody (cetuximab) combined with ixabepilone given to the TNBC patients (pts) in the neoadjuvant setting. This study was designed to detect an increase in pathological complete response (pCR) rate, defined as no residual disease in the breast, from 20% to 40% in each arm, using a Simon optimal two stage design, with one-sided alpha=10% and power=80%. At least three responses out of 12 patients were needed to proceed with second stage for each arm. **Methods:** All pts received 4 cycles of preoperative ixabepilone 40 $mg/m^2$ every 3 weeks. In addition, patients were randomized to receive either 12 infusions of weekly cetuximab (400$mg/m^2$ on week 1, then 250 $mg/m^2$) or not. Race, proliferation rate, and TILs was correlated with pCR. **Results:** To date, a total of36 pts with stage II-IIIA TNBC were enrolled. Median age was 54 years (range 35-79 years) with median tumor size of 6.1 cm (range 2-18 cm). The median proliferation rate (Ki-67) was 67.2% (range 8%-95%). Pts were Hispanic (36%), White (39%), African-American (19%) and others (6%). In ixabepilone alone arm, pCR was observed in only 14.3%, and this monotherapy arm did not progress to second stage. To date, pCR was observed in 31.3% in ixabepilone/cetuximab arm, with 6 patients still on treatment. Adverse events for the combination arm were modest, mainly grade 1-2 (neutropenia: 4%, skin: 83 %, GI: 50 %, fatigue: 100 %). Grade 3 febrile neutropenia in 3 % were observed. No statistically significant correlation with race, Ki67, and TILs with pCR rate was observed. **Conclusions:** The addition of cetuximab to ixabepilone may improve the rate of pathological complete response in TNBC pts. There was no association between race or proliferation and response to ixabepilone and cetuximab. Evaluation of EGFR, p-EGFR and EGFR pathway -associated genes, PTEN, mutational analysis of PI3K/mTOR pathway and next generation genomic analysis is underway to evaluate for potential predictive biomarkers of response to EGFR inhibition. Clinical trial information: NCT01097642.

**TPS1134 General Poster Session (Board #227A), Mon, 8:00 AM-11:45 AM**

**FINESSE: An open, three-cohort, phase II trial testing oral administration of lucitanib in patients with FGFR1-amplified or nonamplified estrogen receptor-positive metastatic breast cancer.** *Presenting Author: Fabrice Andre, Department of Medical Oncology, Gustave Roussy, Villejuif, France*

**Background:** FGF aberrancy is observed in approximately 25% of breast cancer (BC) patients. Preclinical studies demonstrated that targeting FGFR could lead to antitumor effects. Lucitanib is a multikinase inhibitor targeting FGFR1-2, VEGFR1-3 and PDGFRA/B. In the phase I trial testing lucitanib continuous dosing, 6 objective responses were observed in 12 evaluable patients presenting with FGFR1 and/or FGF3-4-19 (11q) amplification. Based on this, a phase II trial has been initiated. **Methods:** This is a phase II trial testing the efficacy of lucitanib 15 mg daily in patients with ER+/HER2- metastatic BC who have received at least first line endocrine therapy in the metastatic setting. After informed consent, a biopsy of metastatic site is required to assess the presence of FGFR1- and/or 11q-amplification, which will be centrally evaluated using FISH. Testing could be also performed on archived metastatic biopsies. The primary objective is to evaluate the ORR of single agent lucitanib in metastatic BC patients with FGFR1-amplified, FGFR1-non-amplified with neither FGFR1- amplification nor 11q- amplification. Secondary objectives include clinical benefit rate, PFS, safety, pharmacokinetics and exploratory biomarker analyses. A Simon two-stage design will be used for each of the cohorts to test the null hypothesis that the ORR is 5% or less vs 20% using a one-sided test with 5% level of significance and 90% power. In each cohort separately, an initial 21 patients with measurable disease at baseline will be assessed at the end of stage 1. If at least 2 patients respond per the pre-specified criteria, this cohort will accrue additional 20 patients. The null hypothesis will be rejected if there are at least 5 responders among all 41 patients. The trial started in December 2013. It is planned to open in 9 countries and 30 centers. As of January 24, 5 patients have been screened, 1 of them in the FGFR1-amplified arm. **Conclusion:** FINESSE is a phase II trial testing lucitanib, a multikinase inhibitor, in three selected populations in order to define the efficacy of the drug and the predictive value of FGFR1 or 11q amplifications. Clinical trial information: 2013-000288-10.

**TPS1135 General Poster Session (Board #227B), Mon, 8:00 AM-11:45 AM**

**Tailored neoadjuvant epirubicin and cyclophosphamide and nanoparticle albumin bound (*nab*)-paclitaxel for newly diagnosed breast cancer.** *Presenting Author: Mustafa Khasraw, Andrew Love Cancer Centre, Geelong, Australia*

**Background:** Neoadjuvant chemotherapy for breast cancer allows response to be assessed depending on subtype, and to judge impact of response to therapy on progression-free survival (PFS). **Methods:** This study enrols women with breast tumours > 2cm and high likelihood of response, to receive Epirubicin 90mg/m2 and Cyclophosphamide 600mg/m2 Q3 weeks x 4 followed by nab-Paclitaxel (125mg/m2 IV days 1, 8, 15 Q4 weeks) for 12 weeks. Trastuzumab Q3 weeks, will be added to nab-paclitaxel in HER2 positive patients. Forty women; 15 HER2 positive, 15 triple negative and 10 patients with Oncotype DX assay Recurrence Score (RS) >25 will be evaluated for response. We will screen 50 hormone positive women to identify 10 with Oncotype DX assay RS ≥25 and the patients with RS <25 will be included as an exploratory cohort to receive neoadjuvant hormonal treatment. The primary endpoint is rate of pathologic Complete Response (pCR) in the breast. In previous studies, Response Rate (RR) ranged from 12 to 30%. Accordingly, we set RR rate for the null hypothesis (uninteresting) at 30% and for the alternative (worthy of further study) at 50% (CI 95%). Forty patients will be evaluated to discern between RR of 30% and 50% (6% type I error and 87% power). If at the end of the study, 17 or more patients achieve pCR, the regimen will be deemed worthy of further study. Secondary end points include rate of breast conservation, safety and tolerability, PFS and a number of translational endpoints using pre- and post-chemotherapy MRIs and tissue. Translational endpoints include determination of NQO1*2 genotype (P187S) status that may predict anthracycline resistance, isolating cancer stem cells, passing fresh tumour to xenograft, implanting tumours, using aptamers to target implanted tumours and targeting breast cancer stem cells with novel agents including cyclin D and histone deacetylatase inhibitors. Current status: Recruitment began April 2013. A total of 20 patients have been enrolled on to the study as of Feb 2014. Clinical trial information: NCT01830244.

**TPS1136 General Poster Session (Board #228A), Mon, 8:00 AM-11:45 AM**

**A randomized phase II trial of upfront docetaxel and vinorelbine followed by either maintenance oral vinorelbine or observation in patients with HER2-negative locally advanced (LA) or metastatic (M) breast cancer (BC).** *Presenting Author: Fadi Sami Farhat, Lebanese University, Beirut, Lebanon*

**Background:** Vinorelbine (V) and docetaxel (D) are among the most active agents in the treatment of MBC and their combination has a proven efficacy in this setting. V and D both target the tubulin-microtubule system, pre-clinical studies suggest a potential synergy between the 2 drugs. Maintenance therapy has lately demonstrated significant outcome improvement nevertheless the high cost of treatment in developing countries remains an issue. The oral form of vinorelbine (oV) is a convenient and cost-effective treatment, its role as maintenance treatment has not yet been investigated in LA-MBC. The purpose of this study is to assess the efficacy and safety of V+D combination and whether oV used as maintenance therapy can delay cancer progression in patients with LA-MBC. **Methods:** This is a prospective, multicenter, randomized, phase II trial of Docetaxel (60mg/m$^2$ D1) in combination with Vinorelbine (D1, 20mg/m$^2$ I.V and D8, 60mg/m$^2$ Oral), given every 3 weeks for a total of 6 cycles. Patients with objective response or stable disease after 6 cycles are randomized to the arm of maintenance therapy (Oral V 60mg/m$^2$ D1 and D8 at first cycle increased at 2$^{nd}$ cycle to 80mg/m$^2$D1 and D8) or to the observation arm. In the maintenance therapy arm cycles are repeated every 3 weeks until disease progression, unacceptable toxicity or patient refusal. Inclusion criteria were: Pre/post-menopausal women (≥ 18 years) with Her2 negative, LABC or MBC, PS ≤2, disease free survival ≥ 6 months, no symptom or sign of brain metastasis. The primary endpoint (EP) is time to progression (TTP). Secondary EPs include overall response rate (RECIST v1.1), clinical benefit rate, duration of response, 3 years overall survival, safety (CTCAE 4.03) and patient reported outcomes (FACT-B v.4). As of January 2014, 50 patients have been enrolled in the study and 32 randomized. Estimated enrolment is 126 pts. Recruitment is ongoing and planned for 36 months. This study will be the first one to evaluate the role of oral vinorelbine as maintenance treatment in first-line LA-MBC and will provide additional data on the efficacy and safety of D+V combination.

**TPS1137 General Poster Session (Board #228B), Mon, 8:00 AM-11:45 AM**

**MINT: Multi-institutional, neoadjuvant therapy MammaPrint project.** *Presenting Author: Charles E. Cox, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

**Background:** Women with locally advanced breast cancer (LABC) are often treated with neo-adjuvant chemotherapy to reduce the size of the tumor prior to surgery, to enable breast conserving surgery and to observe the clinical effect of therapy in real time. Studies have shown that the 25–27% of individuals who have a pathologic complete response (pCR) to neoadjuvant therapy have a survival advantage of 80% in 5 years, which is double the expected survival of the remaining patients without pCR. If patients who are likely to show a pCR could be identified prior to initiation of therapy, it would enable more informed treatment decisions [von Minckwitz et al. JCO 2006]. Genomic assays, which are widely used to provide prognostic and predictive information in early breast cancer, have the potential to provide information on the likelihood of a patient with LABC responding to neo-adjuvant therapy [Glück et al. BRCRT 2013]. **Methods:** MINT is a prospective study designed to test the ability of molecular profiling, as well as traditional pathologic and clinical prognostic factors, to predict response to neo-adjuvant chemotherapy in patients with LABC. MammaPrint risk profile, BluePrint molecular subtyping profile, TargetPrint ER, PR and HER2 single gene readout, and TheraPrint Research Gene Panel will be analyzed on a fresh or formalin fixed paraffin embedded tumor specimen using the whole genome array. Patients will receive neo-adjuvant chemotherapy pre-specified in the protocol. Response will be measured by pCR and by centrally assessed RCB. The study will include women with histologically-proven invasive breast cancer T2 (≥3.5cm)-T4, N0M0 or T2-T4N1M0, adequate bone marrow reserves and normal renal and hepatic function who signed informed consent. Standard statistical tests such as the Pearson Chi-square test will be used to characterize and evaluate the relationship between chemoresponsiveness and gene expression patterns. A total of 226 eligible patients will be enrolled from 10 US institutions. 85 patients have been enrolled. Clinical trial information: NCT01501487.

**TPS1138 General Poster Session (Board #229A), Mon, 8:00 AM-11:45 AM**

**A phase II study of eribulin in patients with HER2-negative, metastatic breast cancer: Evaluation of efficacy, toxicity, and patient-reported outcomes.** *Presenting Author: Otto Metzger-Filho, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Patient-reported outcomes (PROs) independently and directly describe patient (pt) treatment experiences, are complementary to clinician reports, and are increasingly included in drug development programs. Eribulin (E) has proven activity in metastatic breast cancer (MBC) previously treated with at least two regimens in the advanced setting. However, the clinical activity of E and the pt experience of receiving E in first- and second-line MBC settings, particularly the rates of neuropathy, are not well described, although these data are needed for further drug development. The present study aims to evaluate the activity, safety, and describe PROs of E in an earlier line setting. **Methods:** This is a non-randomized single arm phase II study of E monotherapy for HER2- MBC. Eligible pts have had 0-1 prior lines of chemotherapy for HER2- MBC, and are enrolled into one of two parallel 45 pt cohorts: one HR+ and one triple negative breast cancer (TNBC). E is dosed 1.4 mg/m$^2$ weekly in a 2 wk on/1 wk off schedule; 1 cycle = 3 wks. The primary objective is evaluation of activity by response rate (ORR); additional objectives include progression-free survival and safety. Correlative PRO endpoints include description and comparison of toxicity evaluation by PROs vs provider-report to determine degree of concordance or divergence for each class of toxicity, and description of QOL over time. The experience of neuropathy will be specifically evaluated by the FACT-Neurotoxicity subscale, as well as blood sample collection for exploration of host polymorphisms and the development of neuropathy. PRO instruments (PRO-CTCAE, FACT-B and FACT-Ntx) are administered at cycles 1-3, then every other cycle until end-of-treatment visit; pts complete the surveys on electronic tablets with direct data entry into the database. A sample size of 90 pts is planned, providing 90% power to detect a 22% improvement in ORR for TNBC (22% vs. 44%), and a 23% improvement in ORR for ER+ (30% vs. 53%). Both calculations assume a two-sided, 0.1 type-1 error and an exact binomial test. Clinical trial information: NCT01827787.

**TPS1139 General Poster Session (Board #229B), Mon, 8:00 AM-11:45 AM**

**Use of microRNA to identify stage IV breast cancer patients to be targeted with phospholipase A2 disrupted cisplatin carrying liposomes: An ongoing phase I trial.** *Presenting Author: Ulrik Lassen, Department of Oncology, Rigshospitalet, Copenhagen, Denmark*

**Background:** Cisplatin has shown activity in BRCA associated breast cancer patients but generally the use of cisplatin in breast cancer has been hampered by high toxicity and low response rates of approximately 10% (Baselga et al. JCO, 2013**;** 31:2586-2592.). We address both issues in an ongoing phase 1 study with a third generation liposomal cisplatin which is activated by secretory phospholipase A2 (sPLA2) present on the tumor cells, and in parallel by selecting patients with a companion diagnostic for an optimal cisplatin sensitivity microRNA profile and expression of sPLA2. **Methods:** A validated response prediction method is used in the cisplatin sensitivity prediction. The method uses cell line drug sensitivity data and cell line microarray data and clinical tumor big data analysis (Wang et al. J Natl Cancer Inst; 2013;105:1284–1291.). When the profile was probed on a published cohort of BC there were patients in all breast cancer subgroups that were predicted high likely sensitive. From the literature it is known that 80% of breast cancers are positive for sPLA2 (Yamashita et al. Br J Cancer; 1994;69: 1166-1170.). Methods: sPLA2 is determined by immunohistochemistry, microRNA obtained from formalin fixed paraffin embedded biopsies are assessed by use of Affymetrix chips. After an initial phase 1 dosing d1 q 3 wk reaching 120 mg the dose intensity was increased to d1 and d8 treatment q 3wk, and the 8$^{th}$ dose level has been reached on unselected patients with 120 mg cisplatin administered d1 and d8 and we now plan to extend the phase 1 study and include only biomarker positive patients. Currently 150 formalin fixed paraffin embedded (FFPE) patient biopsies have been screened and only the patients with an optimal profile are treatment candidates. In collaboration with the Danish Breast Cancer Cooperative Group (DBCG) the aim is to screen 600 BC patients with metastatic disease but currently not progressing. At progression only patients with in the highest 10% response likelihood will be candidates for expansion part of the phase 1 trial. Clinical trial information: NCT01861496.

**TPS1140 General Poster Session (Board #230A), Mon, 8:00 AM-11:45 AM**

**Phase I dose-escalating study to evaluate the safety, tolerability, and pharmacokinetic and pharmacodynamic profiles of Foxy-5 in patients with metastatic breast, colorectal, or prostate cancer.** *Presenting Author: Peter Grundtvig Soerensen, Herlev Hospital, Herlev, Denmark*

**Background:** The primary tumor is rarely the cause of death of cancer patients. Instead cancer-associated mortality is generally the result of tumor metastasis. However, most current therapeutic approaches fail to specifically target the dissemination process. A low-level or lack of Wnt-5a protein expression in primary invasive breast carcinomas has been shown to correlate with shortened recurrence-free survival. A similar role for Wnt-5a as a tumor suppressor has been described in thyroid, hematopoietic, prostate and colon cancer tissues. Based on these findings we developed a formulated hexapeptide (Foxy-5) that mimicked the ability of the Wnt-5a molecule to impair cancer cell migration in vitro. Foxy-5 also reduced the metastatic burden in the lungs by 70-90% in vivo in a mouse model (Safholm et al., Clin Cancer Res, 2008). **Methods:** The primary objective of the phase 1 study is to evaluate the safety and tolerability of treatment with Foxy-5. The secondary objectives are to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of Foxy-5 in patients with metastatic breast, colorectal or prostate cancer, to characterize the single and multiple dose pharmacokinetic (PK) profile of Foxy-5, and to characterize the pharmacodynamic (PD) profile of Foxy-5 by assessing evidence of anti-tumor activity of Foxy-5, e.g. by analysing the amount of circulating tumor cells before and after treatment with Foxy-5. All eligible patients are screened for Wnt5a immunoreactivity in their cancer cells and only Wnt5a negative or low patients are enrolled in the study. Clinical trial information: NCT02020291.

**TPS1141 General Poster Session (Board #230B), Mon, 8:00 AM-11:45 AM**

**NSABP B-51/RTOG 1304: Randomized phase III clinical trial evaluating the role of postmastectomy chest wall and regional nodal XRT (CWRNRT) and post-lumpectomy RNRT in patients (pts) with documented positive axillary (Ax) nodes before neoadjuvant chemotherapy (NC) who convert to pathologically negative Ax nodes after NC.** *Presenting Author: Eleftherios P. Mamounas, National Surgical Adjuvant Breast and Bowel Project (NSABP), and the UF Health Cancer Center at Orlando Health, Orlando, FL*

**Background:** This phase III randomized post-NC trial will evaluate if CWRNRT after mastectomy (Mx) or whole breast irradiation (WBI) with RNRT after breast-conserving surgery (BCS) significantly reduces the rate of IBCR-FI in pts who present with histologically positive Ax nodes but become histologically negative Ax nodes →NC. Secondary aims are OS, LRR-FI, DRFI, DFS-DCIS, and second primary cancer. Correlative science will examine the effect of RT by tumor subtype, molecular predictors of outcome for pts with residual disease, and the development of predictors of degree of reduction in loco-regional recurrence. **Methods:** Eligible pts with clinical T1-3, N1 breast cancer with pathologic Ax nodes (positive FNA or core needle biopsy) must complete ≥12 wks of NC (anthracycline and/or taxane-based regimen). HER2-positive pts must receive neoadjuvant trastuzumab or other anti-HER2 therapy (tx). After NC either BCS or Mx will be performed. Ax nodes must be histologically cancer free on sentinel node biopsy with or without axillary dissection (AND) or AND alone. ER/PR and HER-2 neu status before NC is required. All pts will receive additional required systemic tx. Site radiation credentialing with a facility questionnaire and case benchmarking is required. Randomization for Mx pts will be to no CWRNRT or CWRNRT and for BCS pts to WBI or WBIRNRT. 1,636 pts will be enrolled over 5 yrs with definitive analysis at 7.5 yrs. The study is powered at 80% to test the main hypothesis that RT reduces the annual hazard rate of events for IBCR-FI by 35% for an absolute risk reduction in the 5-year cumulative rate of 4.6%. Analysis will be on intent-to-treat with 3 formal interim analyses at 43, 86, and 129 events, with a 4th/final analysis at 172 events. Current accrual is 10. 736 enrolled pts will be evaluated with targeted pt-reported outcome instruments focusing on the effect of RT. Pt assessments will be prior to randomization and then at 3, 6, 12, and 24 mos. Clinical trial information: NCT01872975.

**TPS1142 General Poster Session (Board #231A), Mon, 8:00 AM-11:45 AM**

**Preoperative PARPi and irradiation (POPI) for women with an incomplete response to neoadjuvant chemotherapy (NAC) for breast cancer: A phase I trial.** *Presenting Author: Richard C. Zellars, The Johns Hopkins University School of Medicine, Baltimore, MD*

**Background:** Fifty to seventy percent of breast cancer patients treated with NAC will have an incomplete response and ultimately worse outcomes than those with a pathologically complete response (pCR). Researchers hoping to increase the rate of pCR, added pre-operative radiation to NAC but had little success. One way to further increase the response to neoadjuvant radiation may be the concurrent use of an inhibitor of Poly(ADP-ribose)-polymerase (PARPi). Pre-clinical studies have shown that PARPi sensitizes cancer cells to radiation by inhibiting repair of radiation-induced ssDNA breaks. We hypothesize that POPI will increase the pCR rate in women who have residual disease after NAC. Before we can test this hypothesis, we must determine the max tolerable dose (MTD) of this combined therapy. Thus, we designed and opened a phase I trial of POPI in women with an incomplete response to NAC. **Methods:** Women with pathologically node positive disease before NAC and $>$ 1.0 cm of residual disease after NAC are eligible. After obtaining consent the residual disease is biopsied. Patients with viable disease are enrolled in a standard 3+3 dose finding study of concurrent veliparib and pre-operative radiation. The starting dose of veliparib is 50 mg P.O. BID x 28 days and will increase by 50mg BID to a max of 200 mg BID. Radiation (235 cGy x 16) to the breast and regional nodes overlaps with the first 3 weeks of veliparib. Definitive surgery (lumpectomy/mastectomy) occurs 6 weeks after completion of radiation. The MTD is defined as the dose below the level at which $>$1dose limiting toxicity (DLT) is observed in 3-6 patients. An expansion cohort of 20 patients will be treated at the MTD for further evaluation. Status: This trial opened in 8/2013. Two patients have completed protocol therapy to date. Clinical trial information: NCT01618357.

**TPS1143 General Poster Session (Board #231B), Mon, 8:00 AM-11:45 AM**

**SGN-LIV1A, an antibody-drug conjugate (ADC), in patients with LIV-1–positive breast cancer.** *Presenting Author: Ana Kostic, Seattle Genetics, Inc., Bothell, WA*

**Background:** First identified as an estrogen-inducible gene in a breast cancer cell line, LIV-1 is a multispan transmembrane protein of the solute-carrier family 39 with putative zinc transporter and metalloproteinase activity. As a downstream target of STAT3, it promotes the epithelial-to-mesenchymal transition that is important in the malignant progression to metastasis. LIV-1 is expressed in a number of cancers with the highest prevalence and level of expression in breast, prostate, and melanoma. Additionally, LIV-1 has been linked with malignant progression to metastasis and associated with lymph node involvement in breast cancer. Normal tissue expression is predominantly limited to hormonally regulated tissues, including breast and prostate. SGN-LIV1A is an ADC composed of a humanized anti-LIV-1 monoclonal antibody conjugated to the microtubule-disrupting agent MMAE via a protease-cleavable linker. In vitro, SGN-LIV1A shows target-specific internalization and cytotoxic activity against LIV-1-positive neoplastic cell lines. Significant dose-dependent tumor regression was demonstrated in mouse xenograft models. **Methods:** The primary objective of this phase 1, open label, multicenter study is to evaluate the safety and tolerability, and to identify the maximum tolerated dose of SGN-LIV1A using a 3+3 dose-escalation study design. Pharmacokinetics, immunogenicity, and antitumor activity will also be evaluated. Eligible patients are adult females who have hormone receptor-positive /HER2-negative or triple-negative metastatic breast cancer. Tumor tissue obtained at baseline must be positive for expression of LIV-1 per central assessment. Patients must have received at least 2 prior cytotoxic regimens in the metastatic setting and have measurable disease per RECIST v1.1. Pre-existing neuropathy $\geq$ Grade 2 is not permitted. SGN-LIV1A will be administered IV every 3 weeks at protocol-defined doses starting at 0.5 mg/kg. Patients who achieve an objective response or stable disease will be eligible to continue treatment until disease progression. Enrollment for this US-based trial began in late 2013. Clinical trial information: NCT01969643.

**TPS1144 General Poster Session (Board #232A), Mon, 8:00 AM-11:45 AM**

**A phase 2 single-arm study of the clinical activity and safety of enzalutamide in patients with advanced androgen receptor-positive triple-negative breast cancer.** *Presenting Author: Tiffany A. Traina, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Androgen receptor (AR) expression is observed in 10-30% of patients (pts) with triple-negative breast cancer (TNBC). Experiments using AR+ TNBC cell lines have demonstrated enhanced growth in response to androgen stimulation that is inhibited by enzalutamide (ENZA), a potent oral inhibitor of AR signaling **(**Richer JK. Abstract presented at the AACR Advances in Breast Cancer Research Meeting, San Diego, CA, 2013 October 3-6 and D'Amato NC. Abstract presented at the SABCS, San Antonio, TX, December 4-8, 2012). AR+ TNBC may represent a subtype driven by AR signaling and which may respond to ENZA. **Methods:** Women with advanced AR+ TNBC (ER and PgR $<$1% by IHC and Her2 normal) will receive daily ENZA (160 mg) until disease progression (NCT01889238). The primary endpoint (EP) is clinical benefit rate (CBR) where benefit is defined as complete or partial response (CR or PR) or stable disease (SD) $\geq$16 weeks (wks) as assessed by the Investigator and according to RECIST 1.1. Additional EPs include CBR at 24 wks, safety and tolerability, and the relationship between AR signaling and ENZA activity. If the CBR exceeds 2 in 26 pts, the sample size will increase to 62 pts. Any amount of AR expression (local or central) is allowed, submission of tissue is mandatory. Pts may have bone-only non-measurable disease. Brain imaging is required to exclude patients with CNS metastases. Pts with a seizure history are excluded. The primary EP will analyze pts with centrally defined AR+ TNBC ($\geq$10% nuclear staining by IHC) who have $\geq$1 post-baseline tumor assessment. An ITT analysis will also be reported. The null hypothesis ($H_0$), that the true CBR is 8%, will be tested against a 1-sided alternative. If CBR exceeds 9 in 62 pts in Stage 2, $H_0$will be rejected. This design yields a 1-sided type 1 error rate of 5% and 85% power when the true response rate is 20%. Enrollment is expected to continue through 2014. Clinical trial information: NCT01889238.

**TPS1145 General Poster Session (Board #232B), Mon, 8:00 AM-11:45 AM**

**TBCRC030: A randomized, phase II study of preoperative cisplatin versus paclitaxel in patients (pts) with *BRCA1/2*-proficient triple-negative breast cancer (TNBC)—Evaluating the homologous recombination deficiency (HRD) biomarker.** *Presenting Author: Erica L. Mayer, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Both platinum and taxane chemotherapy have activity in TNBC, however biomarkers predictive for activity of either agent are lacking. The HRD assay detects impaired double strand DNA break repair, and may identify BRCA1/2-proficient tumors with a 'BRCA-like' phenotype suitable for treatment with DNA repair targeted therapies. A significant correlation between HRD score and response to platinum was reported in a preoperative study of gemcitabine, carboplatin and iniparib for TNBC. The current trial will prospectively determine the association between HRD score and response to platinum or taxane preoperative chemotherapy in TNBC, as well as explore other potential novel biomarkers of response. **Methods:** This is a phase II multicenter study randomizing pts with BRCA1/2-proficient, stage I (T1 $>$ 1.5 cm)-III TNBC to preoperative cisplatin 75 mg/m$^2$ q3 wks x 4 or paclitaxel 80 mg/m$^2$ weekly x 12 wks, followed by surgery. Mandatory tissue collection will occur at baseline and surgery. Pts with significant residual disease after 12 weeks will have a tumor biopsy, be classified as a non-responder (RCB$>$1), and can cross-over to alternative treatment. The primary objective is to determine the association of HRD score with pathologic response, defined as RCB 0-1, to neoadjuvant platinum or taxane in TNBC. Secondary objectives include overall clinical and pathologic responses and the positive predictive value of HRD for platinum therapy. Correlative analyses include evaluation of markers: NtAI, LST, HRD combined score, Hereditary Cancer Profile, PMS2 and CHEK2 HCP, RAD17/RAD50 expression values, PAM50, Vanderbilt TNBC subgroups, tumor infiltrating lymphocyte predictor, and signatures of taxane response; whole exome and RNA sequencing will be used to identify novel markers of response. Target accrual is 160 pts randomized 1:1. Assuming response rates of 40% to cisplatin and 30% to taxane and a drop-out rate of 12%, there will be 91% and 87% power, respectively, to detect a difference of 0.75 standard deviations in HRD score by RCB score. Clinical trial information: NCT01982448.

**TPS1146 General Poster Session (Board #233A), Mon, 8:00 AM-11:45 AM**

**tnAcity: A phase II/III trial of weekly *nab*-paclitaxel (*nab*-P) plus gemcitabine (gem) or carboplatin (carbo) versus gem/carbo as first-line treatment for metastatic triple-negative breast cancer (mTNBC).** *Presenting Author: Denise A. Yardley, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN*

**Background:** TNBC, which is characterized by a lack of estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2) overexpression, is associated with a poor prognosis. In combination with gem or carbo/bevacizumab, *nab*-P has demonstrated high response rates as first-line treatment for mTNBC. tnAcity (triple-negative Albumin-bound paclitaxel combination international treatment study) is a phase 2/3 trial evaluating the efficacy and safety profiles of 2 *nab*-P combination regimens (with gem or carbo) as first-line treatment for mTNBC, using gem/carbo as a control. **Methods:** The phase 2 portion of the study will evaluate 240 patients (pts), randomized 1:1:1 (stratified by disease-free interval [DFI]: $\leq$ 1 y vs $>$ 1 y) to *nab*-P 125 mg/m$^2$ plus gem 1000 mg/m$^2$, *nab*-P 125 mg/m$^2$ plus carbo area under the curve (AUC) 2, or the control regimen of gem 1000 mg/m$^2$ plus carbo AUC 2, all given days 1 and 8 of a 21-day cycle. Eligibility criteria include measurable mTNBC (defined as ER and PgR in $<$ 1% of tumor cell nuclei and HER2 IHC 0 or 1+ or 2+ and FISH-negative); no prior chemotherapy for metastatic disease; prior adjuvant/neoadjuvant anthracycline use required if indicated; adjuvant/neoadjuvant treatment with a taxane, platinum, or gem is permitted if completed $\geq$ 12 months prior to randomization; ECOG performance status $\leq$ 1; peripheral neuropathy grade $<$ 2; and absence of brain metastases. The primary objective of the phase 2 portion is to identify the *nab*-P combination arm to be evaluated in the phase 3 study by a ranking algorithm of 5 efficacy and safety parameters. In the phase 3 portion, 550 pts will be randomized 1:1 (stratified by DFI [$\leq$ 1 y vs $>$ 1 y] and prior taxane use) to the *nab*-P combination arm selected from the phase 2 portion or to the control arm. The primary endpoint of the phase 3 portion is PFS by independent radiological assessment; secondary endpoints include ORR, OS, disease control rate, duration of response, and safety. Biomarker and circulating tumor cell analyses will also be performed. As of the submission deadline, 21 patients have been randomized. Clinical trial information: NCT01881230.

**TPS1147 General Poster Session (Board #233B), Mon, 8:00 AM-11:45 AM**

**Concurrent adjuvant systemic therapy and accelerated radiotherapy in triple-negative breast cancer: A feasibility trial.** *Presenting Author: Rene Eleanor Ashworth, New York University Langone Medical Center, New York, NY*

**Background:** Triple-negative breast cancer (TNBC), which comprises ~15% of all diagnosed breast cancers, behaves aggressively and continues to represent a therapeutic challenge. As such, TNBC is associated with a higher rate of early distant recurrence and breast cancer-related death. For early-stage TNBC, conventional systemic chemotherapy has been the mainstay of treatment; however, there is an unmet need for better therapy. Platinum agents have been shown to have activity against TNBC in both neoadjuvant and metastatic settings (Silver et. al., *J Clin Oncol*, 2010). Concurrent chemo-radiation (CCRT) is also being explored; preclinical studies have proven that radiotherapy has unique biological effects that favorably alter the tumor site microenvironment to enhance anti-tumor immunity (Formenti and Demaria, *J Clin Oncol*, 2008). Furthermore, a multi-institutional collaboration of 105 patients demonstrated that 54% of triple-negative tumor carriers achieved pathological response, comparing favorably to their hormone-receptor positive counterparts in both 5-year DFS and OS (Adams et. al., *Breast Cancer Res Treat*, 2010). This phase I/II clinical trial is a single-arm study designed to assess the feasibility of combining Carboplatin with radiotherapy (RT) for the adjuvant treatment of TNBC. **Methods:** Eligibility includes patients with stage I/II TNBC who are eligible for RT after segmental mastectomy. The primary endpoint is acute skin toxicity related to CCRT. Secondary endpoints include additional toxicities-pain and fatigue, quality of life, and late toxicities- fibrosis and telangiectasia. 35 patients are required to achieve a power of 80% in order to detect a significant increase in occurrence of grade II dermatitis or greater; 27 patients have been enrolled to date. Carboplatin, AUC 2.0, is administered weekly for 6 weeks, with 3 weeks of concurrent RT initiated at week 2. RT is delivered prone using 3D-CRT or IMRT. The whole breast is treated to 40.5 Gy in 15 fractions, with a 3 Gy boost to the tumor bed on weeks 2 and 3, for a total dose of 46.5 Gy. Additional adjuvant chemotherapy is given at the discretion of the treating physician. Clinical trial information: NCT01289353.

**TPS1148 General Poster Session (Board #234A), Mon, 8:00 AM-11:45 AM**

**TBCRC028: A phase Ib/II trial of GDC-0941 (a PI3K inhibitor) in combination with cisplatin in metastatic androgen receptor-negative triple-negative breast cancer (TNBC).** *Presenting Author: Vandana Gupta Abramson, Vanderbilt-Ingram Cancer Center, Vanderbilt University, School of Medicine, Nashville, TN*

**Background:** We recently reported six distinct molecular subtypes of TNBC, including two basal-like subtypes with cell cycle and DNA damage response (DDR) gene expression (GE) signatures (BL1 and BL2) and a luminal androgen receptor (LAR) subtype which expresses AR by immunohistochemistry. BL1 and BL2 cell lines respond to DNA damaging agents, including cisplatin. Consistent with the frequent alterations in DDR and PI3K pathways in TNBC, the combination of cisplatin and the pan-PI3K inhibitor GDC0941 was very active against AR-negative TNBC cell lines in preclinical studies. This trial will evaluate the benefit of the addition of GDC-0941 to cisplatin in patients with metastatic AR-TNBC. **Methods:** This is an open-label phase Ib/II multiple institution trial in which patients with metastatic AR-TNBC will be randomized to: a) cisplatin 25 mg/m$^2$ on days 1, 8, and 15 of a 28 day cycle, or b) cisplatin with GDC-0941. Biopsy of a metastatic lesion at baseline, at day 5-10, and at progression is required. Staging scans will be performed at baseline and every 2 cycles thereafter. Upon progression, patients on the cisplatin arm have the option to crossover to the combination arm with GDC-0941. The primary objectives are: to determine the safety and tolerability of cisplatin + GDC-0941 in patients with AR-TNBC (phase Ib) and efficacy, as measured by the overall response rate (phase II). Secondary objectives are to determine the clinical benefit rate and time to disease progression of both study arms. Correlative analyses will evaluate mechanisms of inherent and acquired resistance. Gene expression profiling to assign a TNBC subtype and whole exome analysis will be performed; the predictive effects of PI3K pathway mutations (PIK3CA, AKT, PTEN) will also be examined. Approximately 125 patients will be enrolled (80% power to detect a 20% improvement in the ORR with a type 1 error of 0.05). Clinical trial information: NCT01918306.

**TPS1149 General Poster Session (Board #234B), Mon, 8:00 AM-11:45 AM**

**Phase III study evaluating safety and efficacy of the addition of veliparib plus carboplatin versus the addition of carboplatin to standard neoadjuvant chemotherapy in subjects with early-stage triple-negative breast cancer (TNBC).** *Presenting Author: Gunter Von Minckwitz, German Breast Group/University Frankfurt, Neu-Isenburg, Frankfurt, Germany*

**Background:** Emerging data suggests that TNBC may be sensitive to DNA-damaging chemotherapy agents, including carboplatin (Cb). Veliparib (V; ABT-888), a potent, competitive poly (ADP-ribose) polymerase (PARP)-1 and -2 inhibitor, enhances the activity of several DNA-damaging agents. In I-SPY2, the addition of V and Cb to standard neoadjuvant therapy for early TNBC doubled the pathologic complete response (pCR) rate (52% vs. 26%). This study will evaluate the addition of Cb or V + Cb to neoadjuvant paclitaxel (P) followed by doxorubicin + cyclophosphamide (AC). **Methods:** A phase 3, randomized, placebo-controlled, double-blinded, multinational, multicenter study will enroll 624 patients (pts) with histologically confirmed, invasive, TNBC (T2-T4 N0-2 or T1 N1-2) who are candidates for potentially curative surgery. No prior breast cancer treatment or sentinel lymph node biopsy is permitted. Pts will be stratified by BRCA status, lymph node stage (N0 versus N1-2), and schedule of AC administration (q2 weeks versus q3 weeks), and randomized in a 2:1:1 ratio to: (Arm A) P 80 mg/m$^2$ weekly + Cb AUC 6 mg/mL/min q3weeks x 4 + V 50 mg PO BID for 12 weeks followed by AC (60 mg/m$^2$/600 mg/m$^2$ q2 or 3 weeks x 4); (Arm B) P + Cb + PO placebo followed by AC; (Arm C) P + IV placebo + PO placebo followed by AC. After completing study therapy, pts will undergo surgery with sentinel node sampling or axillary lymph node dissection. Post-op radiotherapy is at MD discretion. The primary objective of the study is to assess the incidence of pCR defined as absence of residual invasive cancer in resected breast tissue and lymph nodes (i.e., ypT0/is N0 per AJCC staging system). Assuming pCR rates in the V + Cb, Cb only and control arms are 60%, 45% and 40%, respectively, the study has $>$ 80% power at 2-sided $\alpha$ level of 0.05 to detect a statistically significant treatment effect in pCR for the V + Cb arm compared to either of the other two arms using chi-square test. Secondary objective is the rate of eligibility for breast conservation after therapy. Other endpoints are residual cancer burden, EFS and OS. The study opened in Jan 2014. Clinical trial information: NCT02032277.

ABSTRACT WITHDRAWN

**1501** **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**Predictors of colorectal cancer screening adherence among African Americans.** *Presenting Author: Praveen Ramakrishnan Geethakumari, Albert Einstein Heathcare Network, Philadelphia, PA*

**Background:** Low colorectal cancer (CRC) screening rates among African Americans (AAs) contribute to higher CRC mortality and lower CRC survival among AAs than whites. We conducted a randomized controlled trial to determine if a preference-based mail and telephone navigation intervention could increase CRC screening adherence among AA patients. **Methods:** The trial included AA patients who were 50-75 years old, eligible for screening, and received care through primary care practices in Philadelphia. Eligible patients (n=764) were consented, surveyed by telephone, and randomized to a Standard Intervention (SI) Group (n=380) or Tailored Navigation Intervention (TNI) Group (n=384). The SI Group was sent colonoscopy instructions and a stool blood test kit, followed by a reminder. The TNI Group received mailed screening contacts keyed to preference, and also received telephone navigation and a reminder. An endpoint survey was administered and an endpoint review of medical records was performed to determine screening adherence status at 6 months. Multivariable analyses were performed to assess intervention impact on adherence. **Results:** Background characteristics of study participants were: female (69%), 50-59 years of age (71%), < high school education (59%), and unmarried (69%). At 6 months after randomization, CRC screening adherence was substantially higher in the TNI Group (38%) than the SI Group (24%), a difference that was statistically significant (OR=2.04, 95% CI: 1.47-2.84). Participants who were > 60 years of age also had a significantly higher screening rate than those who were 50 to 59 years of age (OR=1.92, 95% CI: 1.33, 3.77). Screening adherence was marginally higher among participants who were female, married, and had a higher screening decision stage. **Conclusions:** Exposure to the preference-based mail and telephone navigation intervention increased CRC screening adherence compared to the mailed intervention. Further research is needed to determine how the intervention can be modified to maximize impact and to assess its effect on screening disparity between whites and AAs. To our knowledge, this is the first study to test preference-based tailored navigation for CRC screening in a solely AA patient population. Clinical trial information: NCT00893295.

**1502** **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**Breast cancer screening in younger women.** *Presenting Author: Nina Beri, Duke University Medical Center, Durham, NC*

**Background:** The 2009 US Preventative Services Task Force (USPSTF) guidelines for breast cancer screening have proven controversial. Previously, annual screening was recommended for women over 40, but new guidelines recommend screening only for high risk women under 50. Other guidelines still recommend annual screening for young women on the basis of reduction in breast cancer mortality. In a population of rural insured women we sought to determine which younger women received mammograms, and the factors that motivate them to do so. **Methods:** Surveys were mailed to 1,000 randomly selected women between the ages of 40 and 49, insured by the National Rural Electric Cooperative Association (NRECA). A study specific survey evaluated screening patterns, knowledge of guidelines, and sociodemographic information. **Results:** Overall, 639 women responded (response rate 63.9%). Median age was 45, 92% were white, 75% resided in rural areas, and 34% reported 4 year college education. The majority (67%) had a screening mammogram within the past year. 81% had their mammograms paid for by NRECA and 66% reported no out of pocket costs. 43% had a family history of breast cancer and 69% had friends with the disease. 71% felt that they understood current guidelines, though less than 1% reported that mammograms for women under 50 were not routinely recommended. 15% were aware that expert recommendations vary. 58% believed that annual mammograms are recommended for women <50. Less than 1% reported that the media coverage of expert recommendations made them less likely to obtain screening, while 44% felt it had no effect. Reported barriers to screening included: lack of time (29%), fear of test (5.6%), fear of diagnosis (4.2%), and discomfort (12%). Women with friends or family with breast cancer were more likely to report screening within the past year (70% vs 54%, *p* 0.003). Education and geographic residence did not correlate with screening. **Conclusions:** The majority of younger insured women in rural America are not aware of USPSTF guidelines and continue to undergo screening mammography. However, modifiable barriers persist and there is a need for consensus and education regarding the current evidence for screening so that younger women can make informed choices about early detection of breast cancer.

**1503** **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**Menopausal hormone therapy and breast cancer by body mass index (BMI) and African ancestry.** *Presenting Author: Rowan T. Chlebowski, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA*

**Background:** In the Women's Health Initiative (WHI) randomized, placebo-controlled clinical trials, estrogen plus progestin (E+P) increased breast cancer incidence while estrogen alone (E alone) decreased incidence. Nonetheless, some observational studies report breast cancer findings combining these approaches and additionally suggest breast cancer safety for "HRT" use in obese and African American women. **Methods:** We examined E+P and E alone influence on breast cancer incidence by BMI and race/ethnicity in the WHI trials (with 16,608 in the E+P trial, 5.6 yrs intervention and 10,739 in the E alone trial, 7.2 yrs intervention ) with 13 yrs of cumulative follow-up. Hazard ratios (HRs) were estimated using Cox proportional hazards models. Additionally, HRs were estimated in a case-only analysis incorporating African admixture, measured for self-identified African Americans using genetic ancestry information from 656,852 markers. **Results:** Both for the previously reported overall results (E+P HR 1.28 95% CI [1.11-1.48], p < 001; E alone HR 0.79 [0.65-0.97], p = 0.02) (JAMA 2013; 310:2) and by BMI and race/ethnicity, E+P and E alone had opposite effects on breast cancer incidence. There was no interaction with BMI for either E+P (p = 0.58) or E alone (p = 0.86). For Black women in the E+P trial, breast cancer results were similar to White women regardless of % African Ancestry. For Black women in the E alone trial, a somewhat greater reduction in breast cancer incidence for E alone use was seen (HR 0.47 [0.26-0.82]) compared to White women (HR 0.84 [0.67-1.05]). In the case-only analysis, HRs for Black women 0.45 [0.24-0.87]), Black women with < 79% African ancestry (0.62 [0.26-1.48]) and Black women with ≥ 79% African ancestry (0.32 [0.12-0.86]) suggest CEE effect modification on breast cancer risk by African ancestry (p-trend = 0.04). **Conclusions:** Observational study analyses of hormone therapy influence on breast cancer should separately consider E+P and E alone. Current randomized trial findings do not support breast cancer safety for E+P use in obese or African American women. The suggestion that greater African ancestry is associated with greater reduction in breast cancer incidence with E alone use warrants further study. Clinical trial information: NCT00000611.

**1504 Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**Effects of equivalent weight loss, with or without exercise, on sex hormones related to breast cancer risk in postmenopausal women: The SHAPE-2 trial.** *Presenting Author: Anne Maria May, University Medical Center Utrecht, Utrecht, Netherlands*

**Background:** Physical activity is a known protective factor for postmenopausal breast cancer. Exercise intervention studies suggest that physical activity influences breast cancer related sex hormone levels mainly through concordant weight loss. The aim of this study is to investigate whether there is an additional beneficial effect of exercise beyond the effect of weight loss. **Methods:** After a 5-week run-in period, 243 inactive, overweight and postmenopausal women were randomly allocated to either a diet group (n=97), exercise group (n=98) or stable weight control group (n=48). The aim of both intervention groups was to lose 5-6 kilograms weight. The diet group followed an energy restricted diet. The exercise group participated in a 16-week endurance and strength training program (4 hrs/wk) and were prescribed a small caloric intake restriction. Primary outcomes were assessed at baseline and after 16 weeks, and included serum levels of estron, (free) estradiol, androstenedione, (free) testosterone and sex hormone binding globulin (SHBG). **Results:** Both the diet and exercise group achieved the aimed weight loss (-4.9 kg and -5.5 kg, respectively), while the control group remained stable (+0.06 kg). Compared with control, all estrogens decreased significantly in the exercise group, while in the diet group only free estradiol was significantly decreased ($p<0.05$). Also, compared with diet, the exercise group showed more favorable effects on all estrogens ($p\leq0.05$). For androgens, only the exercise group showed beneficial effects on free testosterone compared with control (p=0.01) and diet (p=0.07). Positive effects on SHBG were significant in both intervention groups ($p<0.0001$) and larger in the exercise group compared with diet (p=0.07). **Conclusions:** Exercise induced weight loss resulted in stronger favorable effects on breast cancer related hormones and SHBG, than diet induced weight loss, demonstrating the importance of exercise for postmenopausal breast cancer risk reduction. Clinical trial information: NCT01511276.

**1505 Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**Effect of weight loss intervention on inflammatory and metabolic markers in breast cancer survivors: The lifestyle, exercise, and nutrition (LEAN) study.** *Presenting Author: Erikka Loftfield, Yale School of Public Health, New Haven, CT*

**Background:** Obesity and physical inactivity are associated with poorer prognosis among breast cancer survivors. Inflammatory and metabolic pathways may explain these associations. We hypothesized that diet- and exercise-induced weight loss would decrease insulin, glucose, IGF-I, C-reactive protein (CRP), TNF-$\alpha$, IL-6 and leptin, but increase adiponectin in breast cancer survivors. **Methods:** Ninety-seven overweight or obese breast cancer survivors were identified from the Yale-New Haven Hospital Tumor Registry and randomized to usual care (n=33) or weight loss counseling by a registered dietitian (n=64) for 6 months. The usual care group was provided with AICR nutrition and physical activity brochures. Weight was measured and fasting blood samples were drawn at baseline and 6-months by trained staff. We conducted analyses using the intention-to-treat procedure with baseline values imputed for missing 6-month values (n=16). We used analysis of covariance, adjusted for baseline biomarker levels, to evaluate mean biomarker changes across groups. In secondary analyses, we evaluated the effect of weight loss on biomarkers among women randomized to intervention. **Results:** On average, women randomized to intervention and usual care groups lost 6% and 2% body weight (p=0.0003), respectively. Women in the intervention group experienced decreases in insulin, glucose, CRP, leptin and TNF-$\alpha$ and increases in adiponectin and IGF-I. CRP decreased by 30% in the intervention group and 1% in the usual care group (-1.05 mg/L vs. -0.06 mg/L, p=0.05). Compared to intervention women who lost <5% body weight, those who lost ≥5% body weight had larger decreases in CRP (-1.58 mg/L vs. -0.54 mg/L, p=0.02), insulin (-3.21 $\mu$U/mL vs. -0.59 $\mu$U/mL, p=0.048), leptin (11.08 ng/mL vs. -0.76 ng/mL, p=0.002) and IL-6 (-0.20 pg/mg vs. +0.59 pg/mg, p=0.02) but an increase in IGF-I (+9.19 ng/L vs. -11.11 ng/L, p=0.01). **Conclusions:** Weight loss resulting from a 6-month, 11-session counseling program had favorable effects on some inflammatory and metabolic biomarkers associated with breast cancer survival. IGF-I may not be a mechanism through which weight loss improves breast cancer survival.

**1506 Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**Proportion of *BRCA* mutation frequency in young black women with breast cancer.** *Presenting Author: Tuya Pal, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

**Background:** Young Black women are disproportionately afflicted with breast cancer, a proportion of which may be due to *BRCA1* and *BRCA2* (*BRCA*) gene mutations. Prior studies suggest *BRCA* mutations account for ~5% of breast cancers in young breast cancer survivors. We evaluated the prevalence of *BRCA* mutations and variants detected through full gene sequencing and large rearrangement testing in a population-based sample of young Black women with breast cancer. **Methods:** Black women diagnosed with invasive breast cancer < age 50 between the years 2009-2012 were recruited through the Florida Cancer Registry. Participants completed genetic counseling, a study questionnaire, and consent for medical record release. Saliva specimens were collected for *BRCA* sequencing and large rearrangement testing through MLPA. Data analysis included frequencies and Pearson Chi-square tests. **Results:** Of 283 participants, 28 (9.9%) had *BRCA* mutations (including 26 through sequencing and 2 through MLPA) and 93 (32.9%) had detection of one or more variant of unknown significance (VUS). Of 28 carriers, 18 (64.3%) had a *BRCA1* mutation and 10 (35.7%) had a *BRCA2* mutation. Among all participants, 94 (33%) were clinically tested prior to enrollment; those with prior clinical testing were more likely to have insurance at diagnosis than those not tested previously ($p<0.001$). Compared to those without an identified mutation, those with a *BRCA* mutation were significantly more likely to have: 1) triple negative (TN) cancer (20% vs. 48%); 2) a >10% prior probability of having a mutation based on the Myriad Prevalence Table (31% vs. 54%); and 3) previous genetic testing (31% vs. 50%) (all $p<0.05$). **Conclusions:** Our findings suggest that a higher than expected *BRCA* mutation frequency may partially account for the disproportionately higher incidence of breast cancer observed in young Black women. Furthermore, the high VUS rate is partly attributed to the disparity in *BRCA* testing in Blacks. Thus our results further highlight the importance to increase awareness and access to genetic testing services in Blacks, to help address the growing health disparities in clinical cancer genetics.

**1507 Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**The impact of oophorectomy on survival after breast cancer in BRCA1 and BRCA2 mutation carriers.** *Presenting Author: Kelly A. Metcalfe, University of Toronto, Toronto, ON, Canada*

**Background:** Oophorectomy is often recommended to women with BRCA-associated breast cancer in order to prevent a second primary breast cancer and ovarian cancer. However, it is unclear if oophorectomy has an impact on survival in women with BRCA-associated breast cancer. The objective of the current study was to estimate the impact of oophorectomy on survival from breast cancer for women with a BRCA1 or BRCA2 mutation **Methods:** 760 women with Stage I or Stage II breast cancer and a BRCA1 or BRCA2 mutation, between the ages 25 and 65, were followed for up to 20 years from diagnosis. The impact of oophorectomy on survival was evaluated in a Cox proportional hazards model, adjusting for age, gene (BRCA1 versus BRCA2), tumour stage, ER status and other treatments. **Results:** Of the 760 women, 455 had an oophorectomy, either prior to or after the diagnosis of breast cancer. The 20-year survival for the entire patient cohort was 74.3%. The un-adjusted hazard ratio for death associated with oophorectomy was 0.62 (95% CI: 0.42 to 0.90; p = 0.01) and the adjusted hazard ratio was 0.66 (95% CI 0.42 – 1.02; p = 0.06). The hazard ratio was 0.59 (95% CI: 0.34 – 1.01; p = 0.05) for BRCA1 carriers and was 0.81 (95% CI: 0.35 -1.85; p = 0.61) for BRCA2 carriers. The adjusted hazard ratio was 0.77 (95% CI 47 – 1.28; p = 0.29) for women diagnosed under age 50 and was 0.38 (95% CI: 0.12 to 1.15; p = 0.09) for women diagnosed over age 50. The hazard ratio was 1.21 (95% CI: 0.55 to 2.67; p = 0.65) for women with estrogen receptor-positive breast cancer and was 0.27 (95% CI: 0.11 to 0.67; p = 0.005) for women with estrogen receptor-negative breast cancer. **Conclusions:** Oophorectomy is associated with a decrease in mortality in women with early-stage breast cancer and a BRCA1 mutation. Women with estrogen receptor-negative breast cancer and a BRCA1 mutation should consider oophorectomy shortly after diagnosis as part of their treatment plan.

**1508 Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**Quality of life in BRCA1 and BRCA2 mutation carriers (B1/2) following risk-reducing salpingo-oophorectomy (RRSO).** *Presenting Author: Susan M. Domchek, University of Pennsylvania, Philadelphia, PA*

**Background:** RRSO is associated with a decreased risk of breast cancer, ovarian cancer and improved survival in B1/2. Timing of RRSO must balance the known benefits against the impact of early menopause. A better understanding of the long term impact of RRSO is required to aid decision making. **Methods:** B1/2 were ascertained from FORCE, a national advocacy group for hereditary breast and ovarian cancer. Demographics and medical history were obtained by online questionnaires. QOL measures evaluated executive cognition function (BADDS), menopausal symptoms (Greene), sexual function (FSFI), sleep (PSQI), stress (PSS), anxiety (HADS-A), and depression (HADS-D). **Results:** 637 B1/2 with RRSO were enrolled. Median age was 47. Median age of RRSO was 45. 43% had prior cancer history (of whom 87% had breast cancer and of these 60% chemotherapy). 27% were currently using HRT. Self reported HTN was present in 14%, osteopenia/osteoporosis in 32%, and depression in 36%. Suboptimal scores were present in the majority of patients for the majority of measures: specifically 60% of BADDS, 57% of Greene vasomotor, 73% of FSFI, 61% of PSQI, 56% of PSS, 16% of HADS-A, and 15% of HADS-D scores fell in the abnormal range. Earlier age of oophorectomy predicted suboptimal scores in sleep, stress, menopausal symptoms, anxiety and depression scales ($p<0.04$ for each). High school education or less (compared to some college or more) predicted poorer results in stress, anxiety, sexual functioning and menopausal symptoms ($p<0.02$ for each). Single status (as opposed to married or living as married) was associated with poorer scores on stress and sleep scales ($p<0.01$). In the subgroup of B1/2 with no cancer history and RRSO $<50$ years-old, current HRT use was associated with improved sleep ($p=0.02$) and vasomotor symptoms ($p<0.0001$). **Conclusions:** In this large series of B1/2 ascertained through FORCE, the majority of women reported sexual dysfunction, menopausal symptoms, cognitive issues, and poor sleep. Interventions are needed to mitigate the negative impact of RRSO.

**1509 Clinical Science Symposium, Mon, 8:00 AM-9:30 AM**

**Multigene panel testing in patients suspected to have Lynch syndrome.** *Presenting Author: Matthew B. Yurgelun, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Multigene panels are increasingly used for assessing hereditary cancer risk due to their ability to analyze numerous cancer susceptibility genes in parallel. Our aim was to study the outcomes of multi-gene panel testing in patients undergoing clinical testing for Lynch syndrome (LS). **Methods:** The study cohort was 1,260 consecutive patients with a history of LS-associated cancer and/or polyps who had undergone clinical genetic testing for LS in a commercial laboratory. Genomic DNA mutations were identified using a 25-gene hereditary cancer panel based on emulsion PCR and next generation sequencing. Germline sequence variations and large rearrangements were classified for pathogenicity. Patients' personal/family histories of cancer were obtained from test request forms submitted with clinical LS testing. **Results:** Panel testing found $\geq$1 pathogenic mutation in 160/1,260 (13%) patients and $\geq$1 variant of uncertain significance in 552/1,260 (44%) patients. Of the 160 mutation carriers, 116 (73%) had a mutation in one of the 5 LS genes, whereas 48 (30%) had a mutation in one of the 20 non-LS genes tested including 4 (3%) with both LS and non-LS mutations. Of the 48 non-LS mutations, 15 (31%) were in *BRCA1/2*, 10 (21%) were in genes underlying other hereditary colorectal cancer syndromes (*APC*, biallelic *MUTYH*, *PTEN*, and *STK11*), and the remaining 23 (48%) were in other cancer susceptibility genes (*ATM*, *BARD1*, *BRIP1*, *CHEK2*, *NBN*, *PALB2,* and *RAD51C*). Based on their personal/family histories, a large majority of patients met NCCN criteria for LS testing but not hereditary breast/ovarian cancer (HBOC) testing (Table). **Conclusions:** In this large cohort of patients suspected to have LS, 30% of mutation carriers identified by panel testing had non-LS cancer susceptibility gene mutations. With more comprehensive genetic testing approaches, many unexpected mutations will be found in patients who do not fulfill classic clinical criteria for their syndrome.

| | Met NCCN LS criteria | Met NCCN HBOC criteria |
|---|---|---|
| **Total cohort** | 1112/1,260 (88%) | 312/1,260 (25%) |
| **All mutation carriers** | 150/160 (94%) | 30/160 (19%) |
| **LS carriers** | 111/116 (96%) | 20/116 (17%) |
| **All non-LS carriers** | 43/48 (90%) | 11/48 (23%) |
| ***BRCA1/2* carriers** | 14/15 (93%) | 5/15 (33%) |

Rows/columns are not mutually exclusive.

**1510 Clinical Science Symposium, Mon, 8:00 AM-9:30 AM**

**Prevalence of mutations in a panel of breast cancer susceptibility genes in patients with early onset breast cancer.** *Presenting Author: Kara Noelle Maxwell, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA*

**Background:** Approximately 5-10% of breast cancers are attributable to inherited single gene mutations. Clinical testing for germline variation in multiple cancer susceptibility genes is available using massively parallel sequencing. However, data is needed on the spectrum of mutations and variants of uncertain significance (VUSs) in defined patient populations. **Methods:** We performed massively parallel sequencing using targeted capture of 19 cancer susceptibility genes in 277 *BRCA1/2* negative patients with early onset breast cancer (EOBC). **Results:** Excluding synonymous variants, 60% of patients were identified to have at least one rare variant. Twenty-eight patients (10%) were found to have a pathogenic mutation (Class 5 variant) or likely deleterious VUS (Class 4). Seven of these patients (2.5% overall) were found to have Class 4/5 variants in genes for which clinical guidelines exist for management, namely *TP53* (4), *CDKN2A* (1) and *MSH2* (2). Twenty-one patients (7.6%) had Class 4/5 variants in a moderate penetrance cancer susceptibility gene for which clinical guidelines are lacking. Four patients (1.4%) were heterozygous carriers of a pathogenic *MUTYH* mutation. In addition, 49 patients (18%) were found to carry a Class 3 VUS in a high penetrance or moderate penetrance gene. **Conclusions:** These data show that massively parallel sequencing identifies reportable (Class 3, 4 or 5) variants in known cancer susceptibility genes in 30% of patients with early onset breast cancer. However, only rare patients (2.5%) have definitively actionable mutations given current clinical management guidelines. Large-scale cooperative group studies are therefore needed to determine the clinical utility of multiplex panel testing in patients with early onset breast cancer.

**1511 Clinical Science Symposium, Mon, 8:00 AM-9:30 AM**

**A study of ovarian cancer patients tested with a 25-gene panel of hereditary cancer genes.** *Presenting Author: Lucy R. Langer, Northwest Cancer Specialists, Portland, OR*

**Background:** With advances in next-generation sequencing, patients receiving hereditary cancer testing can be tested for more genes, more efficiently. Patients with ovarian cancer are at risk for several different hereditary cancer syndromes—Hereditary Breast and Ovarian Cancer (HBOC) and Lynch syndrome (LS) in particular. **Methods:** We queried a laboratory database for patients affected with ovarian cancer and tested with a 25-gene panel of hereditary cancer genes from September 4, 2013 through December 27, 2013. All patient data regarding clinical history was obtained by health care provider report on test requisition forms. **Results:** We identified 263 patients with a personal history of ovarian cancer who received genetic testing using a 25-gene hereditary cancer panel. Of these patients, 77.2% met NCCN guidelines for HBOC, 0.8% met for NCCN guidelines for LS and 22.1% met guidelines for both syndromes. Deleterious or suspected deleterious mutations were identified in at least one gene in 16.3% of ovarian cancer patients. These included mutations in *BRCA1* or *BRCA2* (11%) and *ATM* (3.4%). Positive mutations were also identified in *APC* (3 patients), *BRIP1* (2 patients), and 1 patient each in *RAD51C*, *MSH6*, *CHEK2*, and *NBN*. We detected 137 variants of uncertain significance (VUS) in 263 patients with a range of 0 to 4 VUS identified per patient. No VUS were detected in the majority (61.6%) of patients. **Conclusions:** Testing patients using a 25-gene hereditary cancer panel increased the number of positive test results in ovarian cancer patients by 48% over *BRCA1* and *BRCA2* testing alone, showing the benefit of using a panel approach in this population.

**1512 Poster Highlights Session (Board #1), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Patient-reported outcomes and behavioral risk factors as predictors of chemoprevention adherence among women in the National Surgical Adjuvant Breast and Bowel Program (NSABP) Breast Cancer Prevention P-1 trial.** *Presenting Author: Stephanie R. Land, National Cancer Institute, Rockville, MD*

**Background:** Despite a 50% reduction in the risk of breast cancer (BC) for tamoxifen (T) vs. placebo (P), many women at risk of BC do not adhere to the 5 year course. Using prospectively-collected data from the double-blind NSABP P-1, we evaluated whether patient-reported outcomes were associated with drug adherence, and whether baseline behavioral risk factors modified those associations. **Methods:** 13,338 women at high risk of BC were randomly assigned to T vs. P (20 mg/day); we analyzed the 11,064 enrolled more than 3 years before trial unblinding 5/98. Mixed effects logistic regression was used to evaluate whether baseline and 3-month (mo) SF-36 mental (MCS) and physical (PCS) quality of life scales, depressive symptoms (CES-D), and possible treatment-related symptoms (BCPT symptom scales) predicted 12-mo drug adherence (using over 75% of assigned medication), accounting for Gail model estimated breast cancer risk and education; and whether associations were modified by baseline smoking status, alcohol consumption, body mass index (BMI, continuous variable), T vs. P, and age (continuous variable). **Results:** At 12 mo, 10,572 women were expected to be on therapy (excluding patients who never initiated therapy or experienced protocol required discontinuation); 84.2% were adherent. Sexual symptoms at 3 mo were associated with reduced adherence, but only among younger women (for example at age 45, odds ratio (OR) 0.8, p=.048); other symptoms predicted greater adherence among normal weight (OR=1.5 per 1 point, p=.016) but not among overweight women; 3-mo PCS predicted higher adherence among smokers (OR=1.4 per 10 points, p=.02), 3-mo MCS predicted adherence among women assigned to P (OR=1.4 per 10 points, p<.001). No significant associations were found with CES-D. **Conclusions:** Quality of life and symptoms at 3 months were associated with chemoprevention adherence at 12 months, and the associations differed according to age, treatment, BMI, and smoking status. Behavioral risk factors and patient-reported outcomes will help identify particular patients who may need greater adherence support. Clinical trial information: NCT00003906.

**1513 Poster Highlights Session (Board #2), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Risk of tobacco-related cancers in *CDKN2A* mutation-positive melanoma families.** *Presenting Author: Hildur Helgadottir, Department of Oncology-Pathology, Stockholm, Sweden*

**Background:** Germline mutations in the tumor suppressor gene *CDKN2A* occur in 5-20% of familial melanoma cases. A single founder mutation, p.Arg112dup, accounts for the majority of *CDKN2A* mutations in Swedish carriers. This mutation alters the peptide sequences of tumor suppressors p16-INK4A and p14-ARF. The aim of this study was to assess cancer risks in *CDKN2A* p.Arg112dup carriers and their first (FDRs) and second degree relatives (SDRS). **Methods:** In this prospective cohort study, cancer diagnoses in *CDKN2A* p.Arg112dup mutation carriers (n=120), non-carriers (n=111), carriers' FDRs (n=275) and SDRs (n=321) and controls (n=3976) were obtained from the Swedish Cancer Registry. Relative risks (RR) for cancers were calculated (number of cancers/person years). Due to the finding of high risks in mutation carriers of cancers that are normally associated with tobacco smoking, data was retrospectively collected on smoking history in carriers. Odds ratios were calculated to compare smoking (ever-smoker/never-smoker) in carriers with or without a diagnosis of non-melanoma cancer. Two-sided 95% confidence intervals (95% CI) were calculated for all RRs. **Results:** In carriers prospective RR for non-melanoma cancers was 5.0 (95% CI=3.7-7.3), for pancreatic cancer 43.8 (95% CI=13.8-139.0), for cancers in upper digestive tissues 17.1 (95% CI=6.3-46.5), and in respiratory tissues 15.6 (5.4-46.0). In FDRs and SDRs, RRs were significantly elevated for cancers in pancreas, respiratory and upper digestive tissues. In ever-smoking carriers compared with never-smoking carriers, the odds ratio of cancers in pancreas, respiratory or upper digestive tissues was 9.3 (95% CI= 1.9-44.7). **Conclusions:** *CDKN2A* p.Arg112dup mutation carriers from melanoma-prone families and their FDRs and SDRs have elevated risk for pancreatic, lung, head and neck and gastro-esophageal carcinomas. These cancers were mainly seen in ever-smoking carriers. This is the first study that shows association between smoking history and cancer diagnoses in *CDKN2A* mutation carriers. Germline *CDKN2A* mutations may confer an increased sensitivity to carcinogens in tobacco smoke. *CDKN2A* mutation carriers should be counseled to abstain from smoking.

**1514 Poster Highlights Session (Board #3), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Effect of exercise and dietary fish consumption on risk of recurrence in colon cancer: A multinational study.** *Presenting Author: Mohammed Shaik, Michigan State University, East Lansing, MI*

**Background:** Dietary factors and physical activity have been associated with the risk of occurrence of colon cancer(CCa) but their role in the recurrence of colon cancer(rCCa) has not been established. The aim of our study was to examine the association between dietary intake, exercise, and other risk factors with the rCCa. **Methods:** Data were obtained from the Global Epidemiological Study(GES), a multinational database to assess disease risk factors. Patients(pts) were recruited from Poland, Vietnam, Western Europe and the USA. Pts diagnosed with CCa gave informed consent to provide data including their exercise activity and dietary intake. Chi-square and t-test were used for categorical and continuous variables. The association[adjusted odds ratio(aOR)] between rCCa and risk factors was obtained using logistic regression. **Results:** A total of 1,515 pts were surveyed, of which 188 pts had rCCa later in life. The average age and the no. of current smokers with rCCa and those without rCCa were, 63 yrs *vs.* 64 yrs and 21(11.1%) *vs.*164(12.3%), respectively. There were 54.3% males and 46.7% females. Those with and without rCCa were compared regarding food intake, exercise, tobacco and alcohol use. In LR, food intake besides fish did not influence rCCa, neither did smoking duration or alcohol consumption. Fish intake of less than 2 servs per week had an aOR of 2.58 (1.07-6.29) and exercise less than 60 minutes per week had an aOR of 2.68 (1.02-7.0, Table). **Conclusions:** Fish consumption of more than 2 servs per week and also 60 minutes of weekly exercise, were each independently associated with a reduced risk of recurrence of colon cancer.

**Predictors of rCCa.**

| Variables | Adjusted OR (CI) | p-value |
|---|---|---|
| **Fish (< 2/wk *vs.* > 2/wk)** | 2.58 (1.07-6.29) | 0.03 |
| **Whole grain (<3/day *vs.* >3/day** | 1.44 (0.40- 5.17) | 0.57 |
| **Dairy (< 2/day *vs.* > 2/day)** | 1.16 (0.63-2.14) | 0.62 |
| **Vegetables (< 2/day *vs.* > 2/day)** | 0.75 (0.43-1.32) | 0.32 |
| **Fruits (< 2/day *vs.* > 2/day)** | 0.82 (0.47-1.43) | 0.49 |
| **Meat (< 2/wk *vs.* > 2/wk)** | 1.07 (0.68-1.69) | 0.74 |
| **BMI** | 1.02 (0.99-1.05) | 0.18 |
| **Nonsteroidal use (no *vs.* yes)** | 0.94 (0.59-1.51) | 0.82 |
| **Total years of smoking (<25 yrs *vs.* >25 yrs)** | 0.90 (0.56-1.43) | 0.66 |
| **Alcohol (no *vs.* yes)** | 1.23 (0.77-1.98) | 0.37 |
| **Exercise (<60 min/wk *vs.* > 60 min/wk)** | 2.68 (1.02-7.0) | 0.04 |

**1515 Poster Highlights Session (Board #4), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Antioxidant micronutrients and renal cell carcinoma: Results from the Women's Health Initiative.** *Presenting Author: Won Jin Ho, Department of Internal Medicine, University Hospitals Case Medical Center, Cleveland, OH*

**Background:** Renal cell carcinoma (RCC) is the 8$^{th}$leading cancer in women, commonly diagnosed at more advanced stage. Oxidative stress has been considered to play an important role in the pathogenesis of RCC. Various dietary micronutrients have antioxidant properties, including carotenoids, vitamin C, and vitamin E, and thus diets rich in these nutrients have been evaluated in relation to renal cancer prevention. The aim of this study is to explore the relationship between antioxidant micronutrient and RCC risk in the Women's Health Initiative (WHI). **Methods:** A total of 91,913 postmenopausal women enrolled between 1993 and 1998 and followed through July 2013 were included in the analysis. Dietary micronutrient intake was estimated from the baseline WHI food frequency questionnaire, and data on supplement use was collected via interview-based inventory procedure. RCC cases were ascertained from medical records and centrally adjudicated. Risk for RCC associated with $\alpha$-carotene, $\beta$-carotene, $\beta$-cryptoxanthin, lutein+zeaxanthin, lycopene, vitamin C, and vitamin E was analyzed using Cox proportional hazards analysis, adjusted for confounders. **Results:** There were 383 RCC cases identified in the WHI during follow-up. Lycopene intake was inversely associated with RCC risk (p = 0.001); compared to the quartile of lowest lycopene intake, the quartile with highest lycopene intake was associated with a 45% lower risk of RCC (HR 0.55; 95% CI, 0.38 to 0.80). There were no significant associations with RCC for any of the other micronutrients. No substantial correlation was found among micronutrients to suggest multicollinearity. **Conclusions:** These results suggest that further investigation into the relationship between dietary lycopene intake and RCC risk is warranted.

**1516 Poster Highlights Session (Board #5), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Atypical glandular cells and atypical cells of unknown origin in screening and subsequent risk of cervical cancer.** *Presenting Author: Par Sparen, Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden*

**Background:** Atypical glandular cells (AGC) in cervical screening may signal a wide range of conditions from reactive changes to malignancies in the cervix. Atypical cells of unknown origin (AUO) is a rare cytological finding in the Swedish cervical screening program which currently is referred to colposcopy. We set out to investigate the epidemiological evidence for AGC and AUO to be treated as high grade findings that should prompt a direct referral to colposcopy and endocervical evaluation and sampling. **Methods:** A population-based cohort study was defined as all Swedish resident women who had AGC and AUO findings, respectively, in cervical screening program from 1969 to 2011, retrieved from the National Quality Register for cervical Cancer prevention. Information on subsequent cervical cancer between 1969 and 2011 was obtained from the National Cancer Register. Prevalent cancers and long-term cancer risks after AGC and AUO diagnoses, respectively, were examined, and compared with low-grade and high-grade squamous intraepithelial lesions (LSIL and HSIL). Risk ratios (RR) and hazard ratios (HR) with 95% confidence intervals (CI) were calculated as effect measures. **Results:** 20,041 women diagnosed with AGC, and 33,253 women diagnosed with AUO, in Pap smear without any other abnormalities before were identified. Among these, 262 were diagnosed with invasive cervical cancer within half a year after AGC (1.31%), and 303 within half a year after AUO (0.91%), which implies possibly prevalent cancers. RR compared to LSIL was for AGC 6.83 (CI=5.92, 7.88), and for AUO 4.76 (CI=4.16, 5.46). RR compared to HSIL was 0.53 (CI=0.47, 0.60) for AGC and 0.37 (CI=0.33, 0.41) for AUO. HR half a year after AGC was 1.91 (CI=1.64, 2.23), compared to LSIL, and 1.32 (CI=1.12, 1.55), compared to HSIL. Correspondingly for AUO, HR=1.67 (CI=1.46), compared to LSIL, and HR=1.15 (CI=1.01, 1.33), compared to HSIL. **Conclusions:** Both AGC and AUO implies high risk of prevalent or long-term invasive cervical cancer, which warrants direct diagnostic measures and close follow up to find precursors or early carcinomas in the endocervix. We are currently exploring the possibility of increased risk also for endometrial cancer.

**1517 Poster Highlights Session (Board #6), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Thailand experiences on cervical cancer prevention using vinegar.** *Presenting Author: Khunying Kobchitt Limpaphayom, Department of OB& GYN, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*

**Background:** Cervicare Thailand is a visual inspection using acetic acid(VIA)and cryotherapy in a single visit approach(SVA) project that was initiated by Jhpiego,an affiliate of the Johns Hopkins University, and funded by Bill and Melinda Gates Foundation. Since 2002 the program has been supported locally. Purpose of this paper is to report of the results of scale up of the cervical cancer prevention initiative. **Methods:** The cervical cancer screening and treatment data were retrieved from service statistics that were routinely report in national health information system.We focused our data capture and analysis on 34 provinces where SVA is available. Additionally we utilized reports of training to supplement our data review. **Results:** Since 2000, there were 63 courses for SVA resulted in 1388 nurses qualified provide SVA in 34 of 77 provinces across Thailand. Another 149 clinical trainers were prepared to assist in training more providers and also conduct supportive supervision .Up to December 2013,749,407(22.8%)from a total of 3,285,585 women aged 30-45 have been screened with VIA. Positive VIA result were found in 27,978(3.7%) of which 15,396(55.0%) received treatment with cryotherapy at the same visit. The number of VIA positive cases referred for additional care was 12,582(45%).The referral were gynecologic problem and/or lesion ineligible for cryotherapy. Another 9,101(1.2%) women had suspicious cervical cancer finding, which required further diagnosis and treatment. **Conclusions:** SVA can be provided and made sustainable in Thailand. This approach increased accessibility and addresses health inequity for women in remote area.The scaled up has also identified the challenges and issue attendant to scaling up as well as the key lesson learned in improving the cervical cancer prevention in Thailand. While impact has yet to be measured nationally, the report from one of the province is promising. Roi-et where they have fully scaled up SVA, hospital based cancer registry show a declining trend for invasive cervical cancer year 2006 and 2011, reporting a drop from 65 cases to 54 cases.

**1518 Poster Highlights Session (Board #7), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Estimating the impact of screening on three decades of cervical cancer incidence.** *Presenting Author: Daniel Xiao Yang, Yale School of Medicine, New Haven, CT*

**Background:** In the U.S., the Pap smear has become a widely practiced, effective tool for the early detection and prevention of cervical cancer. However, the total number of cervical cancer cases that have been prevented by screening is unknown, as well as the impact of screening on racial disparities. **Methods:** We estimated national cervical cancer incidence from 1976 to 2009 using the Surveillance, Epidemiology, and End Result database. Screening data from 1951 to 2010 were obtained from literature and National Cancer Institute Progress Reports. We examined trends in early (localized) and late (regional, distant) stage cancer incidence and estimated the number of cancers prevented due to screening over the past three decades. Race was categorized as white, black, and other (Asian/Pacific Islander, Alaskan Native, and American Indian). **Results:** After rising steadily from 1951-1981, the percentage of all adult women who received cervical cancer screening stabilized at 71.7% in 1982 to 73.8% in 2010. Overall, from 1976 to 2009, there was a significant decrease in the incidence of early stage cervical cancer, from 10.2 to 5.4 cases per 100,000 women ($p < .001$). Late stage disease incidence also decreased, from 5.2 to 3.7 cases per 100,000 women ($p < .001$). After adjusting for "pre-screening era" rates of cervical cancer, we estimate that Pap smears were associated with a reduction of between 105,000 to 492,000 cases of cervical cancer over the past three decades in the U.S. The combined incidence among black women decreased from 26.9 to 9.7 cases per 100,000 women ($p < .001$), a greater decline compared to that of white women (13.7 to 8.5 cases per 100,000, $p < .001$), and women of other races (16.0 to 7.4 cases per 100,000, $p < .001$). **Conclusions:** We estimate that a large number of early and late stage cervical cancers were prevented, and the racial disparity in cancer rates was reduced during an era of increased screening. Given disparate access to the HPV vaccine, it will be important to continuously assess national cervical cancer incidence to measure the additional benefit of the vaccine against the known benefit of screening, and to ensure equal access and outcomes for all women.

**1519 Poster Highlights Session (Board #8), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Use of a SNP panel to refine risk estimates in women at high risk of breast cancer: Results from two randomized tamoxifen prevention trials.** *Presenting Author: Jack M. Cuzick, Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, London, United Kingdom*

**Background:** An assessment of how panels of single-nucleotide polymorphism (SNP) breast cancer risk factors might improve risk assessment among high-risk women is needed for better targeting of preventive therapy and other risk reduction measures. **Methods:** A case-control study was designed using leukocytic or tissue DNA from two tamoxifen prevention trials (IBIS-I and Marsden). SNPs were assayed on the Sequenom platform and a relative risk score for 15 SNPs (SNP15) was formed using the most recent iCOGS SNP risk estimates. Baseline questionnaires were used to estimate 10-year relative risks from the Tyrer-Cuzick model (TC). Conditional logistic regression was used to assess performance. An updated panel using all validated risk SNPs (approx. 70) is also being evaluated and will be presented at the meeting. **Results:** 440 cases and 686 controls had median age at baseline of 49 (inter-quartile range 45 - 54). Hardy-Weinberg equilibrium was verified. SNP15 and TC appeared uncorrelated (Spearman 0.037, P=0.209). The odds ratio (OR) between 25$^{th}$, 75$^{th}$ percentiles of SNP15 was 1.24 (95% CI 1.05 - 1.46) with AUC 0.568; TC had OR 1.41 (1.21 - 1.64), AUC 0.578; combined OR 1.54 (1.30 - 1.83), AUC 0.600. The observed risk was 48% (11 – 84) of predicted for SNP15 and 77% (42 – 110) for TC. SNP15 was more predictive for estrogen receptor (ER) positive tumours (318 cases, OR 1.36 (1.12 – 1.64), AUC 0.587, 67% (25-109) of predicted) but not for estrogen-receptor (ER) negative cancer (122 cases, P = 0.76); TC was significantly associated with both ER types. Little difference in performance was seen between tamoxifen and placebo treatment arms. The proportion of untreated women with 10-yr predicted risk above 8% was <1% for SNP15, 18% for TC and 25% for the combined risk score. **Conclusions:** A SNP panel is useful for refining risk estimates in women with phenotypic risk factors for breast cancer, and adds important information to classic phenotypic factors but does not appear to vary according to potential to benefit from tamoxifen. Clinical trial information: ISRCTN91879928 (ref: CCT-NAPN-14839).

**1520 Poster Highlights Session (Board #9), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Frequency of occult findings in contralateral prophylactic mastectomy as it relates to preoperative MRI or BRCA testing.** *Presenting Author: Lillian M. Erdahl, Mayo Clinic Rochester, Rochester, MN*

**Background:** Contralateral prophylactic mastectomy (CPM) rates in patients with unilateral breast cancer are increasing in the U.S. Preoperative MRI screening and genetic testing may influence surgical planning for patients undergoing CPM. The aim of our study was to determine the impact of breast MRI and BRCA mutation status on the rate of finding an occult high risk lesion (HRL) or occult malignancy (OM) in a CPM. **Methods:** We identified 740 women with unilateral breast cancer undergoing concurrent therapeutic mastectomy and CPM from 10/2008 to 6/2013 with no history of cancer in the CPM breast. We reviewed medical records for use of preoperative bilateral breast MRI and genetic testing for a BRCA 1 or 2 mutation. Likelihood ratio chi-square tests and multivariate logistic regression were used to assess potential impact of MRI and genetic testing on the likelihood of occult findings in the CPM breast. **Results:** Of 740 patients, 494 (67%) had a preoperative breast MRI and 244 (33%) had BRCA testing [197 (80.7%) BRCA 1/2 negative, 38 (15.6%) positive for BRCA 1/2 deleterious mutation, and 9 (3.7%) variant of unknown significance (VUS)]. Both MRI and BRCA testing were more likely to be performed in younger patients ($p<0.0001$). A clinically occult HRL or OM was identified in 108 (14.6%) CPM breasts: 78 (10.5%) HRL and 30 (4.1%) OM. There was no difference in the rate of occult lesions by use of MRI (14.2% MRI vs 15.5% no MRI, $p = 0.63$). BRCA 1 or 2 mutation was not associated with a higher rate of occult findings: 10.5% for BRCA 1/2 positive, 11.1% for VUS, 11.2% for BRCA 1/2 negative, and 16.4% for not tested ($p = 0.28$). A multivariate model adjusted for age, index breast cancer characteristics, and neoadjuvant chemotherapy, showed that neither preoperative breast MRI or BRCA 1/2 mutation was associated with occult findings on CPM. **Conclusions:** Patients not undergoing preoperative MRI were not more likely to have an occult malignancy or HRL identified in the CPM. The presence of a deleterious mutation in BRCA 1 or 2 is not associated with a higher rate of occult finding on CPM. Factors other than preoperative MRI or mutation status should be used to guide operative management of patients electing CPM.

**1521 Poster Highlights Session (Board #10), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**RPFNA cytologic atypia and short-term breast cancer risk in the prevention era.** *Presenting Author: Whitney L. Michaels, University of Kansas Medical Center, Kansas City, KS*

**Background:** In 2000 we published our initial observation from a high risk cohort of 480 women that cytologic evidence of hyperplasia with atypia in tissue obtained by random periareolar fine needle aspiration (RPFNA) was associated with a 5 fold increased risk of developing DCIS or invasive breast cancer (IBC) at a median follow-up (FU) of 45 months (Fabian et al. JNCI 2000). Few women had any exposure to prevention agents as NSABP-P1 was not reported until 1998. We began a new high risk cohort in 2002 as our tissue processing methods changed to Thin Prep which provided better nuclear detail. Women in the 2$^{nd}$cohort, in addition to counseling about standard prevention options, were given information about clinical trials and told that RPFNA atypia was a risk factor. The purpose of this initial analysis was to determine the predictive value of RPFNA atypia in the prevention era. **Methods:** A total 1,162 women, eligible on the basis of family history, prior LCIS or atypical hyperplasia and/or prior contralateral DCIS or IBC were enrolled in our 2$^{nd}$ cohort between 2002 and 2012. We used the same methods as with our earlier cohort where the first two aspiration results within 21 months were combined. The same cytopathologist (CZ) and same primary aspirator (CF) were utilized for both cohorts. Women were censored at the time of prophylactic mastectomy, development of other site cancer or death. 5 year Gail model risk, instead of 10 year Gail risk, was calculated for women 35 or older who did not have prior LCIS, DCIS or IBC. Kaplan-Meier hazard plots and Cox regression analysis were used for time to development of DCIS or IBC and effects of joint variables, respectively. **Results:** Median age at entry was 47 and 59% were premenopausal. 32% had cytologic evidence of atypia. At median FU of 55 months, neither 5 year Gail risk nor cytologic atypia was significantly predictive of subsequent development of breast cancer. However, 33% of women with atypia had taken a SERM or AI as part of a prevention trial and/or as standard of care and 12% of women <50 had a prophylactic oophorectomy. **Conclusions:** In a setting where many women with RPFNA atypia undergo a prevention intervention, cytologic atypia does not predict short term risk for breast cancer.

**1522 Poster Highlights Session (Board #11), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Founder effect and a high prevalence of BRCA1 mutations among young Mexican triple-negative breast cancer (TNBC) patients.** *Presenting Author: Cynthia Mayte Villarreal-Garza, Instituto Nacional de Cancerologia, Mexico City, Mexico*

**Background:** Previous studies have shown that the prevalence of BRCA mutations among young TNBC patients is elevated. Current guidelines recommend that women ≤60 years with TNBC be referred for genetic counseling. Different studies in Mexico have shown an early age of onset of BC and a high prevalence of TNBC, which suggests that BRCA mutations may account for a higher proportion of breast cancers in this population. However, there is limited information regarding BRCA mutation prevalence mainly due to lack of access to clinical BRCA gene analyses in Mexico. **Methods:** The purpose of this study is to analyze BRCA mutation frequency in a cohort of young Mexican TNBC patients using a panel assay of 114 recurrent BRCA mutations found in women of Hispanic ancestry (HISPANEL) on the Sequenom platform. Mexican women diagnosed with TNBC at or before age 50 were prospectively recruited from the National Cancer Institute in Mexico City. Patients were screened by HISPANEL and by PCR for the Mexican founder BRCA1 ex9-12del large rearrangement. **Results:** Among 190 consecutive TNBC cases, the median age of diagnosis was 42 years old and 69% were younger than 45 years. The majority of patients presented with locally advanced disease (69%). A BRCA mutation was detected in 43/190 (23%) of patients (42-BRCA1, 1-BRCA2), and BRCA1 ex9-12del accounted for 42% of the mutations. Only 45% of the BRCA mutation carriers had a family history of breast and/or ovarian cancer. Samples were processed in a two-week period, with a total cost of $4,000 USD. **Conclusions:** There is a remarkable prevalence of BRCA1 mutations among young TNBC patients in our population. The first documented Mexican founder mutation, BRCA1 ex9-12del, was the most frequent BRCA mutation and is likely responsible for a significant burden of disease in women from Southern Mexico. The HISPANEL can be completed within 72 hours from sample collection, at a modest cost of $20 USD per sample, and implementation among women of Mexican ancestry could reduce overall genotyping cost and increase access to cancer prevention among underserved women in Mexico and the U.S.

**1523 Poster Highlights Session (Board #12), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Association of the single nucleotide polymorphism TNRC9 rs3803662 on mammographic density and estrogen receptor-positive breast cancer risk in Japanese women.** *Presenting Author: Nobuyasu Yoshimoto, Oncology, Immunology and Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan*

**Background:** The incidence of breast cancer in Japanese women has doubled in all age groups over the past two decades. We recently created risk prediction models for estrogen receptor (ER)-positive breast cancer in both pre- and post- menopausal women using genetic factors (single nucleotide polymorphisms (SNPs)), environmental risk factors, serum hormones and growth factors, by logistic regression analysis. However, mammographic density is also considered to be a risk factor for breast cancer. To acquire some insight into the relationships among SNPs, mammographic density and breast cancer risk, we analyzed the correlation between these factors. **Methods:** The study population comprised 913 consecutive Japanese women with breast cancer, and 278 control Japanese women. We analyzed the correlation between genetic factors (14 SNPs) and breast cancer risk in both premenopausal and postmenopausal women. We also analyzed differences in mammographic density between the SNP genotypes (homozygotes of major alleles, heterozygotes and homozygotes of minor alleles) in the combined population of both premenopausal and postmenopausal women. **Results:** CYP19A1 rs10046 TT genotype and TNRC9 rs3803662 AA genotype were both found to have a significant association with ER-positive breast cancer in premenopausal women (OR 0.55: $P = 0.019$, OR 1.59: $P = 0.027$), while ESR1 rs6905370 GG genotype and TP53 rs1042522 CC genotype were significantly associated with ER-positive breast cancer in postmenopausal women (OR 1.83: $P = 0.033$, OR 0.54: $P = 0.045$). Mammographic density differed significantly among CYP2C19 rs4917623 genotypes (CC 50.23 +/- 18.82%, CT 46.69 +/- 20.03%, TT 49.04 +/- 19.22%, $P = 0.009$), among ESR1 rs827421 genotypes (AA 49.97 +/- 20.77%, AG 47.63 +/- 18.51%, GG 45.19 +/- 19.20%, $P = 0.048$) and among TNRC9 rs3803662 genotypes (AA 49.35 +/- 18.43%, AG 48.43 +/- 20.45%, GG 44.12 +/- 18.41%, $P= 0.026$). **Conclusions:** TRNC9 rs3803662 AA genotype was considered to confer an increased risk of ER-positive breast cancer by increasing mammographic density. ESR1 rs827421 AA genotype might also increase ER-positive breast cancer risk by the same mechanism.

**1524 Poster Highlights Session (Board #13), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Pharmacokinetic analysis of tamoxifen metabolites in premenopausal women with early breast cancer: A substudy of NCIC CTG MA.12 randomized clinical trial.** *Presenting Author: Shahbal Bill Kangarloo, Alberta Health Services, Tom Baker Cancer Centre, Calgary, AB, Canada*

**Background:** The clinical impact of CYP2D6 genetic polymorphisms on tamoxifen (Tam) remains unclear. Active metabolite levels of Tam can be influenced by drug interaction and compliance. This study evaluated the association of steady state plasma levels of Tam and its metabolites with clinical outcomes in samples collected in MA.12. Premenopausal women (n=672) with high risk node negative and node positive breast cancer following adjuvant chemotherapy were randomized to Tam or placebo. There was an improvement in DFS (HR 0.77; p=0.056) but not OS (HR 0.78; p=0.12) favoring Tam. **Methods:** TAM, N-desmethyl-tamoxifen (NDM), 4-hydroxy-tamoxifen (4-OH), and endoxifen (Endo) were quantified in serum by liquid chromatography–tandem mass spectrometry. Samples collected after 120 days on Tam were analyzed, (n=121 Tam, n=121 Placebo). Exploratory analyses assessed the association of DFS and OS with each metabolite level, as a continuous variable, as well as a categorical variable using an optimal cut point. Cut points were determined using the minimum p-value. Factors associated with DFS or OS were evaluated in a multivariate Cox model adjusting for age, performance status, chemotherapy, receptor status, nodal status, histology and tumor stage. **Results:** Baseline characteristics of the substudy were similar to the full trial population. Descriptive metabolite levels in the Tam cohort are listed in the Table. There was no crossover at 120 days. As a continuous measure, none of the metabolite values were significantly correlated with DFS or OS. As a categorical variable, only 4-OH was associated with clinical outcomes. In a multivariate Cox model, the optimal 4-OH cutpoint (1.72 ng/mL) was significantly correlated with 5 year DFS HR 0.30 [95% CI(0.10-0.95), p=0.04)] and 5 year OS HR 0.21 [95% CI(0.05-0.93), p=0.04]. **Conclusions:** In this exploratory, hypothesis generating analysis of MA.12, wide ranges in serum concentrations of Tam metabolites were observed. Only 4-OH levels were associated with clinical outcomes.

| Metabolite | Mean serum [ng/mL], (range) | % Coefficient of variance |
|---|---|---|
| **NDM** | 126.6, (0.61-293.1) | 50.2 % |
| **4-OH** | 1.47, (0-4.26) | 56.9 % |
| **Endo** | 16.6, (0-52.7) | 65.9 % |

**1525 Poster Highlights Session (Board #14), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Mammographic density and breast cancer in women from high-risk families.** *Presenting Author: Marina Pollán, National Center of Epidemiology, Instituto Salud Carlos III, Madrid, Spain*

**Background:** Mammographic density (MD) is one of the strongest determinants of breast cancer (BC). In this case-control study, we compared MD in *BRCA1/2* mutation carriers and non-carriers from *BRCA1/2* mutation-positive families and investigated the association between MD and BC among *BRCA1/2*mutation carriers per type of mutation and tumor subtype. **Methods:** The study was carried out in female members of *BRCA1* and *BRCA2* mutation-positive families followed-up at 16 Spanish Genetic Counseling Units. A total of 1039 women signed the informed consent and answered the questionnaire. Participants´ density was scored retrospectively from available mammograms by a single blinded radiologist using a 5-category scale (<10%, 10-25%, 25-50%, 50-75% and >75%). In cancer cases, mammograms were selected among those taken prior to diagnosis or from the contralateral breast. In controls, the last screening mammogram was evaluated. MD distribution in carriers and non-carriers was compared using ordinal logistic models, and the association between MD and BC in *BRCA1/2* mutation carriers was studied using logistic regression. Huber-White robust estimators of variance were used to take into account correlations between family members. A similar multinomial model was used to explore this association by BC subtype. **Results:** We identified and scored mammograms from 353 *BRCA1*, 360 *BRCA2* mutation carriers and 247 non-carriers. MD was associated with subsequent development BC (OR per category of MD: 1.41; 95%CI: 1.15-1.73, p = 0.001), with no significant differences between *BRCA1* and *BRCA2* mutation carriers (p = 0.69). However, MD was significantly lower among *BRCA2* mutation carriers compared to non-carriers (OR=0.70; p = 0.031). Finally, no statistically significant differences were observed in the association of MD with specific BC subtypes. **Conclusions:** *BRCA1/2* mutation carriers do not present higher MD compared to non-carriers, but our work confirms that MD is also an independent risk factor for BC in this population.

**1526 Poster Highlights Session (Board #15), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**EGFR mutation screening in non-small cell lung cancer: Results from an access program in Brazil.** *Presenting Author: Luciola De Barros Pontes, HCor Onco, Sao Paulo, Brazil*

**Background:** Epidermal growth factor receptor (EGFR) mutation testing allows for optimal selection of therapy with tyrosine kinase inhibitors in patients with non-small-cell lung cancer (NSCLC). Previous studies have shown a variation in EGRF genotype according to ethnic background, with scarce data about EGFR mutation status among brazilian patients with NSCLC. **Methods:** Between 2011 and 2013, as part of a program sponsored by a pharmaceutical company in Brazil, tumor samples of patients with stage IIIb/IV NSCLC were submitted, at the discretion of the attending physicians, for EGFR mutation testing. All analysis were performed at 02 reference laboratories, as follows: after microdissection, DNA was isolated from serial sections of formalin-fixed, paraffin-embedded tumor tissue to obtain at least 70% tumor cells. Exons 18, 19, 20 and 21 of the EGFR gene were analysed using Sanger sequencing. EGFR mutation rate was calculated and its frequency compared between clinical subgroups using chi-square test. Data about smoking status was incomplete and thus not included in this analysis. **Results:** 3,771 (1,799 male; 1,942 female) samples were analysed, of which 3364 provided informative results. Frequency of EGFR mutation was 25.5% (857/3364). Deletions in exon 19 were the most frequent alterations detected (54%; 463/857), followed by point mutations in exon 21 (28%; 240/857), exon 20 (9.7%; 83/857) and, less frequently, mutations in exon 18 (8.3%; 71/857). The median age for patients with a positive test was 66 years (range, 28-95). The most important predictors for the presence of EGFR mutations were adenocarcinoma histology (p<0.001), with 89% of positive tests occurring in this histology (331/370 - available data), and female gender (p<0.001), in which 30.2% of the patients tested were positive. No differences in EGFR mutation frequency were found between age groups. **Conclusions:** To the best of our knowledge, this is the largest study to assess EGFR mutation status in Latin America and in Brazil. Our findings suggest that the frequency of EGFR mutation in this cohort was lower than that found in Asia, but higher than in Caucasian populations, confirming findings seen in other Latin American countries.

**1527 Poster Highlights Session (Board #16), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Clinical and molecular characteristics of non-small cell lung cancer patients harboring PIK3CA mutations.** *Presenting Author: Sebastian Yves Friedrich Michels, University of Cologne, Cologne, Germany*

**Background:** Somatic mutations of the *PIK3CA* gene have been described in non-small cell lung cancer (NSCLC), but limited data is available on their biological relevance. This study was performed to characterize PIK3CA-mutated NSCLC clinically and genetically. **Methods:** Tumor tissue collected consecutively from 1,144 NSCLC patients within a molecular screening network between March 2010 and March 2012 was analyzed for *PIK3CA* mutations using dideoxy-sequencing and next-generation sequencing (NGS). Clinical, pathological, and genetic characteristics of these patients are described and compared with a control group of *PIK3CA*-wildtype patients. **Results:** Among the total cohort of 1,144 patients we identified 42 (3.7%) patients with *PIK3CA* mutations in exon 9 and exon 20. These mutations were found with a significant higher frequency in sqamous cell carcinoma (8.9%) compared to adenocarcinoma (2.9%, p<0.001). Overall, they were significantly associated with smoking (p=0.012). The most common *PIK3CA* mutation was exon 9 E545K. The majority of patients (57.1%) had additional oncogenic driver aberrations. Further, *PIK3CA*-mutated patients had significantly higher incidence of malignancy prior to lung cancer (p<0.001). The median overall survival of these patients treated with systemic medication at stage IV was 9.5 months (95% CI, 2.3 – 16.8 months) and 32.1 months (95% CI, 17.9 – 46.3 months) for the local stages. **Conclusions:** Analysis of the largest cohort of *PIK3CA*-mutated NSCLCs described so far shows clinical and genetic heterogeneity of this subgroup in adenocarcinomas as well as in squamous cell carcinomas. In addition, we found that *PIK3CA* mutation positive lung cancer frequently develops in patients with prior malignancies.

**1528 Poster Highlights Session (Board #17), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Racial/ethnic variations in lung cancer incidence and mortality, adjusted for smoking behavior: Results from the Women's Health Initiative.** *Presenting Author: Manali I. Patel, Stanford University Medical Center, Menlo Park, CA*

**Background:** It is unclear whether there are racial/ethnic disparities in lung cancer incidence and mortality among women. Therefore, we examined lung cancer incidence and mortality in the Women's Health Initiative (WHI), a prospective cohort of post-menopausal women. **Methods:** Lung cancer diagnoses were centrally adjudicated by pathology review. Logistic regression models estimated odds of incidence and mortality by race/ethnicity adjusted for age, education, calcium/vitamin D, BMI, smoking (status, age at start, duration and pack-years), alcohol, family history, oral contraceptive, hormones, physical activity, and diet. **Results:** The analytic cohort included 129,951 women -108,487 (83%) white (47.5% current/past smoker); 10,892 (8%) Black (47.7% current/ past smoker); 4,882 (4%) Hispanic (33.7% current/past smoker); 3,696 (3%) Asian/Pacific Islander (A/PI) (26.2 % current/past smoker); 534 American Indian/Alaskan Native (48.3% current/past smoker) and 1994 (1.4%) other (41.6% current/past smoker). In unadjusted models Hispanics had 66% lower odds of lung cancer compared with whites (OR 0.34 95% CI (0.2-0.5)), followed by A/PI (OR 0.45 95% CI (0.27-0.75)) and blacks (OR 0.75 95% CI (0.59-0.95). In fully adjusted multivariable models, decreased risk of lung cancer for blacks, Hispanics, and A/PI compared to whites was no longer statistically significant. In unadjusted models Hispanics and A/PI had decreased risk of death from compared to whites (OR 0.3 95% CI (0.15-0.62), OR (0.3 95% (0.16-0.75)), respectively); however, no significant racial/ethnic differences were found in risk of death from lung cancer in fully adjusted models. **Conclusions:** We found no racial/ethnic disparities in lung cancer incidence or mortality in a population of post-menopausal women after adjusting for socio-demographic, clinical, and behavioral factors. Clinical trial information: 1757.

**1529 Poster Highlights Session (Board #18), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Circulating microRNA signature and lung cancer outcome in low-dose computed tomography (LDCT) screening.** *Presenting Author: Stefano Sestini, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

**Background:** The efficacy of low-dose computed tomography (LDCT) screening is currently being tested in prospective randomized trials worldwide. Some of these trials are also investigating the value of non-invasive biomarkers, to improve the cost-benefit ratio of LDCT by individual risk assessment. In the present study, we have analyzed the capacity of a miRNA signature classifier (MSC) based on 24 previously refined microRNAs circulating in plasma to predict the outcome of lung cancer patients within the LDCT screening program. **Methods:** Between 2000 and 2010, 3411 heavy smokers were enrolled in a screening program, with annual (2225) or biennial (1186) LDCT. During the first five years of screening, a total of 111 consecutive subjects developed lung cancer. The actuarial five-year survival according to clinical and pathological characteristics was calculated for all patients, and for the subset of 76 patients suitable for plasma MSC analysis, according to three different risk groups (High, Intermediate or Low). Median follow-up of the alive patients was 4.5 years (Inter Quartile Range = 6.5). **Results:** Five-year survival was 55% in overall (median 7.9 yrs), 63% for LDCT-detected cases (median nc), 90% for pStage I (median nc), 9% for pStage II-IV (median 1.5 yrs, $p<0.001$), 68% for cancers detected in the initial two years of screening (median nc), and 38% for years 3 to 5 (median 3.0 yrs, $p<0.004$). None of the 13 interval cancers survived 4 years (median 0.8 yrs, $p<0.001$). In the subset suitable for plasma MSC analysis , survival was 76% for low- to intermediate risk MSC (median nc), and 35% for High risk MSC (median 2.9 yrs, $p=0.002$). The prognostic power of MSC persisted when the analysis was restricted to LDCT-detected cases after exclusion of interval cancers (85 vs. 38% respectively, $p<0.001$). No cancer deaths were observed in the subset of 28 patients with pStage I and low- to intermediate risk MSC. **Conclusions:** Patients developing interval lung cancer or with a Stage higher than I had a very poor outcome, despite LDCT monitoring. Plasma MSC predicted lung cancer outcome effectively, and might improve the individual risk assessment and performance of LDCT screening in the near future. Clinical trial information: INT 05-53.

**1530 Poster Highlights Session (Board #19), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Lung cancer detection by low-dose computerized tomography (LDCT) and digital tomosynthesis (DT) for lung cancer screening in a high-risk population: A comparison of detection methods.** *Presenting Author: Natthaya Triphuridet, Chulabhorn Hospital, Bangkok, Thailand*

**Background:** Low-dose computerized tomography (LDCT) recommended as a screening tool for lung cancer in a high risk population has some limitations with respect to its high false positive rate, accumulated radiation exposure and relatively high costs. Digital tomosynthesis (DT) is a multi-section imaging technique which can improve detection ability of small lung nodules and renders much lower radiation dosage and operation costs. **Methods:** 624 Thai heavy smokers (>30 pack-years) were enrolled in a prospective study starting from July 2012 to October 2013. All participants underwent LDCT and DT on the same day while the results were independently viewed with 1-week interval apart. Abnormal findings were categorized into 3 groups: negative, indeterminate (maximum diameter of pulmonary nodule 5-9.9 mm or volume 50-500 $mm^3$), and suspicious for primary lung cancer (maximum diameter of pulmonary nodule >10 mm or volume >500 $mm^3$, consolidation, obstructive atelectasis, pleural effusion, or mediastinal lymphadenopathy). **Results:** Ten lung cancer cases were detected in this high-risk group (10/624, 1.6%). LDCT and DT classified 23 and 20 cases, respectively, as suspicious for primary lung cancer. DT detected 8 primary lung cancers as frequently as did LDCT. LDCT classified 68 cases as indeterminate while DT classified 21 as such cases. Two additional primary lung cancers were detected at a 3-month follow-up; all were identified as indeterminate by baseline LDCT and only one case was indeterminate by baseline DT. The positive predictive value (PPV) for all suspicious for primary lung cancer findings by LDCT and DT was 34.8% and 40%, respectively. The sensitivity and specificity of LDCT and DT was comparable at 80% and 98%, respectively. The PPV for pulmonary nodule >10 mm or volume >500 $mm^3$ was 30% and 42% in LDCT and DT, respectively. The PPV for pulmonary nodule >5mm or volume 50-500 $mm^3$ was 9% and 22.5% in LDCT and DT, respectively. **Conclusions:** DT is a lung cancer screening modality that is comparable to LDCT, particularly for pulmonary lesions of 10 mm. and larger.

**1531 Poster Highlights Session (Board #20), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Death less than one month from diagnosis in children with cancer: A population-based analysis.** *Presenting Author: Adam L. Green, Dana-Farber Cancer Center Institute/Boston Children's Cancer and Blood Disorders Center, Boston, MA*

**Background:** Childhood cancer outcomes continue to improve, but a proportion of patients still die soon after diagnosis. While many of these deaths may be preventable, this group of patients has not been well characterized and may be underreported. **Methods:** We retrieved data from SEER 13 on the 34,878 patients 0-19 yrs with cancer diagnosed between 1992 and 2010. Early death (ED) was defined as death within the first month from diagnosis. Demographic, clinical, and socioeconomic factors were analyzed using chi-square testing. Socioeconomic data for each county were derived from Census 2000 and divided into two categories according to the median value for the cohort. **Results:** 1.8% (n=644) patients died within one month of diagnosis. Compared with the entire cohort, the ED group had a significantly higher percentage of infants (25.3% vs.7.2%, $p<0.0001$). In comparison to the whole cohort, diseases overrepresented in the ED group included infant ALL (2.0 vs 0.6%, $p<0.0001$), AML (18.2 vs 5.0%, $p<0.0001$), CNS tumors (24.8 vs 17.7%, $p<0.0001$), and hepatic tumors (3.7 vs 1.4%, $p<0.0001$). Diseases underrepresented included ALL, lymphomas, and renal, bone, and soft tissue tumors. Patients in the ED group were more likely to be of non-white race (24.5% vs. 20.4%, $p=0.03$) or Hispanic ethnicity (33.8% vs. 26.1%, $p<0.0001$). These patients were also more likely to live in counties with high rates of poverty ($p<0.0001$), unemployment ($p=0.03$), language isolation ($p=0.0004$), and immigration ($p=0.003$), and a low rate of high school education ($p=0.02$). Early death rate decreased over the period of analysis (APC -2.6%). **Conclusions:** Risk factors for ED in childhood cancer include infancy, specific diagnoses such as AML and CNS tumors, racial and ethnic minority, and disadvantaged socioeconomic status. The disease-specific rates of early death found in this population analysis were uniformly higher than those reported in large cooperative clinical trials, suggesting that many ED patients are lost to the medical literature. This group should be described prospectively, and initiatives to identify patients at risk and develop preventive interventions should be undertaken in the primary and specialty settings.

**1532 Poster Highlights Session (Board #21), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Influence of metformin use on the transformation of monoclonal gammopathy of undetermined significance into multiple myeloma.** *Presenting Author: Su-Hsin Chang, St. Louis Veterans Affairs Medical Center, St. Louis, MO*

**Background:** Multiple myeloma (MM) is the second most common hematologic malignancy in the United States and is preceded by monoclonal gammopathy of undetermined significance (MGUS). Stimulation of the insulin-like growth factor receptor pathway is a hypothesized mechanism for the progression of MGUS to MM; therefore, alteration of this pathway with metformin could reduce the risk of progression. We evaluated the influence of metformin use on the transformation of MGUS to MM in a retrospective cohort. **Methods:** Patients with MGUS and diabetes mellitus diagnosed between 1998 and 2009 were identified in the U.S. Veterans Health Administration (VHA) database. Unique identifiers were used to link data to the pharmacy database to obtain diabetes medications. Two investigators reviewed patient-level clinical information to verify dates of MGUS and MM diagnoses, and abstract additional data, including size of baseline M protein, immunoglobulin (Ig) subtype, and serum-free light-chain ratio, when available. The duration of metformin use was determined by the dates of the first and last prescription before 2013 or MM diagnosis. Several threshold values for dichotomization around the median duration of metformin use for patients developing MM were examined. Cox proportional hazard models, adjusting for age, body mass index, race, sex, Ig subtype, and size of M spike, were used to analyze the association between metformin use and the time from MGUS diagnosis to MM diagnosis. **Results:** 2,116 MGUS patients with diabetes were identified after excluding those with IgM MGUS. Among them, 38% were not treated metformin and 113 patients developed MM. We found that metformin use over 46 months (median duration of metformin use for MM patients) was protective, but not statistically significant (HR: 0.83; 95% CI: 0.55-1.24). However, metformin use over 4.5 years (54 months) was significantly protective with HR: 0.60 and 95% CI: 0.38-0.94. Patients with M protein concentration ≥1.5 g/dL (HR: 6.32; 95% CI: 3.7-10.8) and IgA monoclonal protein (HR: 1.82; 95% CI: 1.15-1.90) had a higher risk of progression. **Conclusions:** Prolonged metformin use was associated with a reduced risk of transformation from MGUS to MM.

**1533 Poster Highlights Session (Board #22), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Risk factors for melanoma among survivors of non-Hodgkin lymphoma in the U.S. elderly population.** *Presenting Author: Clara JK Lam, National Cancer Institute, Rockville, MD*

**Background:** Non-Hodgkin lymphoma (NHL) survivors have increased risk of developing melanoma compared with the general population. Although immune dysfunction may play a role, no previous study has investigated immune-related factors and melanoma risk after NHL. **Methods:** We used the SEER-Medicare linkage to identify a cohort of 44,875 individuals who were diagnosed with first primary NHL during 1992-2009 at ages 65-84 years and survived ≥1 year. Cox regression quantified melanoma risk associated with NHL treatments as well as autoimmune conditions and infections occurring at age ≥65. **Results:** A total of 202 second primary melanomas occurred during 248,917 person-years, including 91 after chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and 111 after other NHL subtypes. Melanoma risk after CLL/SLL was significantly increased among patients who received fludarabine- and rituximab-containing chemotherapy (hazard ratio [HR]=2.99, 95% confidence interval [CI]=1.68-5.33, versus no chemotherapy), whereas risk was not evident for rituximab-containing therapy without fludarabine. Among non-CLL/SLL patients, melanoma risk was significantly elevated for patients receiving cyclophosphamide-containing chemotherapy without rituximab (HR=2.15, 95%CI=1.26-3.65) or rituximab and cyclophosphamide-containing chemotherapy (HR=1.66, 95%CI=1.00-2.75). Occurrence of autoimmune diseases after NHL diagnosis was associated with increased risk of melanoma (B-cell activating diseases: HR=1.43, 95% CI=1.02-2.01; T-cell activating diseases: HR=1.39, 95%CI=0.94-2.04), with particularly elevated risks for asthma occurring after CLL/SLL (HR=2.11, 95%CI=1.09-4.08). In contrast, localized scleroderma was associated with increased melanoma risk both prior to (HR=1.47, 95% CI=1.00-2.16) and after NHL (HR=1.44, 95%CI=0.87-2.39). Similarly, urinary tract infection was associated with increased melanoma risk prior to (HR=1.39, 95%CI=0.99-1.94) and after NHL (HR=1.59, 95%CI=1.05-2.41), but no significant associations were observed for other infections. **Conclusions:** These findings support a role for immune perturbation in the development of melanoma after NHL.

**1534 Poster Highlights Session (Board #23), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Risk of death from cardiovascular disease in long-term breast cancer survivors: A comparison with women from the general population.** *Presenting Author: Milada Cvancarova, Oslo University Hospital Radiumhospitalet, Oslo, Norway*

**Background:** As a result of modern cancer treatment such as surgery, chemotherapy and radiation therapy there is a growing number of cancer survivors. However, it comes at a cost. Cardiovascular disease (CVD) after cancer treatment has gained growing attention in the medical community during the recent decades. Our aim was to compare CVD-related mortality in long term breast cancer (BC) survivors to that in the general population taking into account the competing risk of dying of cancer or other non-CVD causes. We aimed to study the effect of more recent radiotherapy techniques comparing left and right sided BC, and the effect of socioeconomic status measured as the level of income at the time of diagnosis on the risk for dying from CVD. Sosioeconomic status indicators such as low income have been associated with higher prevalence of CVD. **Methods:** In total, 18614 BC patients diagnosed from 1984 to 2002 who survived at least ten years after their cancer diagnosis were matched with 10 women randomly selected from the general population. Each BC case was matched on date of birth and the selected controls had to be alive and cancer free at the time of their case's diagnosis. Income at diagnosis was categorized as low, medium and high. The risk of dying of CVD-related cause was modeled using stratified Cox regression. Separate models were fitted for women irradiated on the left and right body side. **Results:** There was no statistically significant difference in risk of dying due to CVD-related causes between BC cases and their matched controls (HR=1.05, 95%CI[0.98 to 1.12]. However, left-sided irradiated BC survivors had increased risk of CVD-related death compared to their controls (HR=1.17, 95%CI [1.02 to 1.23]. There was no difference between right-sided irradiated cases and their controls (HR=0.99, 95%CI[0.90 to 1.08]. Income at diagnosis was not associated with CVD-related mortality. **Conclusions:** Recent radiotherapy techniques still imply increased CVD-related mortality among left-sided irradiated BC survivors. Therefore further reduction of cardiac radiation doses should be implemented, particularly in women with left sided breast cancer.

**1535 Poster Highlights Session (Board #24), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Cancer patients' preferences for return of somatic and germline whole-exome sequencing results: Data from the CANSEQ study.** *Presenting Author: Stacy W. Gray, Dana-Farber Cancer Institute, Boston, MA*

**Background:** The introduction of whole-exome sequencing (WES) into routine cancer care presents novel challenges for patient education and informed consent. In light of the recent American College of Medical Genetics and Genomics recommendations for the return of actionable germline incidental findings, it is imperative to understand patients' preferences for the return of WES findings. **Methods:** Advanced lung and colorectal cancer patients were offered WES. Preferences for the return of somatic and germline findings were obtained at consent. Attitudes about genetic testing and genetic knowledge were elicited through a baseline survey. **Results:** We approached 97 patients for participation, of whom 92 (95%) enrolled. Eighty-six patients completed the survey (completion rate 93%); 49% lung, 58% female, mean age 65 (standard deviation (sd) 11.4), 79% white, 21% ≤ high school education, 22% ≥ advanced degree. The vast majority of patients wanted to learn about somatic and germline WES findings. Preferences for return of results were highest for somatic findings that can be used to select a clinical trial (97%) and for positive prognostic findings (99%). Most patients also wanted return of germline pharmacogenetic (cancer-related 99%; non-cancer related 94%), cancer risk (96%), and treatable non-cancer risk (96%) results. Preferences for the return of somatic results with negative prognostic implications (86%), results indicating germline risk for non-treatable, non-cancer conditions (85%), and carrier status (88%) were slightly lower. Patients had highly positive attitudes about genetic testing but relatively low genetic knowledge, answering a mean of 54% of items correctly on a 7-item scale (sd 24.7). **Conclusions:** Patients with advanced lung and colorectal cancer express strong preferences for the return of somatic and germline WES findings. Despite patients' positive attitudes about genetic testing, relatively low levels of genetic knowledge may present challenges to adequate informed consent and highlight the need for high-quality sequencing-related patient education.

**1536 Poster Highlights Session (Board #25), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Survival after second primary lung cancer following non-Hodgkin lymphoma: A U.S. population-based study.** *Presenting Author: LINA INAGAKI, Rollins School of Public Health, Emory University, Atlanta, GA*

**Background:** Cancer survivors are known to have a higher risk of developing second primary cancer (SPC). While Hodgkin lymphoma attracts more attention, non-Hodgkin lymphoma (NHL) survivors account for a larger population of those who develop SPC, and lung cancer accounts for the largest risk of SPC among NHL-survivors. Although a follow-up care plan for cancer survivors has been recommended, concrete guidelines for screening for SPC have not been established. **Methods:** Study patients were identified from the SEER program from 1990 through 2009. A total of 863 NHL survivors who developed second primary lung cancer and 3,452 patients among 232,202 first primary lung cancer patients without a history of malignancy were randomly sampled and included in the analysis. The overall survival (OS) between the two groups were compared using a Log-rank test, followed by subset analysis for estimated survival among patients with localized stage lung cancer, in which OS was significantly different, using Cox proportional hazard regression, controlling for sex, race, year of diagnosis, age at diagnosis, histology, tumor grade and marital status. **Results:** NHL survivors experienced significantly inferior survival after lung cancer compared to patients without a history of malignancy at localized stage disease: 5-year OS was 33.0% vs. 44.8% ($p < 0.001$), whereas the survival did not differ significantly for regional stage: 13.9% vs. 19.2% ($p = 0.38$), and distant stage: 0% vs. 2.9% ($p = 0.10$). The subset analysis for patients with localized stage showed that the adjusted Hazard Ratio for death among NHL survivors was 1.38 (95% CI, 1.10-1.73; $p = 0.005$). **Conclusions:** NHL survivors were shown to have inferior survival when diagnosed with localized stage lung cancer compared to the general population. Because NHL survivors may not benefit from screening, the promotion of lung cancer screening to reduce mortality among NHL survivors warrants careful assessment.

**1537 General Poster Session (Board #319), Sun, 8:00 AM-11:45 AM**

**Genetic variant in the microRNA binding site of *DOK3* (rs2279398G>A) and susceptibility to colorectal cancer.** *Presenting Author: Jong Gwang Kim, Kyungpook National University Hospital, Daegu, South Korea*

**Background:** Single nucleotide polymorphisms (SNPs) located in the 3'-UTR of miRNA target genes could affect miRNA-mediated gene regulation, thereby contributing to the susceptibility or prognosis of colorectal cancer. Docking protein 3 (DOK3) is adapter protein that acts as tumor suppressor through modulating RAS signaling pathway. The present study analyzed SNPs located at putative miRNA-binding sites of the 3'-UTR of various genes and investigated their impact on the susceptibility of colorectal cancer. **Methods:** One hundred thirty five SNPs were selected in Silicoanalysis for the current study from 3'UTR SNPs of SNP database, which was based on several miRNA database, calculating miRNA bind efficiency on polymorphism, and HapMap database. Here independent two set of study was designed, 380 healthy controls and 371 colorectal adenocarcinoma patients were enrolled in discovery set, and 524 healthy controls and 521 colorectal adenocarcinoma patients were enrolled in replication set. The SNP genotyping was performed using the Sequenom MassARRAY. **Results:** In discovery set, 16 SNPs were significantly associated with the risk of colorectal cancer in any genetic model from 135 SNP genotyping. Among 16 SNPs, *DOK3* rs2279398G>A was significantly associated in replication set as recessive model (adjusted odds ratio (OR) = 0.65, 95% confidence interval (CI) = 0.44-0.97, $P = 0.03$). In combined analysis, *DOK3* rs2279398G>A was associated with significantly decreased risk of colorectal cancer in codominant and recessive model (adjusted OR = 0.84, 95% CI = 0.73-0.96, P = 0.012, adjusted OR = 0.65, CI = 0.49-0.88, P= 0.004, respectively). **Conclusions:** *DOK3* rs2279398G>A may affect the expression of *DOK3* by altering miRNA binding efficiency on miRNA-binding sites of the 3'-UTR of *DOK3* and impact on colorectal cancer tumorigenesis. This finding suggests that *DOK3* rs2279398G>A may be a useful biomarker for determining the susceptibility to colorectal cancer.

**1538 General Poster Session (Board #320), Sun, 8:00 AM-11:45 AM**

**Analysis of somatic copy number alterations in pediatric solid tumors using array comparative genomic hybridization.** *Presenting Author: Alanna Church, Boston Children's Hospital, Boston, MA*

**Background:** Somatic structural changes in tumor genomes are known to be significant in the diagnosis, prognosis, and therapy of pediatric solid tumors. Translocations, focal deletions and amplifications, whole arm and whole chromosome gains and losses are routinely assayed by karyotype and FISH at the time of diagnosis. Array comparative genomic hybridization (aCGH) is another technique to interrogate somatic copy number alterations (SCNAs). aCGH has the advantage of being compatible with formalin-fixed, paraffin-embedded (FFPE) tissue, and offers higher resolution for SCNAs than other techniques. Here we investigate the clinical utility of copy number assessment in pediatric solid tumors. **Methods:** Patients were enrolled on a multi-institutional translational research study, designed to test the feasibility of using somatic genetic analysis to guide the therapy of advanced pediatric solid tumors. For each patient with adequate available material, tumor tissue was analyzed for both sequence variants and SCNAs. This analysis focuses on copy number changes at 38 pre-selected oncology-related genes. aCGH results were reviewed by an expert panel of oncologists and molecular pathologists. **Results:** Of the 100 patients enrolled, 32 cases have been analyzed by aCGH: 3 carcinomas, 16 sarcomas, 7 embryonal tumors, 4 undifferentiated malignancies, and 2 others. 26 cases (81%) had SCNAs reported, of which 6 cases had focal (<1Mb) changes, and 20 had only large-scale changes. Focal changes included MYC, MYCN, SMARB1 (INI1), CDKN2A, and ERBB2 (Her2). In addition it was occasionally possible to visualize chromosomal translocations, such as EWSR1 rearrangements, with this methodology. 9/32 (28%) of cases had findings with diagnostic, prognostic or therapeutic significance. **Conclusions:** Copy number assessment of pediatric solid tumors by aCGH on FFPE tissue is feasible and reveals clinically relevant findings in a significant number of cases.

**1539 General Poster Session (Board #321), Sun, 8:00 AM-11:45 AM**

**Argentinean Jewish population frequencies for common mutations in BRCA1, BRCA2, and CHEK2.** *Presenting Author: Paola Jablonski, Centro Nacional de Genética Médica, ANLIS, Ministerio de Salud de la Nación, Buenos Aires, Argentina*

**Background:** Specific founder mutations 187_188delAG; 5385_5386insC and A1708E in BRCA1 and 6174delT and IVS2+1G>A in BRCA2 have been reported in Jews of Israel and United States. Moderate penetrance alleles 1100 delC, p.I157T and c.IVS2 +1G>A in CHEK2 gene explain part of non-BRCA aggregation of breast cancer (BC) in this ethnic group. The Jewish population of Argentina is the largest in Latin America and the third in the American continent and their genetic epidemiology is unknown. The aim of this study was to screening for these alleles in an Argentinean series of Jewish high risk families for BC/ovarian cancer (OC). **Methods:** A total of 183 DNA samples were genotype by sequencing for BRCA1/2 mutations and by PCR-RFLP for CHEK2 variants. **Results:** Among 135 unrelated proband cases, 67% were only BC, 4% BC and OC, 6% BC and other cancer; 8% OC, 2% Melanoma, 2% other cancer and 11% asymptomatic individuals. Overall, 20% were mutation carriers, 65,4% in BRCA1, 11/187_188delAG, 6/5385_5386insC and 34,6% in BRCA2, 9/6174delT. One patient was double heterozygous for 187_188delAG-6174delT. Five of the seven OC were in 187_188delAG probands. All the 5385_5386insC carriers with BC were bilateral or associated with other cancer. The 5385_5386insC mutation was found in carriers in whom the diagnoses of BC/OC were made at an earlier age. Seven intronic BRCA1/BRCA2 variants including two previously unreported IVS1-106 A>G in BRCA1 and IVS1-36 C>T in BRCA2 and the missense variant c.6100 C>T in BRCA2 were observed. Bioinformatics predictions suggested that the non coding variants could be polymorphisms and the missense mutation could modify the structure of the BRCA2 protein and their function. The BRCA1/BRCA2 A1708E and c.67+1G>A mutations and the CHEK2 variants were not found in this series. **Conclusions:** This study demonstrates that 187_188delAG; 5385_5386insC and 6174delT mutations were seen in a significant proportion of Argentinean Ashkenazim high risk families of undergoing genetic testing for BC/OC. The two founder mutations A1708E and c.67+1G>A in Jews of Sephardic origin and the three of most predisposing variants of *CHEK2* did not have major contribution in our population.

**1540 General Poster Session (Board #322), Sun, 8:00 AM-11:45 AM**

**Using next-generation sequencing (NGS) to identify causative mutations in Asian cancer (CA) patients with suspected Lynch syndrome.** *Presenting Author: Samuel Guan Wei Ow, Department of Haematology-Oncology, National University Cancer Institute, Singapore, National University Health System, Singapore, Singapore*

**Background:** Although at least 6 known genes are implicated in the causation of Lynch Syndrome (LS), up to 50% of suspected cases are due to undefined genes. We utilised NGS to characterize the mutation profile of high risk CA patients suspected with LS. **Methods:** We enrolled 96 Asian CA patients from our CA Genetics Clinic from 2000 to 2012 with family history (FH) suspicious for LS, and obtained germline DNA for targeted sequencing of 94 CA-predisposition genes using TruSight Cancer (Illumina Inc, San Diego, USA) on the MiSeq platform. Polymorphisms at >1% frequency were removed using 1000 Genomes (Asian) and the remaining non-synonymous variants were classified with reference from InSiGHT database. **Results:** Of the 96 index patients, 81.3% were Chinese, median age at CA diagnosis was 45.5 (range 18-82), 85.4% and 8.3% each had colon CA (CRC) and a LS-like CA. 5/96 patients had FH that fulfilled Amsterdam I/II Criteria (AC), 38 had FH of CRC and at least 1 first degree relative (FDR) with LS-like CA, 28 had CRC with histopathological features suggestive of LS, 30 had young-onset CA <50y (26 CRC, 4 LS-like CA), and 4 had more than 1 primary LS-related CA. 24 cases (not fulfilling AC) have been sequenced to date with a minimum depth of 400X. Among classical LS-related genes, 2/24 patients were found with deleterious mutations in *MSH2* (nonsense mutation at *1255C*>T; splicing mutation at *942G>A*), 2/24 with insertion mutation in *MSH6* resulting in frameshift (*4065_4066insTTGA*) and 1/24 had a possibly deleterious missense mutation in *MLH1* (*1058C>T*). In addition, 18 nonsense mutations were found in the coding regions of *AIP*, *BRIP1*, *BMPR1A*, *CEP57, CHRNA3, ERCC2*, *FANCD2*, *FANCM*, *GATA4*, *GPC3*, *MLPH*, *NSD1, PTCH1, TIMM10B* and *XPC* which warrant further investigations. 15 novel variants in the classical LS-related genes were detected (2 *MLH1*, 6 *MSH2*, 2 *MSH6*, 1 *PMS1*, 1 *PMS2*, 3 *EPCAM*) of which *EPCAM 344T>A* and *515C>A* occurred in 21 and 6 index patients respectively. **Conclusions:** Genetic variants unique to Asian high risk CA patients have been revealed in this study. NGS is a feasible and cost-efficient way to screen for causative mutations in a spectrum of genes in CA patients suspected to have a hereditary predisposition.

**1541 General Poster Session (Board #323), Sun, 8:00 AM-11:45 AM**

**Evaluation of breast cancer incidence in Lynch syndrome patients by MMR gene.** *Presenting Author: Jamie Willmott, Myriad Genetic Laboratories, Inc., Salt Lake City, UT*

**Background:** The current literature is divided as to whether or not breast cancer (BC) is a feature of Lynch syndrome (LS). The aim of this analysis was to investigate the prevalence of BC in patients with mutations in the individual mismatch repair (MMR) genes that cause LS. **Methods:** A retrospective review of patients' personal and family history of cancer was performed on patients with LS-causing mutations. All patients that underwent full sequencing and/or large rearrangement testing for mutations in *MLH1*, *MSH2*, *MSH6*, *PMS2* or *EPCAM* at Myriad Genetic Laboratories between September 2006 and October 2013 were included. Patients were excluded if they only had single site testing for a known LS mutation or if they were known to have a mutation in *BRCA1* or *BRCA2*. A Pearson chi-square test was performed to determine if the prevalence of breast cancer was significantly different among individual MMR genes. Exact confidence limits for binomial proportions were then computed. **Results:** A total of 5,638 patients with a LS-causing gene mutation were identified and the proportion of patients with BC was calculated for each gene. A chi-square test shows that at least one of these proportions is statistically significantly different from the others (p=0.007). The percentages (with 95% confidence intervals (CI)) of patients with BC by gene are 5.9% (4.6% - 7.5%) for *MSH6*, 4.0% (2.2 % - 6.8%) for *PMS2*, 3.7% (3.0% - 4.5%) for *MSH2*, 3.2% (2.5% - 4.1%) for *MLH1*, and 1.8% (0.05% - 9.7%) for *EPCAM*. **Conclusions:** The confidence interval for the proportion of *MSH6* carriers with BC does not overlap with those for *MLH1* and *MSH2*. Our results suggest that a personal history of BC is more prevalent in *MSH6* mutation carriers than in LS patients with mutations in other MMR genes. This may explain some of the confusion surrounding the inclusion of BC as a Lynch syndrome-associated cancer. Rather than taking an approach of accepting or rejecting that BC is associated with LS as a whole, it may be more appropriate to define BC risks by specific MMR gene or a broader panel of genes.

| | *MLH1* N=1857 | *MSH2* n=2372 | *MSH6* n=1032 | *PMS2* n=322 | *EPCAM* n=55 |
|---|---|---|---|---|---|
| Personal history of breast cancer - n (%) [95% CI] | 60 (3.2%) [2.5% - 4.1%] | 87 (3.7%) [3.0% - 4.5%] | 61 (5.9%) [4.6% - 7.5%] | 13 (4.0%) [2.2% - 6.8%] | 1 (1.8%) [0.05% - 9.7%] |

**1542 General Poster Session (Board #324), Sun, 8:00 AM-11:45 AM**

**Analysis of patients with two hereditary cancers (breast/ovarian or colon/endometrial) who met NCCN genetic testing criteria after their first cancer.** *Presenting Author: Jennifer Saam, Myriad Genetic Laboratories, Inc., Salt Lake City, UT*

**Background:** Patients with Hereditary Breast and Ovarian cancer (HBOC) or Lynch syndrome (LS) hereditary cancer syndromes are at a greater risk for developing second cancers after an initial cancer diagnosis. The identification of these patients after the first cancer can lead to the prevention or early identification of second cancers. **Methods:** We surveyed a commercial laboratory database for *BRCA1* and *BRCA2* mutations detected among patients with both breast and ovarian cancer tested from Sept. 2006-Oct. 2013. We also reviewed the database for the presence of LS mutations among patients diagnosed with both colon and endometrial cancers who received testing from May 2008-Oct. 2013. We evaluated the prevalence of mutations based on age of diagnosis of the first cancer and examined patient personal cancer history to determine what percentage of the positive patients would have met NCCN guidelines based on the diagnosis of their first cancer (defined as ovarian cancer at any age, breast cancer at age of 45 or less for HBOC, and endometrial or colon cancer less than age 50 for LS). Personal and family history was provided by the health care provider on the test order form. **Results:** For patients diagnosed with both breast and ovarian cancer (N=9982), the prevalence rate of *BRCA1* and *BRCA2* mutations was 22.4% (peak mutation rate of 35.8% for patients in their 30s). Of *BRCA1* and *BRCA2* mutation carriers, 56.0% met criteria for genetic testing after their first cancer—20.5% diagnosed with ovarian cancer first and 35.5% with breast cancer at or under age 45 as their first cancer. Patients diagnosed with colon and endometrial cancer (N=941) had mutations in the LS genes at a prevalence rate of 28.1% (peak mutation rate of 46.7% for patients in their 40s). Of mutation carriers, 65.2% met guidelines for LS testing after the first cancer, 30.7% with colon cancer at age 49 or younger and 34.5% with endometrial cancer younger than age 50. **Conclusions:** This review of commercial testing data for hereditary cancer syndromes shows the importance of diagnosing patients with hereditary cancer syndromes after their first cancer so a second cancer can be prevented or detected early with improved screening.

**1543 General Poster Session (Board #325), Sun, 8:00 AM-11:45 AM**

**Predictors of weight gain in breast cancer survivors.** *Presenting Author: Iram T. Azam, Northwestern University, Chicago, IL*

**Background:** Obesity and weight gain are important risk factors in the development of breast cancer. Weight gain in breast cancer patients is associated with a decreased response to adjuvant chemotherapy, increased cancer recurrence, and worse overall prognosis. Recent genomic studies indicate specific single nucleotide polymorphisms (SNPs) of the fat mass and obesity-associated gene (*FTO*) are associated with obesity and breast cancer risk. Little is known about factors contributing to weight gain in breast cancer patients receiving different treatment regimens. **Methods:** We performed a prospective cohort study of 120 women recruited from Northwestern University, Robert H. Lurie Cancer Center. Measurements of body mass index, nutritional status, and exercise levels were obtained at baseline and 6 month increments over a 24-month period. Chart review was conducted to obtain demographics, tumor characteristics (ER/PR/HER2 status, tumor size, stage, lymph node metastases), and treatment regimens. Blood samples were genotyped for 4 single nucleotide polymorphisms in *FTO*. **Results:** The percentage of patients gaining weight after diagnosis was 45.3% and 60.9% at the 12 and 24 month follow up, respectively. Chemotherapy and endocrine therapy were not associated with weight gain, even after controlling for age, race, baseline BMI, nutritional status, and exercise levels. PR+ patients were more likely to gain weight (p=0.02). FTO SNPs rs9939609 (A/T) and rs1477196 (A/G) were associated with weight gain. **Conclusions:** The majority of women with breast cancer gained weight after diagnosis, and this was most frequently observed in women with PR+ status and 2 of the identified FTO SNPs. Future studies should explore if the risk for weight gain associated with these factors may be attenuated by specific lifestyle interventions and treatment regimens.

**1545 General Poster Session (Board #327), Sun, 8:00 AM-11:45 AM**

**Effect of reproductive factors and lifestyle on the onset of breast cancer in female BRCA 1 and 2 mutation carriers.** *Presenting Author: Christian F. Singer, Medical University of Vienna, General Hospital, Vienna, Austria*

**Background:** We have recently demonstrated that the onset of breast cancer (BC) in BRCA 1 and 2 mutation carriers is influenced by their birth year, thus indicating a risk-modifying role for reproductive and life style factors. We now examined possible associations between potential risk factors, birth cohorts, and the onset of BC in BRCA1 and 2 mutation carriers. **Methods:** 130 female BRCA1 and 67 BRCA2 mutation carriers who had been identified at the Vienna University Hospital between 1995 and 2013, and who had developed BC were included in the analysis. Individual reproductive and life style factors were identified by questionnaires. Cox regression analysis and log-Rank testing were used to estimate the effect of potential risk factors on the onset of BC. **Results:** BRCA mutation carriers who had never been pregnant developed BC at a younger age than those who had been pregnant at least once (36.4 vs 40.9; p=0.001). Similarly, women who had used oral contraceptives, or had smoked, developed BC earlier than never users (39.3 vs. 44.9 years; p=0,0001, and 39.0 vs. 41.4 years; p=0,05, respectively). In Multivariate analysis oral contraceptive use (HR:1.7; p=0.006), and date of birth ≥1965 (HR:4.5; p=0.001) were associated with an earlier BC-onset. Conversely, the more full-term pregnancies a woman had experienced, the longer her BC-onset was delayed (HR:0.2; p=0.04). Mutation carriers born ≥1965 developed BC at a median age of 42 years whereas the median age at diagnosis for women born <1965 was 58 years (p<0.0001 log Rank test). These women were also more likely to have experienced multiple pregnancies and to have breastfed, but were less likely to have used oral contraceptives or to have smoked. **Conclusions:** We here demonstrate that in BRCA1 and 2 mutation carriers the birth-cohort-associated differences in the onset of BC are profound and largely influenced by reproductive factors such as the number of pregnancies and the use of oral contraceptives.

**1546 General Poster Session (Board #328), Sun, 8:00 AM-11:45 AM**

**How are young women 18-24 counseled on hereditary breast and ovarian cancer (HBOC) testing?** *Presenting Author: Amy Abramowitz, Feinberg School of Medicine, Northwestern University, Chicago, IL*

**Background:** Women often learn about their HBOC risk before the age of 25 (Bradbury 2009), and women 18-24 are often interested in genetic testing (Werner-Lin 2012). While guidelines do not preclude this, they do not provide specific guidance on genetic counseling or testing for women 18-24 (18-24s). We aim to identify how genetic counselors (GCs) counsel these women, what challenges they experience, and how these challenges may be addressed. **Methods:** IRB approved interviews with GCs at NCCN centers. The framework approach of qualitative research and simple frequencies were used for analyses. **Results:** Phone interviews were conducted with GCs from 11 NCCN centers. Although 73% of GCs use age and life stage considerations in counseling, only 45% routinely recommend testing for 18-24s. Those who test 18-24s routinely, cite the following reasons: studies show these women handle testing with maturity; women need genetic information for family / health planning; some 18-24s are diagnosed with cancer; and women consider recommendation to wait until 25 paternalistic. GCs who do not routinely recommend testing to 18-24s (55%) cite these barriers: lack of screening guidelines for 18-24s beyond self-exams; concern that families coerce 18-24s into testing; and perceived lack of understanding of available options by 18-24s. However, 80% of those who do not routinely test 18-24s, may do so on exception: very young HBOC family history, patient requests testing multiple times and demonstrates understanding of implications, or a woman needs the information for family planning. GCs provided recommendations for improving the genetic services for 18-24s: formal training and standardized approach to counseling (55%), frequent and long term follow-up using a "medical home" model (45%), involvement of psychosocial and fertility specialists (27%), and access to 18-24 peer support (27%). **Conclusions:** Lack of guidelines on genetic counseling and testing of women 18-24 result in variability of HBOC counseling and testing practices and potentially sub-optimal care for these women. Counselors and patients would benefit from formalized guidelines and training on genetic assessment for women 18-24.

**1547 General Poster Session (Board #329), Sun, 8:00 AM-11:45 AM**

**The landscape of precision medicine cancer clinical trials in the United States.** *Presenting Author: Nitin Roper, New York Presbyterian Hospital-Cornell & Hospital for Special Surgery, New York, NY*

**Background:** Advances in tumor biology and high throughput genomic analysis have ushered in the era of precision cancer medicine. Little is currently known, however, about the landscape of prospective "precision medicine" cancer clinical trials in the U.S. **Methods:** We identified all adult interventional cancer trials registered on clinicaltrials.gov between September 2005 and May 2013. Trials were classified as "precision medicine" if testing for a specific genomic or protein alteration in tumor tissue was required for enrollment. Characteristics such as type of genomic/proteomic alteration tested, masking, phase, sponsor, accrual and cancer subtype were ascertained for each trial. **Results:** Of the initial 18,797 trials identified, 9,094 (48%) were eligible for inclusion. 905 (10%) were classified as precision medicine trials and 8,189 (90%) were non-precision medicine trials. Compared with non-precision medicine trials, precision medicine trials were more likely to be phase II (OR 1.44 (1.25-1.65), p<0.0001) or phase III (OR 1.27 (1.01-1.60), p=0.0419), randomized (OR 1.19 (1.02-1.38), p=0.0270), sponsored by industry (OR 1.37 (1.19-1.58), p<0.0001), and multi-center (OR 1.63 (1.41-1.88), p<0.0001). The percentage of precision medicine trials compared to the total number of trials increased from 5% in 2006 to 17% in 2013. Precision medicine trials required testing for 33 unique genomic/proteomic aberrations for enrollment. The most common cancer subtypes were breast (40%), skin (15%), lung (9%), and hematologic (6%). **Conclusions:** The proportion of adult cancer clinical trials in the U.S. requiring the presence of a specific genomic/proteomic tumor aberration for enrollment has increased substantially over the past several years. However, such trials still represent a small minority of studies performed within the cancer clinical trials enterprise.

**1548 General Poster Session (Board #330), Sun, 8:00 AM-11:45 AM**

**The clinical experience: Hereditary cancer testing by a 25-gene panel.** *Presenting Author: Elias Obeid, Fox Chase Cancer Center, Philadelphia, PA*

**Background:** Prior to next generation sequencing (NGS) technology, genetic testing for hereditary cancer risk was gene and syndrome-specific. Fox Chase Cancer Center began offering patients a 25-gene panel, utilizing NGS, through a commercial early access clinical program in September of 2013. This panel includes *BRCA1/2* and other high/moderate risk genes for breast, colon, and other cancers. The utilization of this panel test compared to syndrome-specific testing has not been assessed in a clinical setting. Here we describe our clinical experience with this new testing option. **Methods:** Patients were offered a choice between syndrome-specific testing and a 25-gene panel from Myriad Genetics Laboratories. Of 152 tests ordered from September 4, 2013 to January 24, 2014, results were available for 144 patients. All tested patients met NCCN criteria for genetic testing or were deemed appropriate for testing after assessment by a certified genetic counselor. **Results:** Of 144 test results available, 87 had 25-gene panel testing, 26 had syndrome-specific testing for *BRCA1/2*, and 31 had targeted testing (Ashkenazi panel, single site, or deletion/duplication analysis). In the *BRCA1/2* test group, a deleterious mutation was seen in 3/26. Of note, 12/26 patients declined the 25-gene panel. From 87 patients in the 25-gene panel, 8 had clinically positive results for a deleterious gene mutation of which 3 (3/8, 37.5%) were unanticipated test results that influenced clinical management (mutations in *ATM*, *APC*, and *RAD51D*). All 8 individuals were affected with cancer. We found a high rate of variants of unknown significance (VUS) (29/87, 33.3%), as well as a high rate of monoallelic deleterious mutations in *MYH* (5/87, 5.7%). **Conclusions:** Multigene panel testing is now available for patients seeking genetic identification of an inherited predisposition to cancer. Our experience indicates that such a multigene panel may yield results that would not otherwise be discovered through syndrome-specific testing, and may provide additional clinical guidance. However, results can have uncertain clinical impact given the high VUS rate as well as other findings, such as monoallelic *MYH*, for which there is no clear medical management at the present time.

**1549 General Poster Session (Board #331), Sun, 8:00 AM-11:45 AM**

**Implications of following the guidelines for genetic testing and MRI use for breast cancer.** *Presenting Author: Fernanda C. G. Polubriaginof, Massachusetts General Hospital, Boston, MA*

**Background:** Evidence-based medicine is based upon the use of established guidelines and algorithms to increase the quality and decrease the cost of medical care. Genetic testing for breast cancer gene mutations is offered to women who have a risk ≥ 10% of carrying a mutation or that meet the NCCN Guidelines. Screening with breast magnetic resonance imaging (MRI) is recommended for women who have a lifetime risk ≥ 20% of developing breast cancer. Our purpose is to evaluate the impact of using guideline based care for these medical issues. **Methods:** With institutional review board approval, we performed a retrospective analysis of data obtained from consecutive women who presented for breast imaging to the Newton Wellesley Hospital Breast Imaging Center from September 3, 2013 to December 31, 2013. Demographic characteristics and breast cancer risk factors were entered into software to evaluate risk (HughesRiskApps) for BRCA mutation, for genetic testing eligibility, for lifetime risk of breast cancer and for MRI eligibility. Risk of mutation was evaluated by Tyrer Cuzick Versions 6 and 7, BRCAPRO and the Myriad Model. Genetic testing eligibility was determined by risk of mutation ≥ 10% or by meeting the NCCN Guidelines. Lifetime risk of breast cancer was evaluated by Tyrer Cuzick Versions 6 and 7, BRCAPRO and Claus. Eligibility for MRI was determined by a lifetime risk ≥ 20% (Per ACS and NCCN Guidelines). **Results:** A total of 10,604, were evaluated, of whom 9,976 (94.08%) had no personal history of breast cancer and 628 (5.92%) had a personal history of breast cancer. See Table. **Conclusions:** Following the guidelines for BRCA testing and for MRI screening will result in a large number of women undergoing these services. It would be useful to evaluate whether following these guidelines does increase quality and decrease the cost of care.

| Genetic testing eligibility | No. of patients (%) |
|---|---|
| **Without breast cancer (n=9,976)** | |
| **Risk of mutation ≥ 10%** | 346 (3.50%) |
| **Meets NCCN guidelines** | 1,683 (17.00%) |
| **With breast cancer (n=628)** | |
| **Risk of mutation ≥ 10%** | 105 (17.00%) |
| **Meets NCCN guidelines** | 403 (64.00%) |
| **Eligibility for MRI** | |
| **Without breast cancer (n=9,976)** | |
| **Lifetime risk ≥ 20%** | |
| **Tyrer Cuzick 6, BRCAPRO, Claus** | 558 (5.59%) |
| **Tyrer Cuzick 6 and 7, BRCAPRO, Claus** | 1,495 (14.98%) |

**1550 General Poster Session (Board #332), Sun, 8:00 AM-11:45 AM**

**Genetic anticipation in *BRCA1/2* families after controlling for ascertainment bias and cohort effect.** *Presenting Author: Rodrigo Santa Cruz Guindalini, Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil*

**Background:** Although genetic anticipation has been reported in hereditary breast and ovarian cancer syndrome (HBOCS), little is understood about the underlying genetic and molecular mechanisms for *BRCA1/2* families. Two previously unaddressed biases affecting the accuracy of previous studies are ascertainment bias and cohort effect. **Methods:** We retrospectively reviewed 178 pedigrees of *BRCA1/2* families who had at least two consecutive generations of the same cancer (breast or ovarian) in our Cancer Risk Clinic registry. Using paired t-test and BRCAPRO scores as analytical weights in a parametric anticipation model, the calculation of generational differences in breast/ovarian cancer age of onset was performed. This model was then modified to control for ascertainment bias by excluding probands. Multilevel linear regression using breast cancer age of onset, birth year cohort, and generation was applied to study potential cohort effect. **Results:** Earlier onset of breast cancer and ovarian cancer in successive generations was found (Table). After controlling for ascertainment bias, statistically significant anticipation phenomenonpersisted only for breast cancer. In the cohort effect analysis, generational differences in age of breast cancer onset were not significant but earlier onset in later birth cohorts was significant. **Conclusions:** To our knowledge, this is the largest study that exclusively included families with deleterious *BRCA1/2* mutations, controlled for ascertainment bias, and used individual risks of having *BRCA1/2*mutations as analytical weights to address and report significant anticipation phenomenon in HBOCS. The observed anticipation effect is due to a decrease in age of onset in the cohort over time and not generational differences. Future studies are warranted to confirm these findings.

**Anticipation phenomenon in BRCA1/2 families.**

| Breast cancer, N=579 | | | | | Ovarian cancer, N=81 | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Gen | N | Mean AOO (y) | Δ From Gen 3 (y) | P | Gen | N | Mean AOO (y) | Δ From Gen 3 (y) | P |
| **1** | 81 | 51.8 | 9.8 | <0.001 | **1** | 14 | 57.1 | 8.4 | 0.013 |
| **2** | 225 | 48.7 | 6.8 | <0.001 | **2** | 36 | 53.5 | 4.8 | 0.048 |
| **3*** | 242 | 41.9 | 0 (ref.) | | **3*** | 27 | 48.8 | 0 (ref.) | |
| **4** | 31 | 34.7 | -7.2 | 0.002 | **4** | 4 | 38.3 | -10.5 | 0.038 |

Abbreviations: AOO, age of onset; Gen, generation; y, years; ref, reference. *, probands' generation.

**1551 General Poster Session (Board #333), Sun, 8:00 AM-11:45 AM**

**Are immunohistochemical (IHC)/microsatellite instability (MSI) testing necessary as part of Lynch syndrome work-up in the era of multiplex genetic testing?** *Presenting Author: Ahmad Fitri Idris, Mater Misericordiae University Hospital, Dublin, Ireland*

**Background:** IHC for mismatch repair proteins and MSI are commonly used to direct genetic testing for Lynch Syndrome. Abnormal results in the setting of a positive family history often lead to genetic testing for Lynch syndrome. The often cumbersome process of completing IHC/MSI requires obtaining stored tissue +/- blood from a family member affected with cancer. Upfront genetic testing is not favoured due to concerns about identifying variants of uncertain significance. We performed a review of Lynch syndrome work-up in Ireland, and propose a model that is the reverse of the current international standard, and may expedite and simplify work up of these families. **Methods:** Data was ascertained from three cancer genetics services in Dublin and included the following variables: Date of birth, date of request and reporting results for IHC, MSI and genetic tests. Time intervals were determined for LS work-up for all patients who had the process initiated in these 3 centres. **Results:** Probands from 50 families referred for LS work-up were included.The median time from date of IHC request to date of IHC report (total of 50 patients) was 4 weeks (range: 4 days to 36 weeks). The median time between date of IHC request to date of MSI report (n = 32 patients) was 20 weeks (Range: 4 to 56 weeks). The median time from date of genetic test request to date of result (n = 9 patients) was 9 weeks (Range: 2 to 26 weeks). The median time for completion of all 3 tests in one individual (n=3 patients) was 14 weeks (Range: 10 to 60 weeks). **Conclusions:** The diagnostic pathway for Lynch syndrome is cumbersome and often lengthy. Appropriate upfront multiplex genetic testing would expedite the identification of mismatch repair gene mutation carriers. IHC/MSI testing could be used to characterise variants of uncertain significance.

**1552 General Poster Session (Board #334), Sun, 8:00 AM-11:45 AM**

**Impact of an interventional counseling procedure in BRCA families: Efficacy and safety.** *Presenting Author: Erica Sermijn, Familial Cancer Clinic and Medical Oncology, Brussels University Hospital, UZ Brussel, Brussels, Belgium*

**Background:** Predictive genetic testing has high impact on cancer prevention for BRCA carriers. Passing information in BRCA families on the availability of testing is important. In most countries this is mainly proband - mediated, but this path is defective, and denies relatives lifesaving information.This study assessed the safety/ efficacy of an intervention, aiming at actively informing relatives. **Methods:** Sequential prospective study in new BRCA families. First the proband told relatives about the hereditary trait/predictive testing (standard procedure; phase I). After 6 months a letter was sent to adult relatives, who had not been reached (study; phase II). The letter provided vital information, preserving the probands' anonymity. Contact info and an inquiry form probing the acceptability were provided. After the letter a phone call was made to obtain a final notion of their wishes. All subjects received a psychometric test (State - Trait Anxiety Inventory, STAI), an interview, and routine counseling. **Results:** Twenty families were included. Of 172 relatives at risk, 89 participated: 47 by the proband, 42 by the letter as the major trigger to seek counseling. Nearly all of these subjects (98 %) opted for predictive testing, of which 30 were mutation carriers. Subjects were satisfied with the intervention. Twenty-four of the eligible relatives could not be reached; 59 were 'decliners'. Reasons for not participating were: age, being male, having no child, prevention elsewhere, no interest. The intervention is psychologically safe: the 95 % CI for the estimated mean difference in STAI DY1 between phase II/I subjects, ( mean difference - 1.07, 95 % CI (-4.48;2.35), p=0.53), shows that the mean STAI DY1 score for phase II is at most 2.35 units higher than for phase I, which is not relevant. **Conclusions:** The practice of proband - based information tranfer in BRCA families is highly defective. A protocol in which relatives are directly informed by the counselor nearly doubles the number of relatives tested. This approach is psychologically safe and allows more carriers to adopt effective prevention. These results should lead to a change in counseling guidelines in families with a strong germline predisposition for cancer. Clinical trial information: 2005/087.

**1553 General Poster Session (Board #335), Sun, 8:00 AM-11:45 AM**

**Impact of 25-gene panel testing and integrated risk management tool on medical management in hereditary cancer syndrome evaluation.** *Presenting Author: Lucy R. Langer, Northwest Cancer Specialists, Portland, OR*

**Background:** The identification of patients (pts) with hereditary cancer syndromes such as Hereditary Breast and Ovarian Cancer (HBOC) or Lynch syndrome (LS) leads to profound clinical management changes. Using next generation sequencing, more comprehensive gene panels with greater sensitivity have been developed. However, most pts still receive a negative genetic test result. Integrating personal and family cancer history identified during the screening process with genetic test results can offer refined management recommendations. **Methods:** Patients identified using criteria for HBOC or LS were tested using a 25-gene hereditary cancer panel. Recommendations from testing incorporated the genetic test result and a personalized cancer risk and management tool (CRMT) based on a patient's personal and family history and professional guidelines. Health care providers (HCPs) were surveyed for their management advice to the patient for four cancers (breast, ovarian, endometrial and colon) before and after testing. Pre-test surveys were received from 1414 patients at the time of the data analysis. We report data from matched pre and post-test survey pairs for a preliminary 100 pts to be updated upon presentation. Interventions were ranked from least aggressive (surveillance) to most aggressive (surgery). **Results:** In this sample set, 48% of pts had a diagnosis of breast, ovarian, colorectal, endometrial, pancreas, melanoma, stomach and/or prostate cancer, 3% had a history of other cancers and 49% had no personal history of cancer. 65% of pts met NCCN guidelines for HBOC, 10% for LS and 18% met guidelines for both syndromes. Overall, HCPs used the genetic test result with the CRMT to guide their management decisions in 91% of cases. After testing, 25% of pts received a change in management recommendations, 60% of pts with a positive result and 23% of pts with a negative result. Of the management changes, 72% were in surveillance, 16% in chemoprevention, 20% in surgery and 28% other. **Conclusions:** Integrating expanded genetic panel test results with a personalized cancer risk and management tool aids HCPs in providing tailored cancer risk management in both gene positive and negative populations.

**1554 General Poster Session (Board #336), Sun, 8:00 AM-11:45 AM**

**Shortened telomere length to predict initiation of carcinogenesis in Lynch syndrome.** *Presenting Author: Grainne O'Kane, Mater Misericordiae University Hospital, Dublin, Ireland*

**Background:** Lynch Syndrome (LS) is an autosomal dominant cancer predisposition syndrome conferring a 60-80% lifetime risk of developing colorectal cancer in addition to a spectrum of other malignancies. This occurs as a consequence of germline mutations in DNA mismatch repair (MMR) genes. Significant phenotypic heterogeneity exists among LS families. Anticipation has also been reported but remains poorly understood. We investigated an association between age of tumour onset and telomere length in Irish LS families. **Methods:** Family pedigrees were reviewed and parent-child pairs (PCPs) with LS-associated malignancy identified. Patients with genetically confirmed LS were invited to participate in the study. Peripheral blood mononuclear cells were isolated from affected mutation carriers (AC) and unaffected mutation carriers (UAC). DNA was extracted and relative telomere length (RTL) measured by quantitative polymerase chain reaction. Pearson's correlation was used to compare age-adjusted RTL and age at tumour diagnosis. **Results:** Forty-four LS families were identified containing fifty-four PCPs with LS-associated malignancies. Anticipation was present in 90%; the median age of cancer diagnosis occurred 14.5 years earlier in mutation carriers (range 1-45 yrs). Telomere length has been analysed in fifty-one mutation carriers to date. (Table) As expected increasing age at blood withdrawal correlated with shorter telomere length ($p<0.05$). In AC the mean age-adjusted RTL was 1.281 and in UAC 0.980. In AC there was a strong correlation between earlier onset malignancy and shorter age-adjusted RTL ($p=0.004$). **Conclusions:** Anticipation is evident in Irish LS families and patients who develop earlier onset malignancy have shorter telomere lengths. We plan to validate our findings in a larger cohort and compare telomere length in an age and sex matched control cohort.

| | AC (N=25) | UAC (N=26) |
|---|---|---|
| **Male (N)** | 13 | 11 |
| **Female (N)** | 12 | 15 |
| **Median age cancer diagnosis (yrs.)** | 39 (22-77) | ------- |
| **Median age blood withdrawal (yrs.)** | 52.5 (30-88) | 40 (23-63) |
| **Mutation (N)** | | |
| **MLH1** | 14 | 11 |
| **MSH 2** | 9 | 10 |
| **MSH 6** | 2 | 3 |
| **PSM 2** | 0 | 2 |
| **EPCAM** | 0 | 0 |

**1555 General Poster Session (Board #337), Sun, 8:00 AM-11:45 AM**

**Classification of somatic variants in solid tumors detected by next-generation sequencing (NGS) and the need for clinical guidelines.** *Presenting Author: Antonios Papanicolau-Sengos, University of Utah, Salt Lake City, UT*

**Background:** NGS approaches to clinical mutation testing reveal previously uncharacterized, or poorly characterized, somatic variants. A major challenge in reporting is categorization of these variants in the absence of formal guidelines. The process is subjective and the potential for variation between molecular pathologists is significant. **Methods:** To better characterize variation between molecular pathologists we retrospectively reviewed 95 clinical cases sequenced with the Ion Ampliseq Cancer Hotspot Panel v2 at ARUP Laboratories. We focused on variants that were reclassified upon re-review by three molecular pathologists. **Results:** Ninety eight mutations and 31 variants of unknown significance (VUS) were reported in 72 total tumors. There were seven reclassifications (5% of total classifications) in seven different tumors (3 urothelial carcinomas, 1 bladder adenocarcinoma, 1 melanoma, 1 lung carcinoma, and 1 unknown). Most of these were point mutations and involved *FGFR1* (x1), *FGFR3* (x1), *CTNNB1* (x1), *RB1* (x1) and *PIK3CA* (x3). Six of seven were reclassified from mutation to VUS based upon insufficient evidence of oncogenicity. **Conclusions:** Five of the reclassifications involved actionable genes (*FGFR1*, *FGFR3*, and *PIK3CA*). The original classification of these as "mutation" was primarily based on in vitro data. A "mutation" classification implies there is sufficient evidence for an oncogenic change that may be amenable to targeted therapy. In vitro biochemical and cell biologic assays are artificial systems which may not fully recapitulate in vivo tumor behavior. This study emphasizes the subjective nature of variant classification and the need for the development of weighted criteria devised by a multidisciplinary panel of experts. Until then, it is of utmost importance that molecular pathologists develop systematic methods to determine the quality of available data. We propose a simple checklist to optimize the way variants are classified. We suggest that medical oncologists critically scrutinize the classification of variants as they appear in clinical reports.

**1556 General Poster Session (Board #338), Sun, 8:00 AM-11:45 AM**

**The clinicopathologic significance of FOXC1 in *BRCA*-mutant breast cancer.** *Presenting Author: Michael Phillip Choi, Cedars-Sinai Medical Center, Los Angeles, CA*

**Background:** BRCA1 breast cancer (BC) has been associated with the basal molecular subtype and BRCA2 with the luminal subtype but the biological basis for this is unknown. The forkhead box C1 (FOXC1) transcription factor has been identified as a marker of sporadic basal-like BC which correlates with a poor prognosis. Furthermore, loss of BRCA1 function has been shown to increase FOXC1 expression in BC cell lines resulting in aggressive cellular behavior. We investigated the clinicopathologic associations of FOXC1 expression in BRCA1/2 mutant BC. **Methods:** Review of our institutional database identified 37 BRCA1 and 35 BRCA2 mutation carriers treated for BC from 1995 to 2013. Immunohistochemical (IHC) staining of paraffin-embedded tissue sections was performed using a monoclonal FOXC1 antibody against nuclear FOXC1 protein and evaluated by two independent, blinded pathologists. The association of FOXC1 expression with clinical and pathologic variables was analyzed. **Results:** FOXC1 expression was identified in 21/37 BRCA1 mutant BC and 6/35 BRCA2 mutant BC on IHC (Table 1). Univariate analysis showed FOXC1 expression to be associated with younger age, higher tumor grade, higher Ki67%, triple negative/basal molecular subtype, and a lower number of positive lymph nodes. FOXC1 expression correlated with increased locoregional recurrence rates ($p = 0.05$) however there was no significant difference in overall survival between FOXC1 positive and negative BC. **Conclusions:** FOXC1 expression is more commonly seen in BRCA1 mutant BC than in BRCA2 mutant BC and is associated with aggressive pathological tumor characteristics and a higher rate of locoregional recurrence.

| | FOXC1 + *n* | FOXC1 - *n* | P-value |
|---|---|---|---|
| **No. of patients** | 27 | 45 | |
| **Age at diagnosis (mean years ± SD)** | 42.9 ± 13.3 | 50.7 ± 11.7 | 0.006 |
| **BRCA mutation** | | | 0.0007 |
| **BRCA1** | 21 | 16 | |
| **BRCA2** | 6 | 29 | |
| **Tumor Grade** | | | <0.0001 |
| **1** | 0 | 4 | |
| **2** | 1 | 18 | |
| **3** | 26 | 23 | |
| **ER status** | | | <0.0001 |
| **ER +** | 4 | 41 | |
| **ER -** | 23 | 4 | |
| **PR status** | | | <0.0001 |
| **PR +** | 2 | 38 | |
| **PR -** | 25 | 7 | |
| **Ki67 % (mean ± SD)** | 50.9 ± 21.9 | 19.9 ± 13.6 | <0.0001 |
| **Molecular subtype** | | | <0.0001 |
| **Luminal A** | 1 | 16 | |
| **Luminal B** | 1 | 26 | |
| **Basal** | 25 | 3 | |
| **Number of positive lymph nodes (mean ± SD)** | 0.1 ± 0.5 | 2.6 ± 5.6 | 0.009 |
| **Locoregional recurrence** | | | 0.0512 |
| **No** | 24 | 45 | |
| **Yes** | 3 | 0 | |
| **Disease-free survival (mean months ± SD)** | 80 ± 74 | 67 ± 48 | 0.948 |
| **Overall survival (mean months ± SD)** | 102 ± 94 | 78 ± 58 | 0.958 |

**1557 General Poster Session (Board #339), Sun, 8:00 AM-11:45 AM**

**Familial clustering and predisposition to HPV-associated malignancy.** *Presenting Author: Judith Conroy, University College Dublin, Dublin, Ireland*

**Background:** Familial clustering of cervical cancer occurs, with a likely heritable component, but the genetic etiology of this disease is poorly understood. Human Papilloma Virus (HPV) is ubiquitous and HPV infection is common. The majority of infected individuals are asymptomatic. A minority of individuals fail to clear HPV infection and a subset of this cohort develop HPV-associated malignancy. We hypothesized the presence of an inherited predisposition to carcinogenesis following HPV infection in an Irish family with a striking number of HPV-related malignancies, and performed a linkage analysis to identify a susceptibility region. **Methods:** DNA was extracted from blood samples ascertained from an Irish family with multiple individuals affected by HPV-associated malignancies.Twenty-four samples were genotyped using the Illumina HumanCytoSNP-12 microarray (Illumina Inc., San Diego, California). Non-parametric linkage was performed in two phases. The first phase of analysis included only those individuals who had a clinical diagnosis of Cervical or head and neck cancer (n=5) and individuals with no cancer diagnosis, and no abnormal smear tests to date (n=2). The second phase of analysis included an additional 7 female patients who have had positive smear tests. **Results:** One early onset head and neck cancer, 4 cervical cancer, and 7 cases of cervical dysplasia occurred in this family. For phase 1 analysis, five loci with LOD scores >0.5 were identified on chromosomes 2p11.2-q13, 7q32.3-34, 11q23.3-25, 12p13.33-13.2 and 17q12-23.2 (LOD>0.5). Non-parametric linkage ruled out all but one of the Phase 1 linkage peaks. A single linkage peak of length was identified on chromosome 17q21.31-33 (6Mb, Z score > 2.3, LOD >1.13, p<0.01). **Conclusions:** We identified an association between 17q21.31-33 and HPV-associated malignancy in an Irish family with multiple affected individuals. Fine mapping of this region is underway and will be reported.

**1558 General Poster Session (Board #340), Sun, 8:00 AM-11:45 AM**

**Association of the *HOXB13 G84E* mutation with increased risk for prostate cancer and other malignancies.** *Presenting Author: Jennifer Beebe-Dimmer, Karmanos Cancer Institute, Wayne State University, Detroit, MI*

**Background:** A rare non-conservative substitution (G84E) in the highly conserved MEIS-interacting domain of the homeobox transcription factor gene *HOXB13* has been shown to be associated with an increased risk of prostate cancer. The gene is involved in human embryonic development including the prostate gland, but its role in carcinogenesis is unknown. DNA samples from 9,012 male patients included in the Mayo Clinic Biobank (MCB) were genotyped to determine the frequency of the G84E mutation in this population and its association with various reported cancers. **Methods:** Subjects were genotyped using a custom TaqMan (Applied Biosystems) assay for G84E (rs138213197). In addition to donating a blood specimen, all MCB participants completed a baseline questionnaire to collect information on medical history, family history, and behavioral characteristics. The frequency of the allele was determined according to both self-report of invasive cancer diagnoses and report of cancer history among first-degree relatives. **Results:** Forty-nine of 9,012 male patients in the MCB were carriers of G84E (0.5%). Analyses were restricted to those patients with information on history of specific cancers based upon either self-report or electronic medical record. Thirty-one percent (n=2,595) of participants had been diagnosed with cancer, including 46.9% of G84E carriers compared to just 28.7% of non-carriers (p=0.006). G84E was most frequently observed among men with prostate cancer with a carrier frequency of 1.3% compared to 0.4% of men with no history of any invasive cancer (p<0.0001). However, the mutation was also more commonly observed in men with bladder cancer (p=0.06) and leukemia (p=0.01). G84E carriers were more likely to have a positive family history of prostate cancer in a first degree relative compared to non-carriers (43.6% v. 18.6%, p=0.0003). **Conclusions**: Our study confirms the association between the rare *HOXB13* G84E variant and prostate cancer. We have also shown novel associations between G84E and both bladder cancer and leukemia. Future investigation is warranted to confirm these associations in a larger data set in order to improve our understanding of the role of germline *HOXB13* mutations in human cancer.

**1559 General Poster Session (Board #341), Sun, 8:00 AM-11:45 AM**

**BRCAPRO 6.0 model validation in male patients presenting for *BRCA* testing.** *Presenting Author: Zahi Ibrahim Mitri, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Male breast cancer accounts for < 1% of male cancers. Patients carrying a BRCA mutation are at higher risk of developing breast, pancreatic and prostate cancers among others. BRCAPRO is a risk model used during counseling to estimate risk of being BRCA+. The purpose of this analysis is to evaluate the accuracy of BRCAPro 6.0 in estimating the risk of a man carrying a BRCA mutation. **Methods:** This IRB-approved retrospective chart review was of 147 male patients who presented to MD Anderson Cancer Center between 02/1997 and 09/ 2011 for genetic counseling and had BRCA testing performed. All patients had their BRCAPRO risk assessment calculated by using the BRCAPro 6.0 clinical cancer gene assessment software (http://www4.utsouthwestern.edu/breasthealth/cagene/). The statistical software SPSS 20.0 was used to obtain results including descriptive statistics, independent sample t-test and receiver operating curve (ROC). **Results:** The median age of the cohort was 59 years (18-87). Of the 147 patients, 53 (36%) tested positive and 94 (64%) tested negative for a BRCA mutation. Among those who tested positive, 22 patients had a positive BRCA1 mutation, 30 had a positive BRCA2 mutation, and one patient was positive for both BRCA1 and BRCA2 mutation. Of the 147 patients, 50 (36%) underwent predictive testing for a known family mutation. Median BRCAPro score for all patients was 12.16 (range: 0.02-100), 48.93 (range: 0.02-100) for patients who tested positive, and 5.96 (range: 0.05-51.16) in those who tested negative. Forty-five patients (31%) had breast cancer, 16 of which tested positive for a BRCA mutation. 37 patients (25%) had no cancer diagnosis, and 65 patients (44%) carried a different cancer diagnosis: pancreatic (26%) and prostate (12%) cancer were the most common. There were 23 patients (16%) with multiple cancer diagnosis. Independent samples Mann-Whitney test revealed a significant difference between positive and negative test results for BRCAPro 6.0 ($p<0.001$). The ROC curve had an AUC of 0.819 and a standard error of 0.038. **Conclusions:** Given the results of the analysis, BRCAPro 6.0 appears to be a good predictive test to determine BRCA carrier risk in male patients. These results should be further evaluated in a larger cohort.

**1560 General Poster Session (Board #342), Sun, 8:00 AM-11:45 AM**

**Women from certain BRCA1/2-mutation–negative hereditary breast ovarian cancer families and consideration of prophylactic saplingo-oophorectomy before menopause.** *Presenting Author: Rozumna-Martynyuk Nataliya, Mater Misericordiae University hospital, Dublin, Ireland*

**Background:** Prophylactic salpingo-oophorectomy (PSO) is recommended at 35-40 years for BRCA1 mutations carriers and 40-45 years for BRCA2 mutation carrier. The optimal timing of PSO is less certain for women from BRCA1/2 mutation negative hereditary breast ovarian cancer (HBOC) families. There is an increasing trend to defer this surgery until after menopause. We explored the safety of this approach if it were to be adopted in BRCA1/2 wild-type HBOC families. **Methods:** BRCA1/2 mutation negative families with at least one case of ovarian cancer were identified in an Irish cancer genetics clinic. Four generation family pedigrees were reviewed and clinical data recorded including cancer diagnosis, and age at diagnosis. **Results:** 680 women underwent BRCA1/2 diagnostic testing. Forty-four families with breast and ovarian cancer were BRCA1/2 mutation wild-type. 113 (age range: 28-77, median=47.9 years) of 936 women in these families developed breast cancer. There were 40 cases of ovarian cancer (age range: 27-79, median=53.9 years). Sixty-six percent of ovarian cancer occurred at </=60 years and 34% occurred at < /=50 years. Seven families had more than one case of ovarian cancer (OC)(table 1). In one family there were 7 cases. In 5 of these 7 families ovarian cancer was diagnosed at ages </= the average age of menopause (51 years). **Conclusions:** Pre-menopausal prophylactic salpingo-oophorectomy should be considered for women from BRCA1/2 mutation wild-type HBOC families.

| Family No | No of women in the family | OC cases, No | OC diagnosis, age | OC diagnosis, age | OC diagnosis, age | OC diagnosis, age | OC diagnosis, age | OC diagnosis, age |
|---|---|---|---|---|---|---|---|---|
| **688** | 26 | 2 | 48 | 40 | | | | |
| **507** | 15 | 3 | 60 | 40 | 60 | | | |
| **503** | 19 | 2 | 51 | 52 | | | | |
| **185** | 31 | 2 | 64 | 30 | | | | |
| **173** | 10 | 2 | 79 | unknown | | | | |
| **129** | 55 | 2 | 64 | 58 | | | | |
| **1** | 36 | 7 | 61 | 49 | 60 | 49 | 48 | Unknown |

**1561 General Poster Session (Board #343), Sun, 8:00 AM-11:45 AM**

**Biologic pathways, candidate genes, and molecular markers associated with quality-of-life domains.** *Presenting Author: Jeff A. Sloan, Mayo Clinic, Rochester, MN*

**Background:** There is now compelling evidence of a genetic foundation for patient-reported quality of life (QOL) domains. This work reports the results of a systematic review of thebiological pathways, candidate genes and molecular markers involved in fatigue, pain, negative (depressed mood) and positive (well-being/happiness) emotional functioning, social functioning, and overall QOL. **Methods:** We followed a purposeful search algorithm of existing literature to capture empirical papers investigating the relationship between biological pathways and molecular markers and the identified QOL domains. We conducted a computerized literature search on PubMed for the years November 2007- November 2012 to build on our previous work (Sprangers, QOLR, 2009). A gene or molecular marker was included if there is at least one publication (either empirical, meta-analysis or review) reporting a significant association with a QOL domain. **Results:** More than 200 articles were identified and reviewed. Multiple major biological pathways are involved in each QOL domain, summarized into a series of seven tables describing each biological pathway and candidate gene. The inflammatory pathway has the strongest evidence as a controlling mechanism underlying fatigue. Inflammation and neurotransmission are key processes involved in pain perception and the COMT gene is associated with multiple sorts of pain. The neurotransmitter and neuroplasticity theories have the strongest evidence for their relationship with depression. Oxytocin-related genes and genes involved in the serotonergic and dopaminergic pathways play a role in social functioning. Inflammatory pathways, via cytokines, also play an important role in overall QOL. In total, more than 50 candidate genes were identified as having previously published evidence of at least a preliminary relationship with patient-reported QOL-related domains. **Conclusions:** We have produced a set of candidate genes and biological pathways for researchers to use when embarking on studies relating candidate genes and/or molecular markers to QOL.

**1562 General Poster Session (Board #344), Sun, 8:00 AM-11:45 AM**

**Analysis of global gene expression in adrenocortical tumors from Li-Fraumeni syndrome *TP53* germline mutation carriers.** *Presenting Author: Fernanda Fortes, A. C. Camargo Cancer Center, São Paulo, Brazil*

**Background:** Li Fraumeni Syndrome (LFS) is a rare autosomal dominant hereditary cancer syndrome. In Brazil, a variant form of LFS is often due to a founder mutation p.R337H *TP53*. The occurrence of cancer in patients and the age of onset may vary even in patients who carry the same mutation. Patients with mutations in *TP53* gene may develop a broad spectrum of tumors, including adrenocortical carcinomas (ADR). The objective of this study was to evaluate the global gene expression profile of ADR in patients with and without p.R337H *TP53* mutation. **Methods:** Analysis of global gene expression was evaluated by microarray (4x44K, Agilent Technologies). **Results:** The presence of 135 differentially expressed genes between the ADR patients with and without p.R337H *TP53*mutation was detected. Genes which have increased expression and are related to a worse prognosis in adrenocortical carcinoma were identified with decreased expression in carriers of p.R337H mutation. **Conclusions:** This study suggests that a differential expression profile of transcripts in ADR p.R337H *TP53* germline mutation carriers may act as modifiers and exert a protective effect in Li-Fraumeni syndrome patients.

**1563 General Poster Session (Board #345), Sun, 8:00 AM-11:45 AM**

**Single nucleotide polymorphisms and smoking status for prediction of non-small cell lung cancer.** *Presenting Author: Junjie Wu, School of Life Sciences, Fudan University, and Changhai Hospital of Shanghai, Second Military Medical University, Shanghai, China*

**Background:** Lung cancer has become the leading cause of death in all cancer. The 5-year survival rate of lung cancer is less than 15%, but the 5-year survival rate of up to 87.7% after treatment of early stage lung cancer. Therefore, timely detecting early stage lung cancer is the key to influence survival rate. However, the current level of lung cancer diagnosis did not increase the rate of detection of lung cancer. The objective of the current study is to introduce genetic factors SNPs to build predictive models of lung cancer for improving the detection rate of early stage lung cancer. **Methods:** SNPs that were identified of associations to NSCLC in several recent studies were reassessed using a pooled sample size of 3,637 Chinese subjects, with 1,597 cases and 2,040 controls from these studies. Multivariate logistic regression models were used to predict NSCLC using SNPs, age, with or without sex, with or without smoking status as predictors. The performance of prediction was assessed using the area under the receiver operating characteristic (ROC) curve (AUC). **Results:** Overall, the AUC from a logistical regression model using all 6 SNPs plus smoking status and demographics as predictors was 0.63(95% CI: 0.61–0.65; P=1.6×10-38), higher than that of 0.60 (95% CI: 0.59–0.62; P=4.5×10-25) from a non-genetic model using smoking status and demographics. For female group and ever smoking group, the AUC from models only using 5 SNPs and 4 SNPs as predictors was 0.61(95% CI: 0.57–0.65;P=8.44×10-9) and 0.57 (95% CI: 0.55–0.60; P=1.53×10-7) respectively. For Adenosquamous group, the AUC from a model using 3 SNPs plus sex as predictors was 0.71(95% CI: 0.62–0.80; P=3.91×10-5), higher than that of 0.57 (95% CI: 0.48–0.66; P=0.157) from a non-genetic model using sex only. **Conclusions:** The combination of SNPs improved the performance of risk models for lung cancer. This study displays an significative role to integrate SNPs in predictive models for lung cancer risk. These findings show the importance of stratifying analysis by sex, smoking status and histology, to improve the performance of specific risk models for lung cancer.

**1564 General Poster Session (Board #346), Sun, 8:00 AM-11:45 AM**

**Contribution of extended family history in assessment of risk for breast and colon cancer.** *Presenting Author: Benjamin Lev Solomon, University of Vermont, Burlington, VT*

**Background:** Family history is important for identifying candidates for advanced screening and referral for cancer genetic counseling. We identified the percentage of individuals who would not receive recommended screening or referral if only a 1st degree family history was obtained. **Methods:** Family histories were obtained from 626 women getting mammography at the University of Vermont between 5/00-5/01 using a validated questionnaire. ACS guidelines were used to determine eligibility for advanced breast and colon cancer screening. Eligibility for referral for genetic counseling for hereditary breast and colon cancer was determined using FHS-7 and Amsterdam II screening criteria, respectively. **Results:** 499 histories were reviewed (127 histories were excluded due to incorrect completion, personal history of cancer or no family history of cancer). For high risk breast cancer screening, 8 individuals met guidelines using 1st degree family history with an additional 10 meeting criteria when family history was extended. For high risk colon cancer screening, 50 individuals met criteria using 1st degree family history with an additional 12 meeting criteria when the family history was extended. Using only 1st degree family history misses candidates for advanced screening: 55% for breast and 24% for colon cancer screening. 63 individuals met criteria for counseling for hereditary breast cancer using 1st degree family history with an additional 51 and 52 when 2nd and 3rd degree family history were included, respectively. Ten individuals met guidelines for referral for counseling for hereditary colon cancer using 1st degree family history with 21 additional meeting criteria when including 2nd degree family history. 62% of candidates for genetic counseling for hereditary breast cancer and 67% of candidates for hereditary colon cancer were missed when using only 1st degree family history. **Conclusions:** This is one of the first studies to demonstrate that 1st degree family history alone is not adequate for identification of all candidates for high risk screening and referral for genetic counseling for hereditary breast and colon cancer syndromes. Given our small sample, larger studies are required to confirm these findings.

**1565 General Poster Session (Board #347), Sun, 8:00 AM-11:45 AM**

**Cost-effectiveness of aromatase inhibitors versus selective estrogen-receptor modulators for breast cancer prevention in postmenopausal women.** *Presenting Author: Amy Grace Groom, Department of Medicine, Dalhousie University, Halifax, NS, Canada*

**Background:** The selective estrogen-receptor modulators (SERMs) tamoxifen (TAM) and raloxifene (RAL), and more recently the aromatase inhibitor (AI) exemestane (EXE) have all been shown to reduce the risk of breast cancer (BC) in post menopausal (PM) women at high risk. As significant differences in adverse effect profiles and costs exist amongst these agents, determining the preferred strategy for clinical use requires consideration of both the risk-benefit profile and overall cost-effectiveness (CE) of each strategy. Prior studies have examined the CE of SERMs in this setting but similar evaluations of AIs have not yet been performed. **Methods:** We examined the probabilities of various BC prevention strategies, including 1) SERMs (TAM or RAL) relative to placebo and 2) AI relative to SERMs and placebo, meeting the $100,000 per quality-adjusted life year (QALY) gains threshold. A Markov model was constructed for a hypothetical cohort of PM women with varying elevated risks of developing BC and treatment related adverse events. Costs, utilities and probabilities were derived from the literature and relevant BC prevention trials including NSABP-P1, STAR and MAP 3. The analysis took a third-party payer perspective and reports costs in 2013 CDN dollars. **Results:** Substantial variability in the relative CE of each strategy was observed when probabilistic sensitivity analysis was performed and thus cost effectiveness acceptability frontiers (CEAFs) were used to compare the relative CE of each strategy. Both SERMs were associated with incremental gains in QALYs as well as incremental costs compared to no treatment but AI was most often the preferred BC prevention strategy at a willingness-to-pay threshold of $100,000/QALY. **Conclusions:** The use of EXE for BC prevention is associated with incremental QALY gains and is a cost-effective strategy in PM women at high risk of BC. The strategy of choice is dependent upon BC risk as well as the risk of adverse effects and the willingness-to-pay for a QALY gain.

**1566 General Poster Session (Board #348), Sun, 8:00 AM-11:45 AM**

**Low-dose CT lung cancer screening in the community: A prospective cohort study.** *Presenting Author: Vincent K. Lam, University of Maryland Greenebaum Cancer Center, Baltimore, MD*

**Background:** Results from the National Lung Screening Trial (NLST) in 2011 showed that low-dose CT screening in high-risk groups reduces lung cancer deaths. Major professional organizations, as well as the USPSTF, have endorsed low-dose CT screening in these select populations. However, major questions remain about whether widespread deployment of CT screening can achieve results similar to the NLST, especially in the community setting. **Methods:** A prospective cohort study was initiated in November 2010. High-risk participants (age at least 50 years old and history of cigarette smoking of at least 20 pack-years) underwent low-dose CT screening, performed and interpreted at El Camino Hospital in Mountain View, California. Diagnostic follow-up for positive scans were recommended per International Early Lung Cancer Action Program (I-ELCAP) guidelines. Participants were followed for events that occurred through December 31, 2013. **Results:** 157 participants underwent low-dose CT screening with mean follow-up of 2.2 years. Median age at entry was 64 (range 50-95). 59% of the participants are women and 94% are Caucasian. Over 80% also satisfied the more stringent NLST inclusion criteria for smoking history. The rate of positive initial screening tests was 35.7%. One positive screen (3.2%) required invasive diagnostic follow-up, which was uncomplicated. No interval lung cancer was detected. One incident case of small cell lung cancer resulted in death. The rate of timely adherence to diagnostic follow-up was only 43%. Late follow-up was often due to participant or primary care provider preference (68%), with participants lost to follow-up (18%) and lack of insurance (10%) also contributing. **Conclusions:** To our knowledge, this is the first community-based prospective study of low-dose CT lung cancer screening. Compared to the NLST, the higher rate of positive initial screening tests (36% vs 27%), higher overall false positive rate, and significantly decreased adherence (43% vs 95%) in this study highlight the difficulties of generalizing the NLST mortality benefits in the broad deployment of CT screening. Our results support current recommendations that CT screening be performed in a highly structured and integrated setting.

**1567 General Poster Session (Board #349), Sun, 8:00 AM-11:45 AM**

**A population-based comparison of outcomes among screening, symptom, and emergently-detected colorectal cancer (CRC).** *Presenting Author: McKyla McIntyre, University of British Columbia, Vancouver, BC, Canada*

**Background:** CRC screening is recommended in average-risk individuals aged 50 years or older. Our aims were 1) to evaluate the proportion of CRC in a large population-based setting that were diagnosed by screening, symptoms, or emergent presentation; and 2) to examine the characteristics and outcomes of CRC based on their method of detection. **Methods:** All sporadic CRC cases diagnosed and referred in 2008 to any 1 of 5 regional cancer centers in British Columbia, Canada were reviewed and analyzed. Screening-eligible patients were classified into CRC diagnosed by 1) screening endoscopies or stool tests; (2) symptoms prompting outpatient workup; and (3) emergent presentations to the hospital. Using Kaplan-Meier methods and Cox regression, 5-year CRC-specific survival (CRC-SS) and overall survival (OS) were compared. **Results:** A total of 992 CRC patients were included: median age was 69 years (range 50-95), 58% were men, and 54% were colon. Among them, 12% were diagnosed by screening, 75% by symptoms, and 13% by emergent presentation. Comparing across the 3 cohorts, patients who presented emergently tended to be older ($p=0.06$), women ($p=0.02$) and have colonic tumors ($p<0.001$) while individuals with either emergently or symptom-detected tumors were more likely to manifest with metastatic disease ($p<0.001$). In the group that underwent screening, stool tests were the most frequent screening modality. Compared to CRC diagnosed by screening, emergently detected disease showed worse CRC-SS (HR 1.34), but symptom-detected disease showed better CRC-SS (HR 0.66) (p for trend $=0.0095$). Both emergently and symptom-detected CRC were correlated with worse OS relative to screening-detected disease (HRs 2.28 and 1.25, respectively) (p for trend$<0.001$). **Conclusions:** Despite screening guidelines, CRC was more commonly diagnosed by symptoms or emergent presentations. Screening was associated with improved OS, but its impact on CRC-SS was variable. Thus, the observed benefits of screening may be more strongly driven by the presence of other associated preventive or healthy behaviors. Interventions that harness these healthy behaviors may be more effective in improving CRC screening uptake and outcomes.

**1568 General Poster Session (Board #350), Sun, 8:00 AM-11:45 AM**

**Correlation between risk benefit index and uptake of breast cancer chemoprevention.** *Presenting Author: Parijatham S. Sivasubramanian, Columbia University Medical Center, New York, NY*

**Background:** Chemoprevention with antiestrogens, tamoxifen and raloxifene, is under-utilized partly due to concerns regarding side effects such as uterine cancer and thromboembolism. Tamoxifen is indicated for women with ductal and lobular carcinoma in situ (DCIS/LCIS) and has a favorable risk-benefit ratio for high-risk women under age 50. For women 50 years and older, a Risk Benefit Index (RBI) developed by Freedman et al. takes into account a woman's age, race, breast cancer risk, and prior hysterectomy. We examined the correlation between RBI and chemoprevention uptake among high-risk women. **Methods:** From 2007 to 2013, new high-risk women seen at an urban, academic breast clinic were enrolled. Eligibility for chemoprevention included a 5-yr Gail risk$\geq$1.67%, DCIS/LCIS, or BRCA mutation. RBI scores for tamoxifen and raloxifene based upon published algorithm tables were calculated for high-risk women $\geq$50 yrs and classified as strong/moderate evidence of benefits outweighing risks and benefits do not outweigh risks. Women with DCIS/LCIS/BRCA mutation and age$<$50 were excluded from the analysis. **Results:** Among 403 women enrolled, 311 (77%) were eligible for chemoprevention. Among women with DCIS/LCIS/BRCA mutation and age$<$50, 62% (124/201) and 31% (10/32) took an antiestrogen, respectively. Among 60 women with an RBI score, 82% had strong/moderate benefit; 33% took an antiestrogen with 65% in agreement with their RBI score. Among women who did not take an antiestrogen, 80% would have had a benefit to raloxifene or both. **Conclusions:** Among high-risk women who took an antiestrogen, the majority of treatment decisions were in agreement with their RBI score. Most women who refused an antiestrogen would have benefited. High-risk postmenopausal women now have the option of aromatase inhibitors, which may improve the risk-benefit profile for chemoprevention.

| | Took tamoxifen | Took raloxifene | Took neither | Total, N (%) |
|---|---|---|---|---|
| Strong/moderate benefit for both | 0 | 3 | 6 | 9 (15) |
| Strong/moderate benefit for raloxifene | 4 | 9 | 26 | 39 (65) |
| Strong/moderate benefit for tamoxifen | 1 | 0 | 0 | 1 (2) |
| No benefit for both | 1 | 2 | 8 | 11 (18) |
| Total, N (%) | 6 (10) | 14 (23) | 40 (67) | 60 (100) |

**1569 General Poster Session (Board #351), Sun, 8:00 AM-11:45 AM**

**Characteristics of HIV+ lung cancer cases in a large clinical population: Implications for lung cancer screening.** *Presenting Author: Marina Shcherba, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY*

**Background:** Lung cancer (LCa) accounts for ~30% of cancer deaths and 10% of non-HIV-related deaths among HIV(+)s. Compared to those in the general population, even after accounting for smoking, HIV(+)s have a 2.5–5-fold higher risk of LCa, and are diagnosed younger. The National Lung Screening Trial (NLST) demonstrated survival improvements with low dose CT (LD-CT) screening in persons at high lung cancer risk (age 55-74 with ≥30 pack-years [pys] of smoking). We examined the age and smoking histories of HIV+ LCa patients to determine who would have met NLST screening eligibility. **Methods:** The Cancer Registry (42,967 cancer cases) and the HIV Integrated Clinical Database (14,927 HIV+s) at Montefiore Medical Center – Einstein (Bronx, NY) were linked to identify HIV+ cancer cases between 2000-2012. Chart review was performed for those with LCa. **Results:** Of the 935 invasive cancers in HIV+s, 90 (9.6%) were LCa (62% men, 38% women). Histology was 11% small cell, 20% squamous and 37% adenocarcinoma, 2% large cell, and remaining 30% were classified as non-small cell carcinomas. Median age at LCa diagnosis was 54 years ([y]; range: 24–72), with 2% <35y, 52% 35-54y, 46% ≥55y. 4% were never smokers, and 3% had <15pys, 24% 15-29pys, 68% ≥30pys. Overall, 66 cases (73%) did not meet NLST age or smoking criteria. Most cases (85%) had been followed for HIV care. The median CD4+ was 238 cells/$\mu$L, and median HIV viral load was 81 copies/mL. LCa was stage I in 8%, stage II in 11%, stage III in 23%, and stage IV in 58%. All stage I/II cases underwent surgical resection. **Conclusions:** Most HIV+ LCa cases failed to meet NLST criteria for LD-CT screening due to age <55y or pys <30. If LD-CT is to be utilized in this high-risk population, age and smoking thresholds may need to be lowered. Notably, 19% of tumors were diagnosed at stage I/II without routine screening, reinforcing the potential to identify LCa at a treatable stage in HIV(+) persons.

**1570 General Poster Session (Board #352), Sun, 8:00 AM-11:45 AM**

**Randomized trials on mammography screening and the left-to-nature design.** *Presenting Author: Philippe Autier, University of Strathclyde Institute for Global Public Health at iPRI, Lyon, France*

**Background:** Population data suggest that mammography screening does not play a major role in breast cancer mortality declines. The six randomized trials that found decreased risks of breast cancer death with mammography screening were all based on the left-to-nature design where women allocated to control groups were unaware that they were part of a trial. We hypothesized that factors other than mammography screening contributed to reductions in breast cancer mortality seen in the trials. **Methods:** We systematically searched in publications on mammography trials for data on factors other than mammography screening that could have influenced breast cancer size or mortality. We extracted or computed reductions in risks of breast cancer death predicted by reductions in cancer size observed in trials multiplied by size-specific fatality rates observed in trials. We then compared predicted and reported risk reductions. We searched for causes of death other than breast cancer among breast cancers during trials. **Results:** Predicted and reported relative risks of breast cancer death were 0.84 (95% CI: 0.84-0.96) and 0.68 (0.59-0.80) in the Swedish Two-County trial, 0.89 (0.69-1.16) and 0.76 (0.56-1.04) in the Swedish Goteborg trial, 0.96 (0.76-1.22) and 0.71 (0.55-0.93) in the Greater New York Health Insurance Plan trial, and 0.90 (0.80-1.01) and 0.79 (0.78-1.01) in the English Age trial. In the Two-County trial, breast cancer women in the intervention group had a 33% (20 to 63%) increased risk to die from a cause other than breast cancer. Lower predicted reductions in risks of death and more deaths not due to breast cancer reflect the contribution of factors other than earlier detection in reduced risks of breast cancer death. In several trials, interval breast cancers were smaller and more frequently in situ than cancers in control groups indicating that factors other than mammography screening played a role in breast cancer earlier detection. We found evidence that in the Two-County trial, the intervention also consisted in promoting breast awareness and breast self-examination. **Conclusions:** Randomized trials based on the left-to-nature design have overestimated the capacity of mammography screening to reduce the risk of breast cancer death.

**1571 General Poster Session (Board #353), Sun, 8:00 AM-11:45 AM**

**One hundred years of cancer mortality in Scotland (1911-2010).** *Presenting Author: Peter Boyle, University of Strathclyde Institute for Global Public Health at iPRI, Lyon, France*

**Background:** Mortality data by age and gender are available for Scotland for one hundred years, 1911-2010. This allows a unique insight into the changing patterns of cancer over a complete century. **Methods:** Bridging was established manually to ensure that each rubric contained the same cancer sites throughout the period studies. Population data were available throughout the time period. Age-standardised mortality rates per 100,000 could be calculated. It was possible to follow the observed death rates in certain cohorts of men and women born in the late 1800s and the early 1900s. **Results:** Data are available for 20 individual sites of cancer in addition to the combined all cancers. Notable findings include the dramatic reduction in stomach cancer, which fell in men from38 per 100,000 around 1930 to 6 per 100,000 in 2006-2010 (in women the rates fell from 30 to 4 over the same time period). Lung cancer in men fell from its peak of 80 in 1960 to 30 in 2005-2010. One quarter of men born between 1900-1910 died of lung cancer in their lifetime (over 80% of men in Scotland smoked in 1950). Breast cancer mortality in women is now lower than at any other time point during the last century. Downward trends are apparent in birth cohorts at all ages indicating that this favourable trend will continue. Colorectal cancer mortality has declined markedly in both gender groups: in men the rate fell from 39 (1930-34) to attain 15 (2006-2010). The effects of treatment advances in Testis Cancer and Hodgkin's Lymphoma are clearly reflected in the declining mortality rate. **Conclusions:** These data provide insights into the changing pattern of cancer over the last century. The impact of tobacco-smoking on cancer mortality throughout the century has been dramatic although the declines in tobacco-related cancers is confirmation of the effectiveness of anti-tobacco policies. It is harder to explain the substantial declines in stomach, colorectal and breast cancer although they are very welcome.

**1572 General Poster Session (Board #354), Sun, 8:00 AM-11:45 AM**

**A population-based analysis of the impact of physicians on cancer screening.** *Presenting Author: Leo Chen, University of British Columbia, Vancouver, BC, Canada*

**Background:** Despite its ability to reduce morbidity and mortality, participation in cancer screening continues to be suboptimal. Our aims were to 1) characterize the frequency of breast (BR), colorectal (CR), cervical (CV) and prostate (PR) cancer screening in a US population-based setting, 2) describe the clinical factors associated with screening uptake, and 3) examine the effect of patient contact with their physicians and the quality of these interactions in modifying screening behavior. **Methods:** Average risk patients considered eligible for cancer screening were identified from the US Health Information National Trends Survey. We developed a scoring system based on patient-reported patterns of care to characterize the quality of their interactions with physicians. Determinants of screening were assessed with multivariate logistic regression analyses and joint effects models that accounted for the frequency and quality of contact with physicians were developed to explore their influence on screening. **Results:** A total of 7,327 patients were included. In each of the BR (n=1,696), CR (n=2,377), CV (n=2,240) and PR (n=1,014) cancer cohorts, screening rates were suboptimal at 72%, 69%, 76% and 61%, respectively. Advanced age, family history of any cancers, high income earners, individuals who visited their physicians frequently and those who rated the interactions with their physicians highly were generally more likely to have undergone screening (Table). Joint effects models revealed that the quality rather than the frequency of physician contact was a stronger predictor of screening, but the odds of screening were greatest for patients who experienced both frequent and high quality interactions with their physicians. **Conclusions:** Participation in cancer screening remains poor. Contact with physicians and the quality of this interaction were associated with screening behavior. Interventions to improve these provider-related factors may optimize screening.

**Odds ratios for cancer screening.**

| | BR | CR | CV | PR |
|---|---|---|---|---|
| **Advanced age** | 0.99 | 1.05* | 0.96 | 1.06* |
| **Family history** | 1.26* | 1.17 | 1.10 | 1.82* |
| **High income** | 1.08 | 1.22* | 1.18* | 1.22* |
| **Frequent visits with MD** | 1.41* | 1.36* | 1.06 | 1.39* |
| **Good quality interactions with MD** | 1.87* | 1.27* | 1.67* | 1.19 |

*means $p < 0.05$.

**1573 General Poster Session (Board #355), Sun, 8:00 AM-11:45 AM**

**Risk-reducing salpingectomy at the time of benign gynecologic surgery: A survey of ACOG members in New York State.** *Presenting Author: Joshua Stewart, Weill Cornell Medical College, New York Presbyterian Hospital, New York, NY*

**Background:** To determine if Obstetricians and Gynecologists in New York state would offer risk-reducing salpingectomy (RRS) at the time of benign hysterectomy with ovarian preservation or permanent sterilization. **Methods:** An anonymous survey was administered to Ob/Gyn physicians at the 2013 Annual American College of Obstetricians and Gynecologists district II meeting. Physicians-in-training were excluded. The survey instrument assessed provider practice to offer RRS before and after reading a brief summary of the clinical position by the Society of Gynecologic Oncology of Canada, entitled "Salpingectomy and Ovarian Cancer Prevention." **Results:** Ninety physicians completed the survey. Median age was 52 years (range 30-87), and 91% practiced general Ob/Gyn. Median annual surgical volume was 10 hysterectomies (range 0-150) and 11 surgical sterilizations (range 0-100). More physicians were willing to offer RRS at the time of hysterectomy than at the time of permanent sterilization (54% vs. 14%, $p < 0.05$). After reading the position statement, there was a 27% increase in the number of physicians who would offer RRS at the time of benign hysterectomy ($p<0.01$) and 42% at the time of surgical sterilization (p=NS). On univariate analysis, physician practice to offer RRS at the time of hysterectomy was associated with previous knowledge of evidence for RRS (96% of physicians aware vs. 82% not aware, $p = 0.04$), surgeon age ($p<0.05$), and practice setting (academic > community, $p<0.5$). Willingness to perform RRS at time of permanent sterilization was associated with the method of sterilization (laparoscopic, 82%, hysteroscopic, 18%, postpartum tubal, 0% $p < 0.07$) and volume of sterilization cases per year ($p<0.05$). On multivariate analysis, the only factor associated with offering RRS was the number of years in practice, 1.6 (95% CI 1.01-1.53, $p<0.05$). **Conclusions:** Our data suggest that obstetricians and gynecologists would offer RRS at the time of benign hysterectomy in those women who elect ovarian conservation. The link between fallopian tube as the origin of ovarian serous cancer needs to be elaborated to potentially offer high-risk patients a method of prevention with few long-term consequences.

**1574 General Poster Session (Board #356), Sun, 8:00 AM-11:45 AM**

**Vulnerable populations and overconfidence in cancer screening.** *Presenting Author: François Eisinger, Institut Paoli Calmettes, Marseille, France*

**Background:** The EDIFICE surveys have been conducted every 3 years since 2005. The aim is to characterize behavior related to recommended, organized screening services (breast and colorectal). However, we recently focused on levels of confidence in screening efficacy for cancer locations for which only opportunistic screening is available. Results from vulnerable and non-vulnerable populations were compared. **Methods:** Phone interviews were conducted among a representative sample of 1,600 individuals (age 40-75 years), using the method of quotas. Opinions on efficacy of cancer screening were assessed for 8 anatomical locations. Data were analyzed according to a validated vulnerability score. **Results:** For cancer locations with no organized screening services, the level of confidence in screening efficacy is surprisingly high, and significantly higher in vulnerable than in non-vulnerable populations; in decreasing order: lung cancer, 85% vs. 78% ($P<0.05$), leukemia, 69% vs. 60% ($P<0.05$), gastric cancer, 67% vs. 56% ($P<0.05$), liver cancer, 63% vs. 48% ($P<0.05$), esophageal cancer, 59% vs.52% ($P<0.05$), and central nervous system cancer, 34% vs. 27% ($P<0.05$), respectively. In contrast, organized screening programs inspire very similar high levels of confidence in both populations: breast cancer, 95% vs. 96% (NS) and colorectal cancer, 92% vs. 94% (NS), respectively. Risk factors for cancer are more prevalent in vulnerable populations: higher BMI, more active smokers and less frequent sports activities. **Conclusions:** Our results demonstrate an excess of confidence in the efficacy of cancer screening, particularly by vulnerable populations. We have put forward two opposing mechanisms to potentially explain the paradoxical coexistence of overconfidence in cancer screening and greater exposure to cancer risk factors. Firstly, individuals may (wrongly) feel protected within the safe net of screening and therefore allow themselves greater exposure to known risk factors. This has been termed the "Moral Hazard". On the other hand, although they realize they have a high risk of being affected by cancer, they ignore the facts and adopt an attitude of wishful thinking.

**1575 General Poster Session (Board #357), Sun, 8:00 AM-11:45 AM**

**Prevalence of smoking in cancer survivors: National Health and Nutrition Examination Survey (NHANES) III data analysis.** *Presenting Author: Mohammed Shaik, Michigan State University, East Lansing, MI*

**Background:** Smoking is an important risk factor for many cancers. Studies have shown a lower prevalence of smoking in cancer survivors. However, we wanted to determine whether this prevalence is constant or changes the longer the patient is cancer free. **Methods:** Data was obtained from NHANES III, a nationally representative health survey conducted from 1988-1994. Subjects who were diagnosed with solid tumors were included in this study. These subjects were divided into two groups, Group A(GpA) were those within 3 yrs of diagnosis of cancer and group B(GpB) included those more than 3 yrs from diagnosis of cancer. Prevalence of smoking in these groups was analyzed using the chi-square test (proc surveyfreq in SAS 9.3). **Results:** Of 33,994 subjects in the NHANES III database, 780 subjects were diagnosed with solid tumors. Of these, 415 subjects had data regarding their current smoking status. There were 138 subjects who were within 3 years and 183 subjects beyond 3 years of their cancer diagnosis. There were 38.1% males and 62% females, and 83%, 16% and 1% were white, black and other races, respectively. Current smoking in subjects without cancer was 52.3% and 30.1% in subjects with cancer which was consistent with prior studies. The cancer survivors within 3 years of diagnosis had a 22.4% (31/138) prevalence of smoking, and subjects with more than 3 years since diagnosis had a 34%(94/277) prevalence of smoking (p=0.01). (Table) **Conclusions:** The prevalence of smoking in cancer survivors was lower than in the general population as expected. Subjects who survived more than 3 yrs from their diagnosis had a statistically significant higher prevalence of smoking when compared to survivors less than 3 yrs from their diagnosis. Health care providers need to continue to counsel against smoking in cancer survivors for a longer period of time.

**Characteristics of cancer survivors.**

| Variables | Subj <3 yrs from cancer diagnosis (GpA) n=251 | Subj >3 yrs from cancer diagnosis (GpB) n= 480 | p-value |
|---|---|---|---|
| **Mean age (SD)** | 59.7 (1.62) | 59.2 (1.22) | |
| **Males** | 120 | 151 | 0.002 |
| **Females** | 131 | 321 | |
| **Whites** | 189 | 415 | 0.0009 |
| **Blacks** | 57 | 63 | |
| **Other races** | 5 | 2 | |
| **Prevalence of smoking** | 22.4% | 34% | 0.01 |

**1576 General Poster Session (Board #358), Sun, 8:00 AM-11:45 AM**

**Breast cancer incidence among young women of urban China (Shanghai) and in Canada: Implications for prevention.** *Presenting Author: Joseph Ragaz, School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada*

**Background:** Objective of this study: to evaluate, in Urban China and Canada, the long-term BrCa incidence trends, with emphasis on rates among young women age <50. Shanghai, one of the largest regions of Urban China, enjoyed since the late 1970's rapid rates of westernization, i.e. confluence of western lifestyles, urbanization and industrialization. While a good association between the westernization and BrCa incidence has been reported in past studies, BrCa age-specific incidence analyses comparing urban China to western regions such as Canada, are not available. **Methods:** Data were received from Shanghai Municipal Centre for Disease Control and Prevention and from the Public Health Agency of Canada based on the Canadian Cancer Registry database at Statistics Canada. For each region, 5-year age specific BrCa incidence rates [ASIRs] in 5 year cohorts starting at age 35 were estimated and expressed as percent difference between years 1973-79 [baseline, 100%] and the last five years 2000-2004. ASIRs were age-standardized annual new incident cases per 100,000 population, and standardized using the 1960 world population as reference. **Results**: See Table. **Conclusions:** For any age group [including those age >65], ASIR increases were much greater in urban Shanghai than in Canada, but they were particularly dramatic for the very young age 35-39. Incidence rates were however still very high also for the whole group of young women age 40-60. As most women in these young age groups of urban China, as in the western countries, receive [western] BrCa diagnostic and therapeutic approaches, a systematic implementation of BrCa preventive strategies and their larger scale research will be required, particular targeting young adolescent women or school age girls. Our data suggest that these are the age groups who are at sizable risk of subclinical carcinogenesis related to western life-style, and for whom prevention research and interventions may have most meaningful cost/benefit, and overall impact.

| | ASIR | |
|---|---|---|
| **Age group at diagnosis** | **Canada** | **Shanghai** |
| **35 – 39** | 0% | +46% |
| **40 – 44** | -4% | +106% |
| **45 – 49** | -1% | +170% |
| **50 – 54** | +22% | +157% |
| **55 – 59** | +30% | +132% |
| **60 – 64** | +32% | +85% |
| **65+** | +23% | +91% |

**1577 General Poster Session (Board #359), Sun, 8:00 AM-11:45 AM**

**Cancer screening behaviors among spouses in a nationally representative sample.** *Presenting Author: Ashwin A Kotwal, University of Chicago, Department of Medicine, Chicago, IL*

**Background:** Spouses are known to behave similarly across a range of health behaviors, however, little is known about how each spouse influences the other's cancer screening behavior. Using a unique national sample of older couples with detailed information on both partners, we assess whether screening colonoscopy, PSA screening, and mammography rates of each spouse are associated, and identify characteristics of each partner and their relationship that influence cancer screening likelihoods. **Methods:** We use the National Social life Health and Aging Project (NSHAP) Wave 2 sample (2010), a nationally-representative sample of matched older male-female couples (n=953). We use multivariate logistic regression models for each of the four outcomes (PSA screen in last 1 year for husbands, mammography in last year for wives, and screening colonoscopy in last 5 years for both), as a function of sociodemographic, health status, spouses' cancer screening behavior, and relationship quality covariates. **Results:** Controlling for covariates, husbands with wives who had screening mammograms in the last year are more likely to have had screening PSAs in the last year (64% vs 50%; p=0.001). Husbands are more likely to have received screening colonoscopies when their wives have received screening colonoscopies (69% vs 54%; p<0.001), when their wives are more educated (69% vs 55%; p=0.037), and when their wives are happier with the marital relationship (65% vs 49%; p=0.006). Similarly, wives are more likely to receive a screening colonoscopy when their husband has received a screening colonoscopy (67% vs 51%; p<0.001). For mammography, wives are more likely to have had a mammogram in the last year if their husbands have had recent PSA screens (68% vs 56%; p=0.002) or if their husbands have had recent screening colonoscopies (68% vs 54%; p=0.001). **Conclusions:** In a national sample, older spouses' cancer screening behaviors are significantly associated with one another after adjusting for shared sociodemographics. Recognizing how spouses mutually influence screening rates can help providers deliver more effective screening recommendations and improve adherence, particularly when different screening recommendations exist for each cancer.

**1578 General Poster Session (Board #360), Sun, 8:00 AM-11:45 AM**

**Identfying barriers to providing tobacco cessation support for cancer patients.** *Presenting Author: James Roger Marshall, Roswell Park Cancer Institute, Buffalo, NY*

**Background:** The 2014 Surgeon General's Report concluded that smoking caused increased mortality in cancer patients, but data demonstrate that most physicians do not regularly provide tobacco cessation support. The purpose of this study was to identify predictors of providing tobacco cessation support through a large physician provider survey administered through the International Association for the Study of Lung Cancer (IASLC). **Methods:** An online survey was developed and administered to IASLC members asking about tobacco assessment and cessation practices. Barriers to providing cessation support were also asked. Responses were analyzed to identify demographic, perception, and practice related correlates of decreased cessation support. **Results:** A total of 1,507 respondents replied to the survey representing a 40.5% response rate. Respondents from the United States (US) , in an academic practice, and devoting more time to patient care were associated with higher rates of asking about tobacco use. However, only practice in the US predicted for higher rates of providing cessation assistance. Respondents reporting clinicians need more education on cessation and respondents stating they had sufficient education was predictive of regularly providing cessation support. Believing that tobacco cessation does not affect cancer treatment outcome predicted for lower rates of assisting with cessation support. Reimbursement concerns and belief that patients were not receptive to cessation support did not affect physicians regularly providing cessation support. However, lack of resources, lack of training and experience with cessation, and lack of time were all predictive of decreased tobacco cessation support by respondents. **Conclusions:** Lack of time, training, and resources were the primary determinants of providing tobacco cessation support for cancer patients. Efforts are needed to address these issues to improve tobacco cessation support in the standard clinical care of cancer patients.

**1579 General Poster Session (Board #361), Sun, 8:00 AM-11:45 AM**

**Cervical cancer screening: Twelve years experience with high-risk population of southern Mexico.** *Presenting Author: Francisco Gutierrez-Delgado, Centro de Estudios y Prevencion del Cancer, Juchitan, Mexico*

**Background:** Cervical cancer is still the main cause of death from cancer in indigenous population and rural communities in Mexico. We have evaluated both screen-and-treat colposcopy and oncogenic human papilloma virus (HPV)-DNA testing as potential screening programs in high-risk population. Our experience has been previously reported (2006 and 2008 ASCO Annual Meetings; Abstracts 5012 and 16519, respectively). In this study we report a follow-up of both strategies. **Methods:** Between 12/2002 and 11/2013, women were offered colposcopy. From 08/2006 to 11/2013, HPV-DNA testing (Hybrid Capture II (hC2) assay (Digene Corp, Gaithersburg, MD, USA) was offered to women aged 14 to 89 years. Criteria for colposcopy diagnosis, cervical cytology, therapy for HPV diagnosis, CIN2 and CIN 3, and the methodology for (Hybrid Capture II (hC2) assay has been reported elsewhere. Women were followed in their communities **Results:** 17,471 women (median age 39 years, range: 14–87) were underwent colposcopy. 14,487 (83%) of them were evaluated between 2002 and 2008, and 2985 (17%) from 2009 to 2013. The median follow-up was 8 years (range 5-11) and 3 years (range 0-5), respectively. Abnormal colposcopy (HPV, CIN 1, CIN 2 or CIN 3), was diagnosed in 2,528 (14%) out of 14,487 women and 45 (0.31%) had carcinoma. 411 (14%) out of 2,985) women were diagnosed as having an abnormal colposcopy and 11 (0.36%) had carcinoma. 1,110 women were evaluated with the oncogenic HPV-DNA testing. 807 (73%) women were ≥ 30 years old years and 303 (27%) were younger 30 years old. HPV-DNA testing was positive in 134 (16%) and 97 (32%) women, respectively. In women ≥ 30 years old who had a normal colposcopy (n=681), 96 (11.8%) of them had a positive HPV test and in 38 (4.7%) of those who had an abnormal colposcopy. In women younger 30 years old HPV test was positive in 45 (14.85%) women who had a normal colposcopy (n=179) and in 52 (17.16%) diagnosed as having abnormal colposcopy. No new cervical cancer cases have been reported in the follow-up. **Conclusions:** Screen-and-treat colposcopy and oncogenic HPV testing are feasible strategies for cervical cancer screening in selected high-risk population and an alternative to cytology-based screening programs

**1580 General Poster Session (Board #362), Sun, 8:00 AM-11:45 AM**

**The effect of current smoking on mortality in cancer patients.** *Presenting Author: Graham Walter Warren, Medical University of South Carolina, Buffalo, NY*

**Background:** Smoking is the largest preventable health behavior associated with the development of cancer. An evidence-based estimate is needed to assess the effect of current smoking at diagnosis on mortality for cancer patients. **Methods:** A MEDLINE literature search was performed to identify studies between 1990-2012 evaluating the effect of current smoking at or following a cancer diagnosis on overall mortality. Only studies collecting tobacco information in close proximity to diagnosis and with at least 200 patients in the analysis were included. **Results:** A total of 83 studies met criteria reporting on 129,346 patients including 60 studies comparing the effects of current smoking with never smoking and 23 studies reporting the effects of current smoking with former and never smoking combined. Overall 60 studies (72.3%) demonstrated one or more statistically significant negative associations between current smoking and mortality, 6 studies (7.2%) reported near significant negative associations, and 17 studies (20.5%) demonstrated no association. The risks of current smoking were observed across all treatment modalities (surgery, chemotherapy, radiotherapy). Current smoking increased the risk of mortality as compared with never smoking by a median of 52%, as compared with former smoking by a median of 41%, and as compared with former and never smoking combined by 50%. **Conclusions:** Current smoking increases the risk of overall mortality for cancer patients independent of cancer treatment. The effects of current smoking are distinct from the effects of former or ever smoking.

**1581 General Poster Session (Board #363), Sun, 8:00 AM-11:45 AM**

**Pioglitazone as a candidate chemoprevention agent for lung cancer: A pilot window trial in early stage NSCLC.** *Presenting Author: Dennis A. Wigle, Mayo Clinic, Rochester, MN*

**Background:** Multiple lines of evidence support the use of PPARγ ligands in the treatment and prevention of lung cancer. Pioglitazone is a PPARγ ligand that is FDA-approved for type-II diabetes mellitus, and used by millions of diabetic patients worldwide. We evaluated pioglitazone as a candidate chemo-preventive agent for NSCLC by investigating the effects on Ki-67 in NSCLC tumor tissue using a pilot window trial design. **Methods:** Patients with known or suspected stage IA-IIIA NSCLC who were current or former smokers with a ≥ 10 pack-year smoking history were enrolled. Patients underwent fluorescence bronchoscopy with targeted biopsies (normal, suspicious/dysplastic areas) bronchial brushings, and additional tumor sampling to asses Ki67 staining. Patients also underwent a pre-treatment PET scan, followed by pioglitazone, 45 mg once/day for 14-42 days prior to surgical resection. Ki67 staining along with other secondary biomarker endpoints were assessed in repeat bronchoscopy and surgical resection specimens after pioglitazone treatment. **Results:** Of the 10 pre-registered participants, 3 did not have biopsy-confirmed NSCLC and 1 had metastatic NSCLC; a total of 6 participants received pioglitazone. Mean age 64.0 years, 5 males, 1 female; with 2nadenocarcinomas, 3 squamous cell carcinomas, and 1 mixed adenosquamous tumor. Median %change in Ki67 staining in the primary tumor of the 5 eligible participants (1 participant excluded with a solitary non-lung cancer metastasis) was -20% (p=0.06), with all patients having a reduction in Ki67 post-intervention. Gene expression analysis of histologically normal bronchial airway epithelium pre- and post-pioglitazone treatment revealed a number of upregulated genes enriched for complement activation and chemokine signaling (GSEA p <0.05). Genes that were repressed were related to inflammatory and B cell survival pathways (GSEA p<0.05). **Conclusions:** These preliminary data are suggestive of a potential effect for pioglitazone in early stage NSCLC, despite the small sample size. These results need to be confirmed in a larger cohort of patients. Clinical trial information: NCT01342770.

**1582 General Poster Session (Board #364), Sun, 8:00 AM-11:45 AM**

**Lung cancer characteristics in 762 never- and 6,246 ever-smoker patients: Study KBP-2010-CPHG.** *Presenting Author: Daniel Coëtmeur, Centre Hospitalier de Saint Brieuc-Hôpital Yves Le Foll, Saint-Brieuc, France*

**Background:** In 2010, the French College of General Hospital Respiratory Physicians performed a prospective multicenter epidemiological study to describe the baseline characteristics and management of all new cases of primary lung cancer and evaluate survival. The present abstract compares characteristics according to smoking. **Methods:** 7,051 patients ≥18 years presenting with primary lung cancer, histologically or cytologically diagnosed between 1 January and 31 December 2010, and followed-up in the respiratory department of one of the 104 general hospitals participating in the study, were included. A standardized form was completed for each patient at diagnosis. A steering committee checked inclusion exhaustiveness. **Results:** 762 patients were never-smoker and 6,246 ever-smoker (43 missing data). Respectively, 222, 635, and 5,088 of ever-smokers claimed to consume or to have consumed 1-10, 11-20, and >20 pack-year; their median smoking duration was 40 years. Former-smokers stopped smoking 12 years ago (median). 158 never-smokers claimed to have been exposed to passive-smoking. At diagnosis, statistical significant differences between never- and ever-smoker patients (p<0.0001) were found for sex (women: 70%/19%); age (median: 73/64 years); stage of cancer (IV: 71%/59%); cancer type (adenocarcinoma: 69%/43%; small-cell lung cancer: 5%/14%; squamous-cell carcinoma: 8%/28%); EGFR mutation exploration (51%/28%) and positivity (37%/5%). For all these characteristics, significant trends (p<0.0001) were also observed when patients were graded according to consumption: e.g., percentage of adenocarcinoma was 63%, 54%, 50%, and 41% in the 0, 1-10, 11-20, and >20 pack-year groups, respectively. **Conclusions:** This study confirms the main differences between never-smokers and ever-smokers, in particular on histological type and EGFR-mutation, two characteristics that impact treatment.

**1583 General Poster Session (Board #365), Sun, 8:00 AM-11:45 AM**

**Multiple primary malignancies involving primary sporadic colorectal cancer in Japan: Incidence of gastric cancer with colorectal cancer patients may be higher than previously recognized.** *Presenting Author: Takaharu Kato, Department of Surgery, Saitama Medical Center, Jichi Medical University, Saitama, Japan*

**Background:** Improvement in the prognosis of colorectal cancer (CRC) patients has led to increasing occurrences of multiple primary malignancies (MPMs) alongside CRC but little is known about their characteristics. This study was undertaken to clarify the clinical and pathological features of MPMs, especially those at extra colonic sites, in patients with CRC. **Methods:** We reviewed 1,076 patients who underwent operations for primary sporadic CRC between 2007 and 2012. Familial adenomatous polyposis, Hereditary Non-Polyposis Colorectal Cancer, colitic cancer and any metastasis from CRC were excluded. We extracted patients who had developed at least one MPM in an extracolonic site while having synchronous or metachronous CRC. Synchronous MPMs were defined as malignancies detected within 6-month interval before and after the detection of CRC. We compared the clinicopathological features of CRC patients with and without MPMs. As a control, we used a database compiled of patients with gastric cancer (GC) that were detected by mass screening performed in Saitama prefecture, Japan 2010 and compared these with CRC patients with synchronous GC. **Results:** MPMs at extracolonic sites were identified in 134 of 1,076 CRC patients (12.5%). Average age was 67.0 (range, 29-96) versus 71.3 (50-92) (P < 0.001). The incidence of GC (40.0% (53 of 134)) was the highest of all MPMs. All CRC patients with GC were older than 57 years of age. Synchronous GC was detected in 26 patients. On the other hand, out of 200,007 screened people, 225 people were diagnosed as GC in Saitama prefecture. The age-standardized incidence ratio of synchronous GC in CRC patients (0.54%) was significantly higher than in the control group (0.03%) (odds ratio 18.7, 95% confidence interval 18.5-18.9; P < 0.001). **Conclusions:** CRC patients preferentially developed GC synchronously and metachronously when they are older than 50 years. Thus, this patient group should undergo careful perioperative screening for GC.

**1584 General Poster Session (Board #366), Sun, 8:00 AM-11:45 AM**

**A population-based study of incidence and survival trends of 1,261 thymic malignancies (TM): Results from the California Cancer Registry (CCR).** *Presenting Author: Jonathan Riess, Department of Internal Medicine, Division of Hematology/Oncology, University of California Davis Comprehensive Cancer Center, Sacramento, CA*

**Background:** TMs are rare with sparse population-based epidemiologic literature. **Methods:** We used data from the CCR, a comprehensive population-based state registry to examine TM incidence and survival trends in California from 1988 to 2011. Cases were specified by site (thymus), histology (thymic carcinoma and thymoma), and behavior (malignant). Primary endpoint was cause-specific survival (CSS). Hazard ratios (HR) for CSS were calculated using a Cox proportional-hazards model controlling for relevant baseline variables including age, gender, stage, and year of diagnosis, among others. **Results:** We identified 1,261 TM cases with an incidence of 0.17 per 100,000 person-years. Average annual increase was 2% (95% CI 1-3.1%). Earlier stage was associated with improved CSS in the crude (localized HR=0.17, 95% CI 0.11-0.28; regional HR=0.37, 95% CI 0.28-0.49) and multivariate models (localized HR=0.30, 95% CI 0.157-0.567; regional HR=0.44 (95% CI 0.29-0.67). Thymic carcinoma histology was associated with worse CSS in both the crude (HR=2.42, 95% CI 1.74-3.37) and multivariate models (HR=2.57, 95% CI 1.1-6.1). Patients diagnosed between 1995-2001 had improved CSS compared to 1988-1994 (crude HR=0.49, 95% CI 0.35-0.70), even in the multivariate model (HR=0.35, 95% CI 0.18-0.71). Radiotherapy was associated with improved CSS (multivariate HR=0.45, 95% CI 0.21-0.97) for patients treated with partial or total removal of tumor. **Conclusions:** This is the first population-based study of TMs from the CCR that identifies baseline variables significantly associated with CSS. TM incidence appears to be increasing over time: this was also associated with improving CSS over the same period. In addition to stage and non-thymic carcinoma histology, treatment with radiotherapy after partial or total removal of tumor was found to be associated with improved CSS. These findings provide a more contemporary database for future TM outcomes research and generate new hypotheses for clinical evaluation.

**1585 General Poster Session (Board #367), Sun, 8:00 AM-11:45 AM**

**The incidence of testicular cancer in the United States and Europe from 1992 to 2009.** *Presenting Author: Manas Nigam, University of Chicago Pritzker School of Medicine, Chicago, IL*

**Background:** Testicular germ cell tumors (TGCTs) are the most commonly diagnosed cancer in men between 15 and 35 years in the United States and in most European populations. The incidence of TGCTs increased in White, Black, and Hispanic men in the U.S. through 2003. We sought to determine current trends in TGCT incidence in the U.S. and Europe. **Methods:** TGCT incidence data covering the U.S. and European populations were extracted from the Surveillance, Epidemiology and End Results-13 registry and the EUREG database, respectively. Age-standardized incidence rates (ASIRs) were derived from SEER*Stat 8.0.1. Trends were determined using JoinPoint. **Results:** TGCT incidence among U.S. males over 15 years old increased from 1992 (5.7/100,000) to 2009 (6.8) with a significant annual percentage change (APC) (1.1%, $p<0.001$). TGCT ASIRs were highest in White men (1992: 7.5/100,000; 2009: 8.6/1000) followed by Hispanic men (1992: 4.0; 2009: 6.3) and lowest among Asian (1992: 2.0/100,000; 2009: 2.8) and Black men (1992: 0.7; 2009: 1.7). Significantly increasing ASIRs were observed in White men (APC: 1.2%, $p<0.001$) and most prominently in Hispanic men, especially from 2002-2009 (APC: 5.6%, $p<0.01$). Significant increases were observed for localized (APC: 1.2%, $p<0.001$) and metastatic TGCTs (APC: 1.4%, $p<0.01$). Incidence of testicular cancer increased in 15 of 19 (79%) European countries analysed ($p < 0.05$). **Conclusions:** Between 1992 and 2009, testicular cancer incidence in the U.S. continued to increase, notably among Hispanic men, and testicular cancer incidence increased in 79% of European countries analyzed.

**Incidence rates for TGCTs among U.S. men, SEER-13, 1992-2009.**

| | All GCTs | Age-adjusted incidence rate (per 100,000) | | Annual percentage change (APC) |
|---|---|---|---|---|
| | Number of cases | 1992 | 2009 | |
| **All races** | 18,037 | 5.7 | 6.8 | 1.1* |
| **Non-Hispanic white** | 13,454 | 7.5 | 8.6 | 1.2* |
| **Non-Hispanic black** | 419 | 0.7 | 1.7 | 1.4 |
| **Hispanic** | 3,052 | 4 | 6.3 | 0.7 (1992-2002)[a] 5.6* (2002-2009) |
| **Other** | 1,112 | 2.2 | 4.4 | 2.9* |
| **Age at diagnosis** | | | | |
| **15-26 years** | 4,288 | 6.2 | 8.6 | 2.5* |
| **27-32 years** | 4,202 | 11.3 | 13.8 | 1.0* |
| **33-39 years** | 4,461 | 10.0 | 9.9 | 0.1 |
| **40+ years** | 5,086 | 3.3 | 3.9 | 0.8* |

* Significant at a 0.05 confidence level. [a] JoinPoint can produce different APCs for different year intervals.

**1586 General Poster Session (Board #368), Sun, 8:00 AM-11:45 AM**

**Cancer patients' acceptability of incorporating an epidemiology questionnaire within a clinical trial: A patient preference study and subanalysis of the NCIC clinical trials group HN.6 clinical trial.** *Presenting Author: Sinead Cuffe, Princess Margaret Cancer Centre, Toronto, ON, Canada*

**Background:** Understanding the influence or impact of epidemiological factors on cancer outcomes in clinical trials can broaden our knowledge of disease, trial populations and therapeutic effects thus leading to improved patient care. However, there is a lack of data on cancer patients' compliance with an epidemiology questionnaire in the context of a clinical trial. **Methods:** A wide spectrum of cancer patients from three community, academic and tertiary cancer centres in Ontario, Canada were provided with a hypothetical scenario and surveyed regarding their willingness and preferences to complete an epidemiology questionnaire if incorporated into a cancer therapy trial. Patient compliance with completing a voluntary epidemiology questionnaire was separately determined in the pan-Canadian, multicentre phase III HN.6 clinical trial (NCT00820248) in patients with locoregionally advanced head and neck cancer. **Results:** Of 617 cancer patients surveyed, the vast majority were willing to complete an epidemiology questionnaire; 45% would do so unconditionally; 31% would do so provided it did not inconvenience them too much; just 4% would refuse. Patients preferred shorter questionnaires of up to 30-50 questions requiring 10-20 minutes to complete, and administered over 1-3 sessions. Patients were less willing, but still compliant, to answer questions relating to sexual history (71%), and household income (66%) relative to other epidemiological questions (all >90%). 18% of patients thought that epidemiology questionnaires should be a mandatory component of clinical trials, with 31% believing that they may benefit personally from such research. Among the 320 HN.6 study participants, 268 (84%) completed the voluntary epidemiology questionnaire, and compliance averaged 94.8 (+/-1.0)% per question. **Conclusions:** Cancer patients appear to be very willing to participate in clinical trials that incorporate epidemiology questionnaires in trial design. The high compliance rates with completion of an epidemiology questionnaire in a phase III multicentre study confirmed this finding. Clinical trial information: NCT00820248.

**1587 General Poster Session (Board #369), Sun, 8:00 AM-11:45 AM**

**Rising incidence of young-onset colorectal cancer in Texas, 1995-2010.** *Presenting Author: Daniel Wang Ying, Baylor College of Medicine, Houston, TX*

**Background:** Although colorectal cancer (CRC) has traditionally been considered a disease of the elderly, the incidence of CRC among young adults in the US has been steadily rising. Examining CRC trends in Texas may, by virtue of its diverse population, shed light on future CRC epidemiology in the US. **Methods:** In this retrospective cohort study, we used 1995-2010 Texas Cancer Registry data to calculate the annual percentage change (APC) of CRC incidence by age, race/ethnicity, and anatomic site. **Results:** Of the 125,987 cases identified, 11% occurred in people <50 years old. The APCs of CRC incidence for individuals >50, 40-49, and 20-39 years old were -2.1% (CI -2.7 to -1.5, $p<.05$), 0.2% (NS), and 1.7% (CI 1.0 to 2.4, $p<.05$), respectively. In the >50 cohort, the incidence of CRC in all colon subsites progressively decreased (see Table). In the 20-39 group, sigmoid/rectum tumors became increasingly more common among Hispanics (APC 2.7% [CI 1.1 to 4.2, $p<.05$]) and non-Hispanic whites (APC 3.4% [CI 1.9 to 4.6, $p<.05$]) but not among African-Americans (APC -0.7% [CI -2.9 to 1.7, NS]), and there was a non-significant rise in right-sided tumors among African-Americans (APC 2.4% [CI -0.5 to 5.4, NS]). Compared to the >50 cohort, patients 20-39 were more likely to present with Stage III/IV disease (65.8% vs 53.2% [$p<.01$]). **Conclusions:** While the incidence of CRC in older Texans has fallen, CRC has become progressively more common in individuals 20-39 years old, a trend largely attributable to a rise in distal tumors in Hispanics and non-Hispanic whites. Younger patients tend to present with more advanced disease, likely due to lack of routine screening and/or more aggressive biology. Young-onset CRC is an emerging disease that warrants further investigation.

**APCs in CRC incidence, 1995-2010.**

| Age | Race/ethnicity | Whole colon | Right colon | Left colon | Sigmoid/rectum |
|---|---|---|---|---|---|
| **20-39** | All | 1.7* | 1.5* | 2.1* | 2.3* |
| | NHW | 2.3* | 1.3 | 3.2* | 3.4* |
| | AA | 0.2 | 2.8 | -1.9 | -0.7 |
| | Hispanic | 2.1* | 1.8 | 2.6* | 2.7* |
| **40-49** | All | 0.2 | 0.5 | 0.1 | 0.1 |
| | NHW | 1.0* | 0.8 | 1.0* | 1.3* |
| | AA | -1.0 | 0.3 | -1.6 | -2.1* |
| | Hispanic | -0.5 | -0.1 | -0.7 | 0.9 |
| **>50** | All | -2.1* | -1.4* | -2.5* | -2.6* |
| | NHW | -2.5* | -1.6* | -3.0* | -3.0* |
| | AA | -1.4* | -0.5 | -1.9* | -2.0* |
| | Hispanic | -0.7 | 0.1 | -1.1* | -1.1* |

*APC significantly different from zero ($p<.05$). AA = African American. NHW = Non-Hispanic whites.

**1588 General Poster Session (Board #370), Sun, 8:00 AM-11:45 AM**

**Frequency and clinical significance of extramammary findings on breast magnetic resonance imaging.** *Presenting Author: Catherine Elizabeth Moore, University of Iowa Hospitals and Clinics, Iowa City, IA*

**Background:** Breast magnetic resonance imaging (MRI), often obtained for management of newly diagnosed breast cancer, or other indications, uncovers extra-mammary findings (EMF) with some frequency. These results often prompt further work-up and cause pt concern. **Methods:** We retrospectively reviewed 1322 breast MRI reports performed at the University of Iowa between 2007 and 2012. We completed a chart review of the radiology reports, patient characteristics, and breast cancer characteristics. We then focused specifically on the EMFs that were detected on breast MRI. The EMFs in the field of breast MRI include lesions in the chest (lung, heart, mediastinum, and chest wall), liver, bone, spleen, lymph nodes, blood vessels, and bones. **Results:** A total of 1,322 MRI reports were reviewed. EMFs were reported in 130 (9.8%). An EMF was more likely to occur in postmenopausal pts ($p = 0.021$) or if the MRI indication was for breast cancer ($p <0.001$). EMFs were more frequent in pts with hormone receptor (HR) positive disease. HER2 status did not impact rate of EMFs. Most EMFs occurred in liver and bone. Of the 130 EMFs, 5 (3.8%) resulted in pts with active breast cancer being upstaged to stage IV disease. Of these 5 lesions, 3 were sternal and 2 were hepatic. One pt had an MRI for a high-risk indication and a sternal lesion was found which represented recurrence of previously treated breast cancer. These 6 studies represented 0.5% of all breast MRIs in this series. There were 2 additional cases where both the MRI and staging studies obtained the same day showed metastatic disease. **Conclusions:** Unexpected EMFs occurred with some frequency on breast MRI. Postmenopausal state, a diagnosis of breast cancer and HR positive disease, were associated with a higher EMF rate. These findings very rarely represented distant breast cancer.

| | EM finding | No EM finding | P value |
|---|---|---|---|
| **Number** | 130 | 1192 | |
| **Median age** | 51 | 50 | 0.0375 |
| **Menopausal status (%)** | | | |
| Premenopause | 8.5 | 91.5 | |
| Menopause | 12.3 | 87.7 | 0.027 |
| **Indication for MRI (%)** | | | |
| Breast cancer | 16.0 | 84.0 | |
| High risk | 6.6 | 93.4 | |
| Clinical significance | 5.5 | 94.5 | |
| Other | 0.0 | 100.0 | <0.001 |
| **HR status (%)*** | | | |
| Negative | 8.4 | 91.6 | |
| Positive | 20.1 | 79.9 | 0.001 |
| **HER2 status (%)*** | | | |
| Negative | 16.3 | 83.7 | |
| Positive | 16.3 | 83.8 | 0.998 |

* For those with active breast cancer.

**1589 General Poster Session (Board #371), Sun, 8:00 AM-11:45 AM**

**Age-related change in breast cancer stage at diagnosis relative to increased mammography detection over time: 1990-2012.** *Presenting Author: Judith April Malmgren, HealthSTAT Consulting, Inc., Seattle, WA*

**Background:** The United States does not have a national mammography screening program and relies on recommendations from the United States Preventive Services Task Force (USPSTF), the American Cancer Society (ACS) and other organizations to encourage screening. It has been hypothesized that mammography screening has not reduced advanced stage breast cancer (BC) from analysis of stage III and IV BC in a national database. **Methods:** Using our institutional breast cancer registry database, we reviewed change in stage distribution (0-IV) over time (OT) related to changes in detection method in the same time period. We restricted our analysis to age groups that have or have had screening recommendations during the time period (age 40 to 74) (N=8754). Pearson chi square tests were used to assess significance. Method of detection was categorized as patient (PtD) (N=3171), physician (PhysD) (n=460) or mammography (MamD) (n=5123) detected as recorded by the physician at time of diagnosis. Patients with unknown or other method of detection were excluded (n= 140). Stage for all years was converted to AJCC 7. **Results:** From 1990-2012 mammography detection of BC increased from 8% in 1990 to 22% in 2012 (+14%) ($p<.001$). MamD BC differed by age, presenting more often among older than younger women ($p<.001$) [age 40-49 = 45%, age 50-64 = 62%, age 65-74 = 68%]. For all groups combined stage shifted increasing 14% for stage 0 and decreasing 15% for stage I/II/III BC combined [stage I -4%, stage II -4%, stage III -7 %] with no change in stage IV ($p<.001$). By the three age groups, stage 0 BC change over time was +16% age 40-49, +14% age 50-64, and +11% age 65-74, stage I was 0% age 40-49, -6% age 50-64, -5% age 65-74; stage II was -10% age 40-49, 0% age 50-64/65-74; stage III -9% age 40-49, -7% age 50-64, -5% age 65-74; with no significant change in stage IV. **Conclusions:** A significant shift to lower stage disease was observed concurrent with increased mammography detection not restricted to stage III BC or including stage IV BC. Evaluation of association between screening recommendations and stage shift have to include change in all BC stages (0-IV) adjusted to a single AJCC grading standard and stratified to account for age related differences.

**1590 General Poster Session (Board #372), Sun, 8:00 AM-11:45 AM**

**Multicenter observational study of reactivation of hepatitis B virus (HBV) caused by chemotherapy for solid tumors (ST).** *Presenting Author: Shunsuke Kondo, Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan*

**Background:** Reactivation of HBV has often been reported in patients (pts) with malignant lymphoma administered combination chemotherapy regimens containing rituximab. Recently, HBV reactivation has been reported even in pts with STs. However, the incidence of HBV reactivation in pts with STs and the treatment outcomes in pts with HBV reactivation have not yet been fully elucidated. Therefore, we prospectively investigated the incidence of HBV reactivation in pts with STs receiving first-line chemotherapy and the clinical outcomes of these patients. **Methods:** ST pts with seropositivity for HBsAg [sAg(+)], or seronegativity for HBsAg and seropositivity for HBcAb and/or HBsAb [c/sAb(+)], receiving first-line chemotherapy including neoadjuvant or adjuvant chemotherapy, were enrolled. HBV DNA was at least measured at the termination of the first-line chemotherapy, and at 3, 6, and 12 months after the termination of first-line chemotherapy. It was also measured in cases where HBV reactivation was suspected, such as based on increase in the serum levels of transaminases. HBV reactivation was defined as a 10-fold or greater increase in the titer of HBV DNA. **Results:** A total of 379 pts [sAg(+), 35 pts; c/sAb(+), 344 pts] were enrolled in this study. Any cancer types and regimens were included, and the median period of measurements of HBV DNA was 74 days (range, 13-248 days). Among the pts with sAg(+), HBV reactivation occurred in 9 pts, and the incidence rates at 6, 12 and 18 months were 6.8%, 30.0%, and 35.8%, respectively. Among pts with c/sAb(+), HBV reactivation occurred in 7 pts, and the incidence rates at 6, 12 and 18 months were 0.6%, 2.0% and 3.1%, respectively. Four of the seven pts with c/sAb(+) showing HBV reactivation improved without antiviral therapy, and there were no pts with increased serum transaminase levels or fulminant hepatitis in this series. **Conclusions:** HBV reactivation in ST pts with c/sAb(+) was rare, and no case with clinically significant HBV reactivation was detected by periodic measurement of HBV DNA and proper management at the first sign of reactivation. Clinical trial information: UMIN000005369.

**1591 General Poster Session (Board #373), Sun, 8:00 AM-11:45 AM**

**A comparative analysis of the association between health expenditure and cancer survival in 168 countries.** *Presenting Author: Felipe Ades, Institut Jules Bordet, Brussels, Belgium*

**Background:** Whereas cancer incidence is higher in high and middle income countries, cancer survival is lower in low income countries. In this analysis we investigated the relationship between health expenditure and cancer-related survival in 168 countries. **Methods:** Health expenditure data from 168 countries and cancer indicators data from 28 cancer types from the same countries were extracted from the World Bank (WB) and the World Health Organization (WHO) databases. The mortality/incidence (M/I) ratio was calculated to evaluate the fraction of patients dying after a cancer diagnosis. A regression analysis was conducted using a lin-log functional form that accounts for a non-linear relationship between (M/I) ratio and health expenditure. The coefficient of determination ($R^2$), indicates the proportion of outcomes explained by the model. **Results:** Health expenditure was significantly higher in high income countries than in middle and low income countries. For cancers with effective screening and/or effective treatment options higher expenditure was strongly correlated with improved survival. For cancers with no screening and moderately efficient treatment options survival was moderately correlated with health expenditure. For cancers with no screening and poor treatment options survival was poorly correlated to health expenditure. The estimated non-linear relationship shows that increases in health expenditure have a much more significant effect when health expenditure is low, especially for the first two groups of diseases. Significant survival improvements are expected from increasing health expenditure of low and middle income countries as in South America, Africa and parts of Asia, and only marginal incremental improvements, if any, in high income countries as the USA and Western Europe. **Conclusions:** Higher health expenditure is correlated with improved survival in cancers with available effective screening methods and/or treatment options. For cancer with no effective treatment options health expenditure has little impact on survival.

| Cancer type | $R^2$ |
|---|---|
| **Breast** | 0,80 |
| **Prostate** | 0,79 |
| **Bladder** | 0,66 |
| **Multiple myeloma** | 0,54 |
| **Esophagus** | 0,20 |
| **Pancreas** | 0,12 |

**1592 General Poster Session (Board #374), Sun, 8:00 AM-11:45 AM**

**The prevalence of severe vitamin D (vitD) deficiency and its effect on tumour indices and clinical outcomes in patients with early breast cancer (EBC).** *Presenting Author: Kasia M. Owczarczyk, Mount Vernon Cancer Centre, Middlesex, United Kingdom*

**Background:** VitD deficiency is a common occurrence in the UK, affecting nearly a quarter of British women. Emerging data suggests that this proportion may be higher in pts with EBC; however, screening and vitD supplementation is currently not recommended in this population. This study was carried out to assess the prevalence of severe vitD deficiency in an ethnically diverse UK EBC cohort and its association with tumour indices and clinical outcomes. **Methods:** Serum vitD levels were prospectively recorded in a consecutive cohort of pts with newly diagnosed EBC presenting to our oncology department from 2006-2010. Severe vitD deficiency was defined as serum total 25-hydroxyvitD <10ng/mL, a threshold for which high dose supplementation is recommended, according to revised national guidelines. $X^2$tests and multiple logistic regression were used to investigate association between vitD and clinical factors, with Cox PH models used to investigate the effect of vitD on time to tumour recurrence. **Results:** Data was available for 259 patients. Median vitD level was 17.6ng/mL 61 patients (23.6%) were severely vitD deficient. vitD deficiency was associated with age <50 years, non-White ethnicity and ER-ve receptor status. In multiple logistic regression, ethnicity and ER were independently associated with vitD deficiency. After a relatively short follow up of 33 mths (IQR 25-42), 33 (12.7%) pts had a local or distant recurrence. Risk of recurrence was increased in pts with vitD<10ng/mL (HR=1.58, 95%CI 0.75–3.32) which is consistent with a recent meta-analysis. **Conclusions:** In this study, nearly a quarter of pts (and more than a third of Asian pts) were severely vitD deficient at diagnosis, more than in most published studies. Given revised supplementation recommendations, both routine testing and adequate supplementation of vitD is recommended.

| | Proportion vitD deficient | Number needed to screen for deficiency | 95% CI |
|---|---|---|---|
| **All** | 61/259 | 4.2 | 3.4-5.4 |
| **Age <50** | 20/52 | 2.6 | 1.9-4.0 |
| **Age ≥50** | 41/207 | 5.0 | 3.9-6.8 |
| **White** | 15/114 | 7.6 | 4.8-13.2 |
| **Asian** | 40/111 | 2.8 | 2.2-3.7 |
| **ER-ve** | 21/50 | 2.4 | 1.8-3.5 |
| **ER+ve** | 40/209 | 5.2 | 4.0-7.1 |
| **Premenopausal** | 23/77 | 3.3 | 2.4-5.0 |
| **Postmenopausal** | 38/182 | 4.8 | 3.6-6.6 |

**1593 General Poster Session (Board #375), Sun, 8:00 AM-11:45 AM**

**Effect of CHRNA9 polymorphisms and passive smoking on the risk of breast cancer in Taiwan.** *Presenting Author: Yi-Chen Hsieh, Taipei Medical University, Taipei, Taiwan*

**Background:** Previous studies have indicated that smoking exposure is associated with increased breast cancer risk, and $\alpha$9-nicotine acetylcholine receptors ($\alpha$9-nAChRs) were involved in breast tumorigenesis. However, there are no studies exploring the $\alpha$9-nAChRs genes (CHRNA9) and cigarette smoking exposure together on breast cancer risk. **Methods:** A case-control study was conducted on 737 breast cancer patients and 719 age-matched healthy controls. Three single nucleotide polymorphisms (SNPs) of CHRNA9 located on promoter were genotyped and compared between cases and controls to identify these SNPs associated with breast cancer susceptibility. A dual-luciferase reporter assay was used to analyze the promoter activity of these SNPs of CHRNA9 gene. **Results:** CHRNA9 -885A/T and -823A/G polymorphisms showed a significant association with susceptibility of breast cancer. Passive cigarette smoking and risk genotypes of -823A/G of CHRNA9 gene had synergistic effects on the risk of breast cancer. The odds ratio for the interaction and the attributable proportion from the interaction and synergy index were 6.3, 0.56 and 2.6, respectively. These findings indicated a multiplicative interaction between passive cigarette smoking and CHRN9 gene. The results further confirmed that the risk genotype of -823A/G of CHRNA9 exhibited stronger transcriptional activation activity than the wild type ($P<0.05$). **Conclusions:** Our findings support that a significant interaction effect exists between CHRNA9 gene and passive cigarette smoking on breast cancer patients.

**1594 General Poster Session (Board #376), Sun, 8:00 AM-11:45 AM**

**The risk of second primary malignancy among male breast cancer patients: A population-based study.** *Presenting Author: Man-Hsin Hung, Division of Hematology and Oncology, Department of Internal Medicine, Taipei Veterans' General Hospital, Taipei, Taiwan*

**Background:** Male breast cancers, thought rare, are in a trend of increasing in recent years. Owning to advances in diagnostic and therapeutic modalities, outcomes for breast cancer have been greatly improved. Therefore issues regarding second primary malignancy in these long-term breast cancer survivors become more important than before and should be further investigated. **Methods:** From the Taiwan National Health Insurance Program Database, patients with newly diagnosed breast cancer from January 1997 to December 2011 were recruited for analysis. The standardized incidence ratios (SIRs) of secondary non-breast primary cancer in male breast cancer patients were calculated and compared with the cancer incidence in the general male population. **Results:** Within a follow-up of 2,773 person-years, there were 73 primary non-breast cancers developed in 578 male breast cancer patients. Compared with the general population, the SIRs of second primary malignancy in male breast cancer patients were 2.17 [95% confidence interval (CI) 1.70- 2.73], which were particularly higher in patients with breast-cancer-diagnosis-age younger than 40 (SIR 29.70, 95% CI 6.12- 86.80; Table) furthermore, the SIRs of thyroid cancer (SIR 13.2, 95% CI 1.60- 47.69), skin cancer (SIR 8.24, 95% CI 3.02 – 17.94) and head and neck cancer (SIR 4.41, 95% CI 2.35 – 7.54) were the highest among all types of second primary malignant diseases observed. **Conclusions:** Compared with the general population, the SIRs of secondary non-breast-cancer malignant disease were significantly higher in male breast cancer patients, particularly in patients with breast cancer diagnosed younger than 40 years of age. Therefore, more intensive surveillance of second primary malignancy may be needed for male breast cancer survivors, particularly for those with high riskfeatures.

| Characteristics | Observed | Expected | SIR (95% CI) |
|---|---|---|---|
| **All cancers** | 73 | 33.63 | 2.17 (1.70–2.73) |
| **Age at diagnosis, years** | | | |
| **30 – 39** | 3 | 0.10 | 29.70 (6.12-86.80) |
| **40 – 49** | 2 | 0.78 | 2.58 (0.31-9.31) |
| **50 – 59** | 11 | 2.95 | 3.73 (1.86-6.68) |
| **60 – 69** | 14 | 6.19 | 2.26 (1.24-3.79) |
| **70 – 79** | 18 | 13.55 | 1.33 (0.79-2.10) |
| **>= 80** | 25 | 10.07 | 2.48 (1.61 - 3.67) |

Abbreviations: SIR, standardized incidence ratio; CI, confidence interval.

**1595 General Poster Session (Board #377), Sun, 8:00 AM-11:45 AM**

**A nomogram associated with high probability of invasive carcinoma on the surgical specimen in patients with preoperative diagnosis of ductal carcinoma in situ of the breast.** *Presenting Author: Takafumi Kondo, St. Luke's International Hospital, Tokyo, Japan*

**Background:** Sentinel node biopsy is frequently performed for patients with preoperative diagnosis of ductal carcinoma in situ (DCIS) by needle biopsy because of a possibility of postoperative diagnose of invasive ductal carcinoma (IDC) on the surgical specimen. Inessential sentinel node biopsy would be omitted, if final postoperative diagnosis could be predicted DCIS accurately. The aim of this study are to determine clinicopathological factors associated with postoperative diagnosis of IDC regardless of preoperative diagnosis of DCIS, and to conduct a model to predict IDC on surgical specimen. **Methods:** Pre- and postoperative pathological diagnosis and radiological findings on 1,251 consecutive patients who were diagnosed DCIS by preoperative core needle biopsy (CNB) or vacuum-assisted breast biopsy and underwent surgical resection from 2003 to 2012 were retrospectively assessed. Multivariate logistic regression was applied to generate the nomogram to predict IDC. **Results:** Of the 1,251 patients, 318 (25.4%) were diagnosed IDC on surgical specimen. On multivariate analysis, no evidence of sclerosing adenosis on preoperative biopsy specimen (odds ratio (OR) 0.46, 95%CI 0.25-0.85, $p = 0.013$), pleomorphic calcifications on mammogram (OR 1.68, 95%CI 1.14-2.47, $p = 0.009$), suspicious of invasive carcinoma on ultrasound and/or MRI (OR 2.13, 95%CI 1.51-3.00, $p = 0.000$), tumor size≧2cm on ultrasound (OR 1.80, 95%CI 1.05-3.06, $p = 0.032$) were independent predictive factors. HER2-positive (OR 1.54, 95%CI 0.98-2.41, $p = 0.062$) and comedo necrosis (OR 1.42, 95%CI 0.99-2.03, $p = 0.056$) were also same trend. A nomogram using these factors predicted the correlation with AUC of 0.67 (95% CI 0.63-0.71). **Conclusions:** Our nomogram showed the correlation of the presence of invasive breast carcinoma on surgical specimen regardless of preoperative diagnosis of DCIS. Prospective external validation is needed before being implemented in clinical practice.

**1596 General Poster Session (Board #378), Sun, 8:00 AM-11:45 AM**

**Incidence and mortality rates of breast and gynecologic cancers and human development index in the pan-American region.** *Presenting Author: Jeovany Martínez-Mesa, Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil*

**Background:** Breast and gynecologic cancers incidence and mortality rates differ between geographical regions. We aim to evaluate if disparities in incidence and mortality cancer rates among women in the Pan-American countries could be related to the country human development index (HDI). **Methods:** This ecological analysis includes 28 countries from the Pan-American region. Age-standardized incidence and mortality rates per 100.000, mortality/incidence ratios for breast , cervical cancer, ovarian cancer and corpus uteri cancer obtained from GLOBOCAN 2012. Data were log-transformed because of strong skewness. The information on HDI was gathered from the UNDP 2012 report. Pearson's correlation test and simple linear regression were performed in Stata 12. **Results:** HDI was strongly and positively associated with breast and ovarian cancers incidence and mortality rates. HDI was negative associated with cervical cancer incidence and mortality rates and also with breast and cervical cancers ratio. HDI was not associated with corpus uteri cancer estimative. Linear regression coefficients ($\beta$) between HDI and each cancer log-rate are shown in the Table. **Conclusions:** HDI should be considered as an indicator explaining inequalities in incidence and mortality rates of breast, cervical and ovarian cancer in women between countries in the Pan-American region.

| | Linear regression coefficient | |
|---|---|---|
| Cancer rates per 100,000 (log-transformed) | $\beta$ (95%CI) | p-value* |
| **Breast cancer incidence** | 4.03 (2.61;5.45) | <0.001 |
| **Breast cancer mortality** | 1.76 (0.32;3.21) | 0.019 |
| **Breast cancer mortality/incidence ratio** | -0.26 (-0.42;-0.10) | 0.003 |
| **Cervical cancer incidence** | -3.28 (-4.78;-1.78) | <0.001 |
| **Cervical cancer mortality** | -4.63 (-6.1;-3.17) | <0.001 |
| **Cervical cancer mortality/incidence ratio** | -0.89 (-1.16;-0.62) | <0.001 |
| **Corpus uteri cancer incidence** | 2.37 (-0.33;5.06) | 0.083 |
| **Corpus uteri cancer mortality** | 0.07 (-2.68;2.82) | 0.960 |
| **Corpus uteri mortality/incidence ratio** | -0.07 (-1.06;0.92) | 0.885 |
| **Ovarian cancer incidence** | 3.26 (1.78;4.75) | <0.001 |
| **Ovarian cancer mortality** | 1.82 (0.44;3.20) | 0.012 |
| **Ovarian cancer mortality/incidence ratio** | -0.42 (-0.91;0.06) | 0.086 |

*Wald test.

**1597 General Poster Session (Board #379), Sun, 8:00 AM-11:45 AM**

**Obesity-induced alteration in iron metabolism via elevated hepcidin and the risk of postmenopausal breast cancer among Caucasians.** *Presenting Author: Puja Agarwal, University of Illinois at Chicago, Chicago, IL*

**Background:** Obesity is an established risk factor for postmenopausal breast cancer and also induces iron dysregulation via elevated hepcidin (hepatic peptide hormone). Hepcidin degrades ferroportin (Fp-only known iron exporter) and traps iron that enhances carcinogenesis within the cell. Breast tumors with high hepcidin and low Fp have poor prognosis. The purpose of this study was to determine if systemic hepcidin independently enhances the established obesity and postmenopausal breast cancer risk. **Methods:** A nested case (n=44)-control (n=44) study was conducted from an ongoing cohort on women seeking breast biopsies enrolled in a study to develop blood-based biomarkers. White postmenopausal women with incident breast cancer were matched for age and BMI to women with a non-proliferative benign lesion. Both cases and controls were stratified by obesity status (50% had a BMI $>$ 30 & 50% $<$ 30). Blood samples, anthropometric and other information were collected prior to biopsy. C-reactive protein, IL-6, leptin, adiponectin, estradiol, soluble transferrin receptor and hepcidin were measured using ELISA and cases and controls were compared with T-test, Wilcoxon Rank test and conditional logistic regression. **Results:** Hepcidin (p=0.02) along with other obesity related factors for breast cancer (inflammation (CRP, IL-6); leptin and estrogen; (all p values $\leq$ 0.05)) significantly differed with obesity status among the controls. Among the cases hepcidin levels were similar in obese and non-obese. Hepcidin ($\beta$=0.04; p value=0.043) was a significant independent predictor of disease (p value) status when controlled for age, leptin, family history of breast cancer, age of menarche and use of hormone replacement therapy and IL-6 in multivariable conditional logistic regression**. Conclusions:** Influence of obesity on hepcidin reported in premenopausal women also occurs post menopause. Hepcidin level is associated with breast cancer and may represent a novel mechanism to explain the link between obesity and breast cancer. Further study of this association is warranted.

**1598 General Poster Session (Board #380), Sun, 8:00 AM-11:45 AM**

**Incidence trends of keratinocytic skin cancers and melanoma in Israel 2006-2011.** *Presenting Author: Tal Sella, Sheba Medical Center, Ramat Gan, Israel*

**Background:** The incidence of skin cancer, both melanoma and keratinocyte cancers (KC) is rising throughout the world, specifically squamous cell carcinomas(SCC) and basal cell carcinoma(BCC), being the most common of all cancers. Objective: To determine trends in incidence of Melanoma, BCC and SCC among 1.7 million members of Maccabi Healthcare Services from 2006 to 2011. **Methods**: Data on newly diagnosed Melanoma, SCC and BCC cases was collected from the MHS Cancer Registry and based on histology reports from the centralized pathology lab. Age-specific and overall age-adjusted European standardized rates were computed. Trends were estimated by calculating Average Annual Percentage Change(AAPC). **Results**: During the six year study period, a total of 16,079 subjects were diagnosed with at least one BCC, 4,767 with SCC and 1,264 with invasive melanoma. Age-standardized incidence rates were 188, 58 and 17 per 100,000 person years for BCC, SCC and melanoma, respectively. All lesions were more common among males and primarily affected the elderly. BCC rates were stable throughout the study period(AAPC -0.7%, 95%CI -4.5% to 3.2%) while SCC incidence increased significantly(AAPC 15.5%, 95%CI: 2.6% to 30.0%). In contrast, melanoma rates showed a continuously decreased with a significant AAPC of -3.0%, 95%CI (-4.5 to -0.1). **Conclusions**: Previously unreported, the incidence of KC in Israel is one of the highest in the world. The disparities in incidence trends between SCC, BCC and melanoma allude to their different etiologies. These findings underscore the importance of continuous monitoring, education and prevention programs in a growing high risk population.

**1599 General Poster Session (Board #381), Sun, 8:00 AM-11:45 AM**

**Impact of antibiotic exposure on the risk of colorectal cancer.** *Presenting Author: Shimon Ben Boursi, Sheba Medical Center, Ramat Gan, Israel*

**Background:** Previous reports revealed colonic dysbiosis in tumor tissue from cases with colorectal cancer (CRC) showing lower levels of microbial diversity and an enrichment of certain bacterial strains. It was suggested that the composition of the microbiota might serve, among other genetic and environmental factors, as a significant promoter of the multistep process of CRC formation. Antibiotic therapy reduces the overall bacterial diversity, with substantial consequences for the resultant functional stability of the colonic microbiota. Aim: To evaluate the association between the type and cumulative dose of antibiotic exposure and CRC risk. **Methods:** We conducted a nested case-control study using The Health Improvement Network (THIN), a large population-based medical records database from the United Kingdom (UK) that contains information on 11.7 million patients with follow up of up to 18 years. Study cases were defined as those with any medical code of CRC. Subjects with known familial colorectal cancer syndromes or IBD were excluded from the study. For every case, 4 eligible controls matched on age, sex, practice site, and duration of follow-up before index date were selected using incidence density sampling. Exposure was defined as any antibiotic therapy at least 6 month before index date. The OR and 95%CI were estimated using conditional logistic regression analysis adjusted for BMI, alcoholism, smoking history, Diabetes mellitus and chronic NSAIDs use. **Results:** 22,023 CRC patients and 85,981 controls were identified with a mean follow up time of 6 years (SD 3.53). The adjusted OR for CRC among user of penicillins, quinolones and metronidazole was 1.08 (95%CI 1.04-1.12), 1.08 (95%CI 1.03-1.14) and 1.11 (95%CI 1.05-1.18) respectively with p$<$0.0001 for all. The modest risk increase remained statistically significant only for remote exposure to penicillins (OR 1.05, 95%CI 1.001-1.09, for exposure 10 years before index date). There was no statistically significant effect with other antibiotic classes, anti-viral or anti-fungal therapy. **Conclusions:** Past exposure to Penicillins is related to a modest elevation in CRC risk, possibly through effects on the colonic microbiota.

**1600 General Poster Session (Board #382), Sun, 8:00 AM-11:45 AM**

**Thyroid hormone replacement and the risk for colorectal cancer.** *Presenting Author: Shimon Ben Boursi, Sheba Medical Center, Ramat Gan, Israel*

**Background:** The association between thyroid hormones and cancer risk was evaluated in several studies with conflicting results. While thyroid hormones can stimulate cancer growth, hypothyroid function can lead to reduced risk and a more favorable outcome in cancer patients. Aim: To evaluate the risk for colorectal cancer (CRC) in patients treated with thyroid hormones replacement. **Methods:** We conducted a nested case-control study using The Health Improvement Network (THIN), a large population-based medical records database from the United Kingdom (UK) that contains information on 11.7 million patients with follow up of up to 18 years. Study cases were defined as those with any medical code of CRC. Subjects with known familial colorectal cancer syndromes or IBD were excluded from the study. For every case, 4 eligible controls matched on age, sex, practice site, and duration of follow-up before index date were selected using incidence density sampling. Exposure was defined as any thyroid hormone therapy at least 6 month before index date. The odds ratio (OR) and 95%CI were estimated using conditional logistic regression analysis adjusted for BMI, alcoholism, smoking history, Diabetes mellitus and chronic NSAIDs use. **Results:** 22,023 CRC patients and 85,981 controls were identified with a mean follow up time of 6 years before index date (SD 3.53). The adjusted OR for CRC associated with use of thyroid hormones was 0.87 (95%CI 0.82-0.93, p$<$0.0001) and remained reduced 5 and 10 years after initiation of therapy (OR 0.84, 95%CI 0.78-0.91 and 0.83, 95%CI 0.74-0.92 respectively). There was no change in OR when analyzing all durations of therapy, including patients treated for less than 6 months (OR 0.88, 95%CI 0.82-0.93). **Conclusions:** Patients using thyroid hormone replacement drugs have a statistically significant reduction in CRC risk. Further research is required in order to evaluate whether this effect is secondary to the primary thyroid disease or direct effects of therapy.

**1601 General Poster Session (Board #383), Sun, 8:00 AM-11:45 AM**

**Long-term breast cancer outcomes in Canada with special analyses of cancer care access and mortality reduction.** *Presenting Author: Joseph Ragaz, School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada*

**Background:** The objective of this study is to compare main Breast Cancer outcomes in two regions of Canada with different access to Provincial Guideline-based cancer care [GCC]. Since the 1960's, British Columbia has had a centralized provincially funded Cancer program, coordinating GCC care. Adjuvant therapies started in late 1970's; and of screening mammography in late 1980's. Both Programs were implemented province-wide, and at least a decade earlier than in Atlantic Provinces (Atl. Prov.). Both regions have had comparable BrCa registry since 1970. **Methods:** From 1970-2007 datawere obtained in collaboration with Public Health Agency of Canada and Canadian Cancer Registry database at Statistics Canada. Estimates for annual age standardized rates /100,000 [with Canada 1991 as population reference] were evaluated for BrCa in-situ [ASR-IS]; incidence of invasive BrCa [ASIRs]; and BrCa-specific mortality [ASMRs]. Results were averaged q 10 years. ASMRs were also expressed [in percent] relative to baseline years 1970-75. **Results:** See Table. **Conclusions:** (1) While in the 1970's the rates of both in-situ and invasive BrCa in Atl. Prov. were significantly lower than in B.C., subsequently both rates have increased to approximate rates in B.C.( 20 ASMR reduction in B.C. is more substantial and observed many years earlier than in Atl. Prov. (3) These results show that uniform guideline-coordinated cancer care favorably impacts BrCa outcomes, and should be implemented in regions with unequal access to cancer care. Reference: Cancer Research: December 15, 2009; Volume 69, Issue 24, Supplement 3.

| | | Period | | | |
|---|---|---|---|---|---|
| **Region** | **Breast cancer outcomes** | **1970-1979** | **1980-1989** | **1990-1999** | **2000+** |
| **B.C.** | **In-situ** | 3.8 | 5.4 | 11.0 | 13.1 |
| | **ASIR** | 75.0 | 77.2 | 81.2 | 74.3 |
| | **ASMR** | 22.5 [100%] | 21.8 [94%] | 18.8 [82%] | 14.2 [63%] |
| **Atl. Prov.** | **In-Situ** | 0.5 | 2.5 | 3.5 | 11.1 |
| | **ASIR** | 59.3 | 64.1 | 77.3 | 76.5 |
| | **ASMR** | 22.1 [100%] | 23.1 [107%] | 21.7 [102%] | 16.2 [75%] |

**1602 General Poster Session (Board #384), Sun, 8:00 AM-11:45 AM**

**Breast cancer risk among women following lifestyle recommendations: A case-control study in Spain.** *Presenting Author: Marina Pollán, National Center of Epidemiology, Instituto Salud Carlos III, Madrid, Spain*

**Background:** In 2007, the World Cancer Research Fund (WCRF) and the American Institute of Cancer Research (AICR) issued 8 general and 2 special recommendations for cancer prevention based on available evidence. The objective of this study was to explore the association between the WCRF/AICR recommendations and breast cancer risk. **Methods:** EpiGEICAM is a nation-wide case-control study, 1019 cases from 23 hospitals were matched to 1019 controls by age and municipality of residence. The cases were sub classified by tumor subtype: 1) Estrogen Receptor(ER)+ or Progesterone Receptor(PR)+ with Human Epidermal Growth Factor Receptor 2(HER2)-; 2) HER2+; and 3) ER-,PR-&HER2- tumors. We constructed a score (0-9) based on 9 of the 10 WCRF/ AICR recommendations. The score was grouped in 4 categories (0 to $<4$, 4 to $<5$, 5 to $<6$ and $\geq 6$) and its association with BC risk was evaluated using conditional logistic regression models adjusted by total calorie intake, smoking habit, age at first delivery, education, history of breast problems, family history of BC and menopausal status. Multinomial logistic regression models were used to evaluate the association of the WCRF/AICR score with each of the intrinsic BC subtypes. These models were adjusted by age, hospital, and the same set of potential confounders described above. **Results:** The women with higher score showed a decreased risk of BC ($OR_{[6\text{-}9]vs[0\text{-}4]}$ =0.51; 95%CI=0.36-0.73 and $OR_{unit\text{-}increase}$=0.82; 95%CI =0.74-0.91; p-trend$<$0.001). This preventive effect was slightly more pronounced in postmenopausal women ($OR_{[6\text{-}9]vs[0\text{-}4]}$ =0.43; 95%CI=0.26-0.70 and $OR_{unit\text{-}increase}$=0.81; 95%CI=0.71-0.93, p-trend=0.001) and in women with ER+/PR+&HER2- tumors ($OR_{[6\text{-}9]vs[0\text{-}4]}$ =0.43; 95%CI =0.30-0.62 and $OR_{unit\text{-}increase}$=0.78; 95%CI=0.70-0.87; p-trend$<$0.001). However, none of the differences in the magnitude of risk by menopausal status and intrinsic tumor subtypes was statistically significant. **Conclusions:** Adherence to the WCRF/AICR recommendations for cancer prevention might reduce breast cancer risk in both pre and postmenopausal women and all cancer subtypes.

**1603 General Poster Session (Board #385), Sun, 8:00 AM-11:45 AM**

**Importance of durational hormone therapy in breast cancer patients in Germany: Retrospective database analysis.** *Presenting Author: Nina Schmidt, Department of Gynecology, Endocrinology and Oncology, Philipps-University of Marburg, Marburg, Germany*

**Background:** The ATLAS trial demonstrated an additional benefit in the extension of treatment of breast cancer patients from 5 to 10 years. However, the longer therapy requires good compliance by the patients. The aim of this study is to investigate the actual duration of therapy of breast cancer patients until treatment discontinuation or scheduled termination of therapy. **Methods:** We used data from the IMS Disease Analyzer database that entails a dataset of more than 20 million patients. Out of this dataset, breast cancer patients with first time tamoxifen (TAM) or aromatase inhibitors (AI) prescriptions between January 1995 to December 2012 in 1,264 genral practitioner and 387 gynecological practices were identified. Treatment discontinuation of hormonal therapy was defined as 180 days without any treatment or switch to an alternative hormonal therapy. Only women, who still visited their physician more than 180 days after therapy end were included in the analysis. For the current persistence analyses, 8,837 women on tamoxifen or aromatase inhibitors met the inclusion/ exclusion criteria. **Results:** The average hormonal therapy duration was 915 days (SD: 784). 88.1% of women discontinued their therapy before the end of the 5th year. Discontinuation rate was 35.4% within first year and increased to 61.4 % within 3 years of follow-up. The compliance rate decreased with increasing age of the patient. **Conclusions:** The retrospective data analysis showed that the share of patients who stay on hormonal therapy for five years is very small. Therapy discontinuation can be due to side effects, suboptimal communication between physicians and patients or other reasons. Compliance in breast cancer therapy needs to be significantly increased for improved outcome in clinical practice.

**1604 General Poster Session (Board #386), Sun, 8:00 AM-11:45 AM**

**Association of diabetes and cancer-diagnoses in primary care practices in Germany.** *Presenting Author: Nina Schmidt, Department of Gynecology, Endocrinology and Oncology, Philipps-University of Marburg, Marburg, Germany*

**Background:** Previously published studies suggest that type 2 diabetes is associated with an increased risk of cancer, particularly in the case of breast, colorectal, bladder and pancreatic cancers. In the present study the incidence of 14 different cancer types was compared among diabetes vs. none-diabetes patients. **Methods:** We used data from the IMS Health Disease Analyzer database focusing on two different groups of patients: patients diagnosed with diabetes and patients without diabetes who were treated in a general practice in Germany. The analysis was performed retrospectively. The proportion of patients with a primary cancer diagnosis following initial diagnosis of diabetes (or in the same period for patients with no diabetes) was determined. The Hazard ratios (HR; Cox regression) for the risk of cancer in diabetic versus none-diabetic patients (follow-up:. maximum of 12 years) were adjusted for demographic and clinical variables. **Results:** 78,599 patients diagnosed with diabetes and 392,995 patients without diabetes were identified. The study population was matched in terms of age (68 $\pm$ 11 years) and gender (male: 47%). The overall risk of cancer was slightly higher in diabetes-patients than in patients without diabetes (HR: 1.06; CI: 1.04 to 1.09). The risk of getting cancer was significantly increased for patients with diabetes with regard to pancreatic cancer (HR: 2.17; CI: 1.86 to 2.52), esophageal cancer (HR: 1.32; CI: 1.03 to 1.69), kidney cancer (HR: 1.30; CI: 1.11 to 1.52), lung cancer (HR: 1.15; CI: 1.05 to 1.28), colorectal cancer (HR: 1.13, CI: 1.04 to 1, 22) and endometrial cancer in women (HR: 1.43; CI: 1.08 to 1.90). In breast, prostate, liver, stomach, thyroid, urinary bladder, gall bladder cancer and non-Hodgkin lymphoma no significant increase in risk was observed. **Conclusions:** In this retrospective database analysis, with a maximum of 12 year observation period, type 2 diabetes was associated with an increased risk of cancer. However, it is not yet clear at this point whether the diabetes or rather certain antidiabetic drugs increase the risk of cancer. Further research is required to understand these correlations.

**1605 General Poster Session (Board #387), Sun, 8:00 AM-11:45 AM**

**Incidence of cardiovascular events in the real-world population of cancer patients treated with targeted therapies.** *Presenting Author: Jonathan G Zaroff, Kaiser Permanente, Oakland, CA*

**Background:** Population-based risks of cardiovascular events (CV) among cancer patients treated with targeted therapies (tyrosine kinase inhibitors (TKIs) or drugs with similar mechanism of action (MOA)) are not available. Most estimates derive from case-series or trials. The study objective was to estimate the incidence of specific CV events in this population. **Methods:** A population-based cohort study of Kaiser Permanente Northern California (KPNC) members. KPNC is an integrated health program with 3.2 million members (~30% of the insured population) in 14 Northern California counties. Inclusion criteria: Cancer registry diagnosis (1997-2009) of any solid tumor excluding non-melanoma skin cancer, and with treatment with any of the following: sunitinib, sorafenib, imatinib or bevacizumab. Main (adjudicated) outcome measures: Acute coronary syndrome, heart failure (HF), ischemic stroke, hemorrhagic stroke, cardiac arrest, hypertension (HTN), deep venous thrombosis (DVT), pulmonary embolus, and CV death. Statistical analysis: The incidence rate (IR) of each CV outcome was measured as the rate of events per 1000 person years (PY) and reported with 95% confidence intervals (CI). Two follow-up periods were defined: early (treatment duration of the targeted therapy plus 60 additional days) and unrestricted (at any time after a prescription until censoring or the end of follow-up). **Results:** In total, ~3,000 patients met inclusion criteria for this analysis including 294 patients with renal cell carcinoma (RCC) and 80 patients with gastointestinal stromal tumor (mean age=59.5 years, 66.8% White and 2005 as a median year of cancer diagnosis). Highest IRs were observed for HTN, DVT and HF for both the early and unrestricted follow-up periods for all cancer types. For early follow up, the IR of HTN was 0 for prostate cancer, 14.6 (95%CI: 9.7-22.0) for breast cancer, and 25.7 (95%CI: 17.0-38.6) for RCC. These IRs increased to 1.8 (95%CI: 0.2-10.4), 20.7 (95%CI: 14.6-29.2), and 30.6 (95%CI: 20.9-44.4), respectively, for unrestricted follow up. **Conclusions:** This was the first population-based study to estimate incidence of CV events among those treated with targeted therapy, by cancer type.

**1606 General Poster Session (Board #388), Sun, 8:00 AM-11:45 AM**

**Gender disparity in breast cancer: A veteran population-based comparison.** *Presenting Author: Anita Aggarwal, VA Medical Center, Washington, DC*

**Background:** Male breast cancer (MBC) is <1% of all cancers in men and continues to rise. Because of rarity, there is paucity in literature. Management of MBC is generalized from female breast cancer (FBC). The Veterans Affairs (VA) Central Cancer Registry (VACCR) provides a unique source for the study of MBC. The objective of this retrospective analysis was to compare and contrast the characteristics and outcome of MBC with FBC in the VA population. **Methods:** VACCR data from 153 VA medical centers were used to analyze the database of VA patients who had breast cancer diagnosed between 1998 and 2013. Primary site codes were identified for breast cancer (50.0-50.9). Data were entered and analyzed using biostatistical software (SAS 9.3). **Results:** In total, 6443 patients' records were reviewed, and 1123 MBC were compared with 5320 FBC patients. The mean age at diagnosis was 70 and 57 years for MBC and FBC, respectively ($P < .0001$). Higher number of MBC (95%) as compare to FBC ( 72%) were age >50years. 75% patients with breast cancer were white in both genders. More MBC (40% vs 24%) presented with higher disease stage (III and IV) in comparison to FBC (21% had DCIS and 53% stage I). The dominant histology was ductal carcinoma. No difference in laterality was observed. Estrogen and progesterone receptor-positive tumors were more common in MBC compared with FBC. 45% and 36% of MBC and FBC, respectively, received hormonal treatment as first course but fewer MBC received chemotherapy and radiation. The mean follow up time was 754 days. As of Dec 2013, 355 (32%) MBC and 791 (15%) FBC died during the course of the study. Males had higher odds of death compared to females after adjusting for age, race, stage, and grade (OR 1.656, 95% CI 1.347, 2.037). **Conclusions:** To the authors' knowledge, this is the largest series of MBC and FBC to date in the Veterans population. The results suggested that males were older at presentation and had higher stage of breast cancer as compare to FBC. The higher mortality rate in MBC may be due to higher stage and /or tumor biology.

**1607 General Poster Session (Board #389), Sun, 8:00 AM-11:45 AM**

**Burden of HPV infection in the United States: NHANES (1999-2012).** *Presenting Author: Erin Dunn, University of Miami, Miller School of Medicine, Miami, FL*

**Background:** Human Papilloma Viruses (HPVs) are a group of over 150 viruses. When certain types of HPV persist, benign tumors such as warts or papillomas can result. Other persistent HPV infections can play a role in causing cancer of the cervix, penis, anus, vagina, vulva, and oropharynx. National population-based surveys of HPV infection provide estimates of population-specific prevalence, trend, and determinants to identify the burden of HPV. Determining the burden of HPV infection is crucial for future public health efforts. **Methods:** We looked at prevalence of HPV infections, both by DNA (females only) and oral testing (females and males) in the US from 1999-2012 National Health and Nutrition Examination Survey (NHANES) to obtain a representative sample of the US non-institutionalized civilian population. NHANES performs in-person interviews and physical examinations and collects biological samples at homes and at mobile examination centers. We provided epidemiology of HPV infection and its types for females and males. Analysis was performed by SAS v9.3 (SAS Institute Inc, Cary, NC USA) with survey procedures to take into account the sampling design. **Results:** Orally-measured HPV infection affected 7.3% of the US population with the most frequent being HPV 16 (n=276,335) and HPV 62 (n=221,320) and least frequent being HPV 26 (n=736.615). Using the oral test, men had the highest prevalence of general HPV infection (74.4%) and high risk HPV (79.4%). Whites had the highest prevalence of HPV infection (61.7%) and of high risk HPV (69.2%). "Other races" had the lowest HPV infection (4.7%) and high risk HPV (3.5%). DNA-measured HPV affected 42.9% of US women, with HPV 62/53 most and HPV 64 least frequently. DNA-measured HPV showed non-Hispanic White women had the highest prevalence in general (62.0%) and for high risk HPV (62.5%). "Other races" had the lowest prevalence of overall HPV (5.1%), while "other Hispanic" had the lowest burden of high-risk HPV (4.9%). **Conclusions:** Using a large population-based survey-,our results show the variation of HPV by test and type. Understanding the burden of HPV infection, especially the types that are linked to cancer, may provide a base for future cancer prevention programs via screening, vaccination, health promotion and literacy.

**1608 General Poster Session (Board #390), Sun, 8:00 AM-11:45 AM**

**The decrease in global cancer mortality.** *Presenting Author: Paolo Boffetta, Ichan School of Medicine at Mount Sinai, New York, NY*

**Background:** A decrease in cancer mortality has been reported in the United States, Europe and other developed regions of the world during the last two decades. Whether similar trends apply to less-developed countries – and globally – is unclear. **Methods:** We aimed at describing the global patterns of cancer mortality by conducting a systematic analysis of the WHO mortality database for countries for which high- or intermediate-quality data on death certifications are available for a period of at least 10 years (typically 2003-2012). We included 60 countries in the analysis, and calculated age-specific and age-adjusted mortality rates. **Results:** A decrease in overall cancer mortality of approximately 1% per year was present in both developed and less-developed regions, and in both genders. For cancers of the esophagus, stomach, larynx and thyroid, the average decrease in global mortality rate was greater than 2% per year. Individual cancers which showed an increase in mortality rates on a global scale are limited to pancreas and brain (both genders), lung (women), melanoma and kidney (men) and endometrium. **Conclusions:** Reasons for the decrease in cancer mortality in less-developed countries may include decrease in cancer incidence, shift in the stage distribution, shift in the proportional contribution of individual cancers, and improved therapy. The increase in the number of cancer deaths, globally and in less-developed countries, is primarily driven by changes in the demographic structure of the population, but the risk of the individual of dying from cancer appears to decrease in all countries with reliable data. Cancers with increasing mortality rates should be given priority for research.

**1609 General Poster Session (Board #391), Sun, 8:00 AM-11:45 AM**

**Prevalence of COPD in a lung cancer case-control study: Variability by assessment method and by race.** *Presenting Author: Ann G. Schwartz, Karmanos Cancer Institute, Wayne State University, Detroit, MI*

**Background:** The association between lung cancer risk and a history of self reported COPD (Chronic Obstructive Pulmonary Disease) is well established, but the association is less consistent when based on CT scan evidence of emphysema. We evaluated the effect of COPD ascertainment method on lung cancer risk estimates in a case-control study focused on genomic variation in lung cancer patients with and without COPD. **Methods:** A total of 899 participants (280 lung cancer cases and 619 controls) have been enrolled; 45% are African American (AA). Participants completed a questionnaire, spirometry and CT scans to assess COPD by radiology assessment and quantitative imaging analysis. Enrollment to the study to analyze genomic variation is ongoing. **Results:** 20% of cases and 10% of controls reported a physician diagnosis of emphysema; lung cancer risk was significantly associated with self-report (OR=2.1; 95%CI 1.4-3.1). A larger percentage of cases (63%) and controls (53%) were classified as having emphysema based on radiology assessment, reducing the association with lung cancer (OR=1.5, 95% CI 1.1-2.1). The percentage of false positives ("yes" on self-report and "no" on the CT) at ~ 3% and false negative reports (self-report "no" and "yes" on CT) at ~ 45% were consistent across racial groups. Risk of lung cancer based on self reported COPD compared to spirometry defined COPD ($FEV_1/FVC < 70\%$) was similar. 40% of cases self reported COPD as did 24% of controls (OR = 2.0; 95% CI 1.4-2.7), while 52% of cases and 35% of controls had a COPD diagnosis based on spirometry (OR = 2.0; 95% CI 1.4-2.7). Significant differences in self-reported versus spirometry-defined COPD were observed in both cases ($p=0.03$) and controls ($p<0.001$), driven by findings in AA. AA cases ($p=0.01$) and controls ($p<0.001$) had evidence of under-reporting of COPD. ORs associated with emphysema on CT were 1.2 (95% CI 0.7-1.8) for whites and 2.1 (95% CI 1.3-3.5) for AA ( $p=0.053$). Quantitative imaging for COPD is underway. **Conclusions:** These results indicate participants under-report emphysema and COPD, under-reporting differs by race, and regardless of measurement method, there is a significant effect of emphysema and COPD on lung cancer risk.

**1610 General Poster Session (Board #392), Sun, 8:00 AM-11:45 AM**

**Statins and survival in a cohort of veterans with chronic lymphocytic leukemia (CLL).** *Presenting Author: Abdullah Mohammad Khan, Rutgers New Jersey Medical School, Newark, NJ*

**Background:** CLL is the most prevalent leukemia in the Veteran (V) population but there is limited information on the clinical characteristics and risk factors in this population. We hypothesized that statins might have a protective effect based on earlier work (ASCO 2013). **Methods:** In an IRB approved protocol, a retrospective cohort of 130 V diagnosed with CLL from 2001 to 2013 were reviewed for demographic, clinical, and laboratory data. Comorbidity was assessed using Charlson Comorbidity Index (CCI), The Kaplan-Feinstein Index (KFI), and the Cumulative Illness Rating Scale (CIRS). Cox regression analysis was performed using STATA 13. **Results:** The median (M) age was 72 years (34-94), height 69.5 inches (60-99), weight 190 pounds (99-287.5), and BMI 27.4 $kg/m^2$ (15.54-42). 42 (32.3 %) served in the Vietnam War and 88 (67.7%) served during World War II and the Korean conflict. At diagnosis, 129 (99%) V had an ECOG Performance Status (PS) of 0-2, 111 (85%) had Rai stage 0-2 disease, and 81 (62%) were on statins. M hemoglobin was 13.6 g/dl (7.3-17.2), white blood cell count 15.8 K/cmm (3.6-282), absolute lymphocyte count 9.35 K/cmm (1.6-161.1), blood urea nitrogen (BUN) 19 mg/dL (4-88), creatinine 1.1 mg/dl (0.4-3.6), albumin 4.2 (2-4.8), lactate dehydrogenase 182 IU/L (101-1635), and beta 2-microglobulin 2.3 mg/dl (0.9-10.9). By immunophenotyping 35 (26.9%) were CD38/ ZAP-70 positive. The CCI was 4.1 (0-9.0), KFI 1 (0-3), CIRS 15 3 (1-6), CIRS 16 6 (1-14), CIRS 17 2 (0-4.5), CIRS 18 0 (0-1), CIRS 19 0 (0-1). The M survival was 1625 days (4-7502). In univariate analysis, age ($p<0.04$), height ($p<0.05$), BUN ($P<0.02$), and albumin ($P<0.01$) predicted survival. In multivariate analysis, statin use ($p< 0.017$), CD38/ZAP 70 ($p<0.013$) and CIRS 17 ($p<0.022$) were able to predict survival. **Conclusions:** In our study, patients with older age, good PS, and early CLL, statin use was a significant predictor of survival. These findings need to be evaluated in a larger cohort. Statin use may be an important stratification criteria for future trials.

**1611 General Poster Session (Board #393), Sun, 8:00 AM-11:45 AM**

**Comparison of false-negative probabilities for digital and film mammography within a large health care organization.** *Presenting Author: Firas M Dabbous, Division of Epidemiology and Biostatistics, University of Illinois at Chicago, School of Public Health, Chicago, IL*

**Background:** Screening mammography as an early detection tool is susceptible to both false positive and false negative results. We compared false negative probabilities (FNP) for Full Field Digital Mammogram (FFDM) and Screen Film Mammography (SFM) in a single large healthcare organization. **Methods:** Screening mammograms between 2001 and 2009 were linked to incident breast cancer cases for the period 2001-2010 from the Illinois State Cancer Registry using probabilistic linkage methods. The linkage rate in a validation subsample of known breast cancers was 99%. A false negative mammogram ("interval cancer") was defined as a normal finding by the original interpreting radiologist in a woman diagnosed with breast cancer in the subsequent 12 months. **Results:** There were 669,222 screens and 4,058 breast cancer cases (3,071 screen-detected, 988 interval cancers). As expected, overall FNP decreased with increasing age and increased with increasing breast density. Contrary to expectation, FNP was higher for FFDM vs. SFM (27% vs. 23%, $p=0.01$), though marginally lower for FFDM vs. SFM among women under age 50 (24% vs. 27%, $p=0.28$). FFDM was not associated with improved FNR for women with denser breasts or for tumor characteristics suggesting more aggressive disease (hormone receptor negative and higher grade). **Conclusions:** Our results run counter to other studies that have foundFFDM to be more accurate than SFM generally and specifically among women with dense breasts. Differences between studies may be in part a reflection of the community based nature of this sample of women and practicing radiologists.

**1612 General Poster Session (Board #394), Sun, 8:00 AM-11:45 AM**

**Is digital mammography associated with a higher risk of false-positive results? Findings from a community setting.** *Presenting Author: Firas M Dabbous, Division of Epidemiology and Biostatistics, University of Illinois at Chicago, School of Public Health, Chicago, IL*

**Background:** Compared to screen film mammography (SFM), full field digital mammography (FFDM) may improve detection of lesions in younger women with denser breasts but may also increase false positives. We compared false positive probabilities (FPP) for FFDM and SFM in a single large healthcare organization. **Methods:** Screening mammograms during 2001 and 2009 were linked to incident breast cancers diagnosed from 2001-2010 from a state cancer registry using probabilistic methods, and 664,342 screens without a cancer diagnosis in the subsequent 12 months were identified. False positive probability was defined as the proportion of screening mammograms without a subsequent breast cancer diagnosis that were nonetheless interpreted as abnormal. Due to the very large sample size, we focus on clinical rather than statistical significance. **Results:** FPP decreased from 16% in women under 50 to 9% for women aged 70 and above. FPP was lower for women with less dense vs. more dense breasts (11% vs. 14%). Non-White ethnicity (13% vs. 12%) was not associated with FPP, whereas a woman's first screen was associated with higher FPP than subsequent screens (17% vs. 10%). In multivariable models, FPP was 1.3 percentage points lower for FFDM than SFM ($p<0.001$) and the difference did not vary substantially by age, race/ethnicity or breast density. **Conclusions:** It does not appear that FFDM as practiced in this community setting comes with a higher risk of false positive results, which should be reassuring to community-based institutions that have or are shifting away from SFM towards FFDM.

**1613 General Poster Session (Board #395), Sun, 8:00 AM-11:45 AM**

**Gastric cancer: Clinical differences among Hispanic and non-Hispanic whites at the John Theurer Cancer Center (JTCC), Hackensack University Medical Center.** *Presenting Author: Narjust Perez-Florez, Department of Internal Medicine, Rutgers University-New Jersey Medical School, Newark, NJ*

**Background:** Gastric cancer is a leading cause of cancer death worldwide and has significant geographical, ethnic, and socioeconomic differences in distribution. The aim of this study was to compare clinicopathological characteristics and survival between Hispanics and non-Hispanic whites with gastric cancer. **Methods:** We reviewed the records of all patients diagnosed with gastric cancer between January 1999 and March 2013 at the JTCC. A total of 638 patients were studied. Demographics, histology, anatomic site, recurrence and survival rate among both Hispanics and non-Hispanic whites were analyzed. Chi-square test was used to estimate differences in categorical data; Kaplan-Meier and Wilcoxon methods were used for the survival analysis. **Results:** There were 101 Hispanics (H) and 537 non-Hispanic whites (NHW). The mean age at diagnosis was 63 years (21-88) in H and 69 years (39-95) in NHW. A significant difference in age at diagnosis was found in the Stage IV subgroup, with a mean of 54 years for H and 67 years for NHW. At diagnosis, 48 (47.5%) of H patients had stage IV disease compared with 195 (36.3%) of NHW ($p<0.003$). H were more likely to have distal cancers and poorly differentiated tumors compared to NHW (43.8% vs. 15.4%, $p<0.0001$; 70.8% vs. 50.1%, $p<0.0001$, respectively). H had a higher recurrence rate than NHW (17.8% vs 8.7%, $p<0.003$). There was a significant difference in median survival between the two groups, being 51 months for H (95% CI: 34.6-66.9) and 99 months for NHW (95% CI: 77.3-120.7) $p<0.0001$. Gastric cancer was the primary cause of death in 66.2% of H vs. 33.0% of NHW ($p<0.0001$). From the entire cohort, 17.8% of H vs. 33.0% of NHW were free of disease at the time of death ($p<0.007$). **Conclusions:** In our cohort, Hispanic patients were diagnosed with gastric cancer at a younger age, were more likely to have distally located and poorly differentiated tumors, to present with advanced disease at diagnosis, and had shorter overall survival when compared to non-Hispanic whites. Further research should aim to elucidate the basis of these differences, as this could potentially impact management and improve survival.

**1614 General Poster Session (Board #396), Sun, 8:00 AM-11:45 AM**

**Ethnic disparities in pediatric Ewing sarcoma and osteosarcoma.** *Presenting Author: Adam L. Green, Dana-Farber Cancer Center Institute/Boston Children's Cancer and Blood Disorders Center, Boston, MA*

**Background:** Ewing sarcoma (ES) and osteosarcoma (OST) are primarily pediatric tumors that become more difficult to cure when they present with locally advanced disease or metastases. The role of socioeconomic disparities in presentation and outcome of patients with ES and OS has not been well studied. **Methods:** We analyzed all patients in the SEER 18 dataset less than 19 years of age at diagnosis with ES or OST between 2004 and 2010. Comparisons were done using the Fisher exact test. Socioeconomic data for each county were derived from Census 2010 and divided into two categories according to the median value for the cohort. **Results:** Hispanic patients were significantly more likely to have metastatic disease at presentation of OST than non-Hispanic patients (27.2 vs 20.3%, $p=0.014$); there was a trend toward higher likelihood of metastatic presentation for Hispanic ES patients (33.1 vs 27.0%, $p=0.07$). No differences in metastatic disease at presentation were observed in either disease based on race, insurance status, or other socioeconomic variables. Hispanic patients with ES had a significantly poorer 2-year overall survival (OS) than non-Hispanics (75.4 vs 85.3%, $p=0.003$); there was a trend toward poorer 2-year OS for Hispanic patients with OST (80.4 vs 84.9%, $p=0.06$). Hispanic patients with localized ES also had a significantly poorer 2-year OS than non-Hispanics (85.7 vs93.6%, $p=0.008$). No OS difference was seen based on race or insurance status. Significantly poorer 2-year OS for all ES stages, and for localized disease, was also found in patients living in counties with higher than average percentage of people with less than a high school education, foreign born, and living in language isolation. No significant differences in 2-year OS between socioeconomic groups were found in OST. **Conclusions:** Hispanic patients are more likely to present with advanced disease in ES and OST; for ES, this extends to poorer survival. The absence of disparities based on race and insurance, and presence of disparities in other groups with potential limited English proficiency, raise the possibility of language-based barriers to care contributing to these differences. These issues merit further study with primary data in order to determine appropriate intervention.

**TPS1615 General Poster Session (Board #397A), Sun, 8:00 AM-11:45 AM**

**A multicenter phase II study of docosahexaenoic acid (DHA) in patients (pts) with a history of breast cancer (BC), premalignant lesions, or benign breast disease.** *Presenting Author: Ayca Gucalp, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Obesity is a risk factor for the development of BC and is associated with poorer cancer outcomes irrespective of BC subtype. Obesity is associated with diffuse white adipose tissue (WAT) inflammation manifest histologically as crown-like structures (CLS). The presence and severity of CLS in breast WAT (CLS-B) are associated with several proinflammatory mediators known to be involved in development of BC including TNF-$\alpha$/COX-2/IL-1$\beta$ and aromatase. DHA, an omega-3 fatty acid, can suppress inflammation by multiple mechanisms including inhibition of TLR4-activated signaling pathways that induce TNF-$\alpha$ and COX-2. We hypothesize that DHA will decrease the expression of key inflammatory mediators and down-regulate aromatase in breast WAT of overweight/obese women. **Methods:** This is a randomized placebo-controlled, double-blinded phase II study of DHA in overweight/obese pts with a history of stage I-III BC, DCIS/LCIS, Paget's disease, or proliferative benign breast disease (NCT01849250). We aim to determine whether oral DHA for 12 weeks at 1,000 mg twice daily as compared to placebo reduces normal breast tissue levels of TNF-$\alpha$. Secondary objective: To evaluate the effect of DHA on the change from baseline in levels of COX-2/IL-1$\beta$/aromatase/CLS-B. Inclusion:1) BMI $\geq$ 25. 2) $\geq$ 6 months from all prior BC treatment. 3) No clinical evidence of disease. 4) One breast unaffected by invasive cancer, which has not been radiated or surgically augmented. Exclusion: 1) DHA supplementation ($>$ 200 mg/day). 2) Daily aspirin/NSAID use in the week preceding the trial. 3) Regular use of steroids or immunomodulators.Percent change in TNF-$\alpha$ mRNA levels in normal breast tissue between DHA and placebo arm will be compared using two-sample t-test. If normality assumptions are violated, a two-sample Wilcoxon rank-sum test will be used. With 30 subjects in each arm, we will have 80% power to detect effect size as small as 0.74 at 0.05 significance level using a two-sided, two-sample, Student t-test. Assuming a 10% dropout rate and 10% non-evaluable rate, up to 76 pts will be randomized. To date, 17 pts have been consented and 9 have been randomized to participate. Clinical trial information: NCT01849250.

**TPS1616 General Poster Session (Board #397B), Sun, 8:00 AM-11:45 AM**

**MELO-D: Antiproliferative effects of melatonin and vitamin D in breast cancer.** *Presenting Author: Punam Rana, Juravinski Cancer Center, Hamilton, ON, Canada*

**Background:** Vitamin D and melatonin have been associated with anticancer activity in epidemiological and experimental studies. However, evidence from controlled trials on their efficacy in cancer prevention is inconsistent, in part related to lack of knowledge on the mechanism of preventive activity. The MELO-D study is the first to use an innovative pre-operative chemoprevention approach to examine the potential anticancer role of vitamin D and melatonin. We hypothesize that vitamin D and separately, melatonin, decreases the proliferative activity in a breast cancer tumor, as measured by Ki67. **Methods:** Using a 2x2 factorial design, 144 women diagnosed with invasive breast cancer are randomized to receive Vitamin D3 (2000 IU daily) or placebo, and to melatonin (20 mg/day) or placebo. The duration of study medication is 3-4 weeks while the subjects wait for definitive breast cancer surgery. The primary outcome is difference in Ki67 between the initial core biopsy and final surgical specimen. The mean difference in Ki67 from baseline to definitive surgery will be compared between groups. The effect of Vitamin D and melatonin will also be examined in relation to other factors including serum vitamin D levels, genetic factors (e.g. VDR polymorphism), and tissue factors (e.g. p53 status). Patients are currently being recruited from the Juravinski Cancer Centre (JCC) and St. Joseph's Healthcare Hamilton. Clinical trial information: NCT01965522.

**TPS1617 General Poster Session (Board #398A), Sun, 8:00 AM-11:45 AM**

**Add-Aspirin trial: A phase III, double blind, placebo-controlled, randomized trial assessing the effects of aspirin on disease recurrence and survival after primary therapy in common nonmetastatic solid tumors.** *Presenting Author: Ruth E Langley, Medical Research Council, Clinical Trials Unit at University College London, London, United Kingdom*

**Background:** Pre-clinical data demonstrate that aspirin inhibits tumour growth and prevents metastases. Meta-analyses of individual patient data from randomized trials evaluating cardiovascular (CV) effects of aspirin show reduced metastases and cancer deaths for those on aspirin. Toxicity concerns have limited aspirin use as a primary anti-cancer prevention agent. In the adjuvant setting, the risk:benefit ratio differs, with higher morbidity and mortality from recurrence potentially outweighing risks. Aspirin, an inexpensive drug with a potential therapeutic role in several common cancers, could have a large impact on the global cancer burden. The Add-Aspirin trial investigates if aspirin use after curative treatment for non-metastatic solid tumours prevents recurrence and prolongs survival. **Methods:** Add-Aspirin is a double blind, placebo-controlled, multicentre, international trial. Eligible participants (n=9,920) from the UK and India will have had potentially curative treatment for non-metastatic cancer. There are 4 separate tumour cohorts – breast (BC), colorectal (CRC), gastro-oesophageal (GOC) and prostate cancer (PC). Following an 8 week active run-in period of aspirin 100mg daily to assess adherence and tolerability, participants are randomised to aspirin 100mg, 300mg or placebo daily for $>$ 5 years. Each tumour specific cohort is individually powered and has a separate disease-specific primary outcome measure: BC (n = 3,100) invasive disease-free survival (DFS); CRC (n = 2,600) DFS; GOC (n = 2,100) overall survival (OS); and PC (n = 2,120) biochemical recurrence-free survival. Secondary outcome measures include adherence, toxicity and CV events. OS across the 4 cohorts is a co-primary outcome measure. Sub-studies include assessment of thromboxane B2 for compliance and methodological work to assess the utility of long-term passive follow up. Blood/tissue specimens collected at enrolment will allow tumour-specific mutations to be used as stratification factors. Recruitment will commence by May 2014. Funder CRUK; Sponsor University College UK. Clinical trial information: 2013-004398-28.

**TPS1618 General Poster Session (Board #398B), Sun, 8:00 AM-11:45 AM**

**Community-based cluster randomized trial of screening with visual examination of oral cavity and double-contrast barium swallow for upper aerodigestive tract cancers.** *Presenting Author: Conjeevaram S Pramesh, Tata Memorial Center, Mumbai, India*

**Background:** Oral, esophageal and hypopharyngeal cancers are common and important public health problems in India. They are highly aggressive neoplasms and are associated with a poor prognosis especially because most patients are diagnosed at late stages of disease. Certain high risk factors like tobacco, betel and arecanut and alcohol use have been associated with the causation of these cancers. Screening may offer the opportunity to reduce the incidence of invasive lesions and also help in decreasing the mortality rates associated with these cancers. **Methods:** We are currently doing a large cluster randomized trial in Ratnagiri district, Maharashtra, India to ascertain whether screening of oral cancers with visual examination by trained health workers and hypopharyngeal and esophageal cancers with double contrast barium swallow (DCBS) will reduce mortality from these diseases. The population between 35 and 65 years of age who have used tobacco and/or alcohol for more than five years are eligible for the trial. The area has been divided into 16 clusters (7,500 individuals per cluster) of which 8 clusters will receive two rounds of screening at three year intervals while all 16 clusters will receive health education about tobacco and alcohol cessation. Individuals with abnormal findings on oral examination or DCBS will undergo clinical examination by a clinician (trained in diagnosing early cancers and precancerous lesions of the oral cavity) or direct laryngoscopy or upper gastrointestinal endoscopy with biopsy of suspicious or definite abnormalities at the base hospital. Patients with a biopsy proven oral, esophageal or hypopharyngeal cancer will undergo routine staging investigations and standard treatment as per the stage at diagnosis. The primary outcome measure is mortality from oral, hypopharyngeal and esophageal cancers. Secondary outcome measures will include overall survival, diagnostic sensitivity of DCBS and cost effectiveness of screening. We have so far completed screening of 17,258 out of 24,398 eligible individuals (70.7% compliance) and detected 27 cancers. The study is expected to be completed in 2010. Clinical trial information: Not yet assigned.

**2000 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Phase III study of radiation therapy (RT) with or without procarbazine, CCNU, and vincristine (PCV) in low-grade glioma: RTOG 9802 with Alliance, ECOG, and SWOG.** *Presenting Author: Jan C. Buckner, Mayo Clinic, Rochester, MN*

**Background:** Early results of R9802 (Shaw et al: J Clin Oncol. 2012; 30(25):3065-70) demonstrated that PCV given with RT at the time of initial diagnosis prolongs progression-free survival (PFS), but not overall survival (OS), compared with RT alone. Herein, we report long term follow up results. **Methods:** Eligibility criteria included age <40 years with subtotal resection or biopsy, age >40 with any extent of resection, and supratentorial grade II astrocytoma (A), oligo-astrocytoma (OA), or oligodendroglioma (O). Patients were stratified by age, histology, Karnofsky Performance Status, and presence versus absence of contrast enhancement on the preoperative imaging study and randomized to RT alone (54 Gy in 30 fractions) or RT followed by 6 cycles of PCV chemotherapy. Wilcoxon test was used to compare survival distributions. Cox proportional hazard models were used to identify prognostic variables. **Results:** 251 eligible patients were accrued from 1998 to 2002. Median follow up is 11.9 years; 55% of patients have died. Patients in the RT + PCV arm have significantly longer median survival time (MST) compared to the RT alone arm (13.3 vs. 7.8 years, p=0.03; HR=0.59) and longer median PFS (10.4 vs. 4.0 years, p=0.002; HR=0.50). 5 and 10 year OS for RT + PCV vs RT alone are 73% vs 64%, and 62% vs 41%, respectively. Cox model identified RT + PCV treatment arm as a favorable prognostic variable for OS (p=0.003; HR 0.60) and PFS (p<0.001; HR=0.49). A or A-dominant OA histology (vs O or O-dominant OA) was prognostic for worse OS (p<0.001; HR=2.16) and PFS (p<0.001; HR 1.85). Male OS but not PFS was worse than females (p=0.02; HR 1.51). Analyses of 1p/19q co-deletions and IDH mutations have not yet been completed. **Conclusions:** For grade 2 glioma patients with less than gross total tumor resection or >40 years of age, PCV + RT prolongs both OS and PFS compared with RT alone. Patients with A or A-dominant OA have worse outcomes, as do males. Multivariable models that incorporate 1p/19q co-deletion and IDH mutational analyses may more fully elucidate the magnitude of treatment benefit for patients with tumors identified by specific histologic type and molecular markers. Clinical trial information: NCT00003375.

**2001^ Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Correlation of molecular subtypes with survival in AVAglio (bevacizumab [Bv] and radiotherapy [RT] and temozolomide [T] for newly diagnosed glioblastoma [GB]).** *Presenting Author: Heidi Phillips, Genentech Inc., South San Francisco, CA*

**Background:** Factors that correlate the extent of clinical benefit with anti-VEGF therapy are poorly understood. Two phase 3 trials in newly diagnosed GB (AVAglio and RTOG-0825) reported that Bv+RT/T prolonged PFS but not OS *v* placebo (P)+RT/T. Specific GB pt subgroups may derive OS benefit from 1st-line Bv; tumor profiling has uncovered intrinsic and prognostic GB molecular subtypes. Bv efficacy in molecular subtypes was evaluated as an exploratory objective in AVAglio. **Methods:** An 800 gene platform capable of reliable gene expression (GE) measurement in formalin-fixed, paraffin-embedded samples was developed/validated. In AVAglio, randomizedpts (n=921) received: RT/T+Bv or P, 6 wks; 28-day break; maintenance T+Bv or P (x6); Bv or P until PD/unacceptable toxicity. Samples from 342 AVAglio pts (Bv/P; biomarker evaluable population) were profiled and classified into known GB molecular subtypes (pre-defined hypothesis); assigned subtypes were correlated with OS. An exploratory outcome-driven analysis to discover novel predictor subtypes more directly associated with OS benefit from Bv was then performed. **Results:** Per recent data from The Cancer Genome Atlas (TCGA), pts with proneural tumors with wild-type isocitrate dehydrogenase 1 (IDH1) had the worst prognosis among all GB subtypes (defined by TCGA [Verhaak, Cancer Cell 2010]/ Phillips, Cancer Cell 2006). Importantly, this analysis uncovered a relationship between molecular subtype and extent of OS benefit in Bv-treated pts. Exploratory outcome-driven GE analyses identified novel gene clusters associated with prolonged OS with Bv *v* P. Pt groups predicted to derive Bv benefit in the outcome-driven method overlapped with, but were not identical to, groups defined by known GB subtypes; thus, novel OS-associated candidate predictors may more precisely identify pts likely to derive benefit from Bv. **Conclusions:** Candidate molecular predictors were identified in AVAglio, suggesting that a subgroup of newly diagnosed GB pts may derive OS benefit from Bv; these data could impact pt stratification and therapy and give insights into Bv mode of action, and warrant further validation in other datasets. Clinical trial information: NCT00943826.

**2002 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**A 6-gene signature for outcome prediction of grade II/III glioma.** *Presenting Author: Tim Lautenschlaeger, Department of Radiation Medicine, The Ohio State University, Columbus, OH*

**Background:** Grade II and III gliomas are very heterogeneous in their outcome, leaving some uncertainty as to what the best treatment is for the individual patient. **Methods:** We used multiple datasets totaling 756 glioma patients to develop a prognostic 6-gene signature for grade II and III gliomas. Three risk groups were defined (low, medium, and high risk). This 6-gene classifier was then validated in multiple independent glioma data sets totaling over 500 patients and translated into a PCR-based assay. **Results:** The classifier was validated in a 214 grade II/III glioma patient independent validation set (TCGA, HR=4.03; 95% CI, 1.82-8.92; p= 0.001, for low vs high risk group) and a 287 patient grade IV glioblastoma set (updated TCGA, HR, 2.42; 95% CI, 1.69-3.47; p< 0.001, for low vs high risk group). The classifier was then translated into a PCR based assay in an independent 32 grade II/III glioma patient pilot cohort (multi-institutional, HR=6.3; 95% CI, 1.7-23.6; p= 0.006, for low vs high risk group). Multivariate Cox regressions validated the risk classifier independent of other clinical or molecular factors (grade, histology, IDH1 status) in all three data sets. ROC analysis for 3 year overall survival demonstrate that the classifier can predict 3 year survival better than grade, histology or IDH1 mutation status (AUC, 0.82; 95% CI, 0.70-0.93; p< 0.0001) in patients with grade II/III tumors. Of note, ROC analysis for 3 year overall survival demonstrated that the 6-gene classifier was also an excellent predictor of 3 year survival in glioblastoma (AUC, 0.84; 95% CI, 0.76-0.91; p< 0.0001). **Conclusions:** The 6-gene classifier can reliably predict 3-year outcome for patients older than 40 years and 7-year outcome for patients younger than 40 years old with grade 2 and 3 gliomas independent of histology, grade or IDH1 mutation status.

**2003 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Radiation therapy and concurrent plus adjuvant temsirolimus (CCI-779) versus chemoirradiation with temozolomide in newly diagnosed glioblastoma without methylation of the *MGMT* gene promoter.** *Presenting Author: Wolfgang Wick, Neurooncology, University of Heidelberg Medical Center, Heidelberg, Germany*

**Background:** Preclinical data indicate activity of mammalian target of rapamycin inhibitors and synergistic activity together with radiotherapy in glioblastoma. The aim of this trial is to assess the therapeutic activity of temsirolimus (CCI-779), an intravenous mTOR inhibitor, in patients with newly diagnosed glioblastoma with unmethylated *O6 methlyguanine-DNA-methlytransferase (MGMT)*promoter. **Methods:** Patients (n=257) with newly diagnosed glioblastoma after open surgical biopsy or resection fulfilling basic eligibility criteria underwent a central *MGMT* promoter analysis using quantitative methylation specific PCR. Patients with glioblastoma harboring an unmethylated *MGMT* promoter (n=111) were randomized 1:1 between radiotherapy (60 Gy; 5 times 2 Gy per week) plus concomitant and six cycles of maintenance temozolomide or radiotherapy plus weekly temsirolimus at 25 mg flat dose to be continued until progression or undue toxicity. Primary endpoint was overall survival at 12 months (OS12). Sample size of the investigational treatment arm required 54 patients to assess adequacy of temsirolimus activity set at 80%. More than 38 patients alive at 12 months in the *per protocol* population was considered a positive signal. A control arm of 54 patients treated with the standard of care was implemented to evaluate the assumptions on OS12. **Results:** Between December 2009 and October 2012, 111 pts in 14 centers were randomized and treated. Median age was 55 and 58 years in the temsirolimus and standard arm, respectively. Most patients (95.5%) had a WHO performance status of 0 or 1. Both therapies were properly administered with a median of 13 cycles of maintenance temsirolimus. In the *per protocol*population, exactly 38 patients treated with temsirolimus (out of 54 eligible) reached OS12. In the intention to treat population OS12 was 72.2% [95% CI (58.2, 82.2)] in the temozolomide arm and 69.6% [95% CI (55.8, 79.9) in the temsirolimus arm [HR=1.16 95% CI (0.77, 1.76), p=0.47]. **Conclusions:** The therapeutic activity of temsirolimus in patients with newly diagnosed glioblastoma with an unmethylated MGMT promoter is too low. Clinical trial information: NCT01019434.

**2004** **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**A randomized, placebo-controlled pilot trial of armodafinil for fatigue in patients with gliomas undergoing radiotherapy.** *Presenting Author: Eudocia Quant Lee, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Fatigue is a common symptom among glioma patients and affects quality of life. Armodafinil, a wakefulness-promoting medication, benefits patients with fatigue of various causes. This study evaluates the effects of armodafinil on fatigue in glioma patients undergoing radiation therapy (RT). **Methods:** Eligibility criteria included age ≥ 18; Karnofsky Performance Status (KPS) ≥ 60; grade 2-4 glioma undergoing RT to a total dose of 50-60 Gy with or without chemotherapy. Patients were randomized 1:1 to armodafinil (A) or placebo (P). Fatigue assessments were made at baseline, Day 22, Day 43, and Day 56 with the FACIT-F Fatigue Scale, Brief Fatigue Inventory (BFI), and Cancer Fatigue Scale (CFS). The primary aim is to detect a difference in the 42-day change in FACIT-F fatigue subscale scores between the two groups using a 2-sample Wilcoxon statistic. Secondary outcomes include a 42-day change in CFS and BFI. **Results:** Data is available for 77 of the 80 patients (40 in A and 37 in P). In the armodafinil arm, median age was 56 (25-79), median KPS was 90 (70-100), 57.5% had glioblastoma (GBM), 35% had anaplastic glioma (AG), 7.5% had another glioma histology. In the placebo arm, median age was 54 (19-78), median KPS was 90 (70-100), 51.4% had GBM, 32.4% had AG, and 16.2% had another glioma histology. The median 42-day change in the FACIT-F fatigue subscale scores in the armodafinil arm was 2 (range -40 to 26) and in the placebo arm was -6.665 (range -65 to 28) with Wilcoxon p-value of 0.066. There was a statistically significant improvement in fatigue in the armodafinil arm vs. the placebo arm based on median 42-day change in the BFI (Wilcoxon p-value of 0.008). Toxicity was rare and similar between arms. There were no cardiac toxicities attributed to treatment. One patient experienced insomnia in the armodafinil arm. **Conclusions:** Treatment with armodafinil is well tolerated in glioma patients undergoing RT. There is a trend towards fatigue reduction in the armodafinil group. Updated results will be presented. Study Sponsored by: Cephalon, Inc., a wholly owned subsidiary of Teva Pharmaceuticals, and the National Brain Tumor Society. Clinical trial information: NCT00766467.

**2005** **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**A randomized, double-blind, placebo-controlled phase 2 trial of dendritic cell (DC) vaccination with ICT-107 in newly diagnosed glioblastoma (GBM) patients.** *Presenting Author: Patrick Y. Wen, Dana-Farber Cancer Institute, Boston, MA*

**Background:** The trial investigated whether adding tumor-antigen-loaded DC vaccine to surgery and chemoradiation would improve overall survival (OS) or progression free survival (PFS). **Methods**: HLA-A1+ and/or -A2+ resected patients with residual tumor $<1$ $cm^3$ received 6 weeks of concurrent temozolomide (TMZ) and radiation. 124 patients were randomized 2:1 to receive ICT-107 (autologous PBMC-derived DC pulsed with 6 synthetic peptide CTL epitopes targeting the GBM tumor and tumor stem cell-associated antigens MAGE-1, HER-2, AIM-2, TRP-2, gp100, and IL-13R$\alpha$2) or its matching control (unpulsed DC). Patients then received induction ICT-107 or control QWx4 followed by maintenance TMZ, 5 days/mo for 12 mos. Booster vaccinations occurred at 1, 3, and 6 mos after induction, and every 6 mos thereafter. The trial concluded and data were evaluated at 67 events. **Results:** ICT-107 was generally safe and well tolerated, with no imbalance in AEs between the treated and control groups. PFS improved by 2 mos in the ICT-107 ITT group (p=0.02 two-sided, hazard ratio (HR)=0.56). In the per-protocol (PP) group (117 patients receiving all 4 induction vaccinations), p=0.01 two-sided, HR=0.53, and the difference in median PFS increased to 3 mos. The median OS favored ICT-107 by 2 mos in the ITT and 3 mos in the PP groups. However, the number of events was small and OS did not reach statistical significance (p=0.58 two-sided, HR=0.87, and p=0.40 two-sided, HR=0.79, respectively). Median follow-up from randomization was 13.6 mos. In the ICT-107 group, vaccine activation markers IL12 and HLA-DR were predictive of OS (p-values $<$ 0.05). There were no correlations in the placebo group. **Conclusions:** This is the first randomized, placebo-controlled immunotherapy trial in GBM to positively affect a clinical outcome, PFS. Although OS improvement was not statistically significant at the 67/124 event point, patients continue to be followed for OS, allowing periodic updating of the primary endpoint and assessment of long-term survival. Analysis of QOL, and correlation of both tumor antigen expression and vaccine immunologic response with OS are in process.

**2006^** **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Final results of APG101_CD_002: APG101 plus reirradiation versus reirradiation in the treatment of patients with progressive glioblastoma.** *Presenting Author: Michael Platten, Neurooncology, University of Heidelberg Medical Center, Heidelberg, Germany*

**Background:** Preclinical data indicate antiinvasive activity of APG101, a CD95-ligand (CD95L)-binding fusion protein, and synergistic activity with radiotherapy in glioblastoma. In healthy volunteers, single doses of up to 20 mg/kg APG101 are safe. **Methods:** Patients (N=91) with progressive glioblastoma after standard radiochemotherapy (± 1 second-line chemotherapy), provided a tumour diameter of 1-4 cm and time since the end of radiotherapy ≥ 8 months, were randomised 1:2 stratified for tumour diameters ≤ or > 2.5 cm between radiotherapy (36 Gy; 5 times 2 Gy per week; rRT) or rRT+APG101 (400 mg weekly i.v.) to be continued until progression. CD95L was evaluated in tumour tissue. This open-label, non-comparative phase II trial (NCT01071837) sought to demonstrate a doubling in the 6-months progression-free survival (PFS-6) rate with rRT+APG101 assuming a 15% PFS-6 rate with rRT alone. The control arm with rRT alone was added to calibrate for the PFS-6 assumption. **Results:** Patient characteristics in the intention-to-treat population [N=84 (26 patients rRT, 58 patients rRT + APG101)] were balanced. The PFS-6 rates were 3.8% (95%-CI: 0.1 - 19.6) rRT and 20.7% (95%-CI: 11.2 - 33.4) for rRT+APG101 (p=0.04). Median PFS was 2.5 (95%-CI: 2.3-3.8) months and 4.5 (95%-CI: 3.7-5.4) months with a hazard ratio (HR) of 0.49 (95% CI: 0.27-0.88, p=0.0162). Cox regression analysis adjusted for tumour size revealed a HR for rRT+APG101 for death of any cause of 0.60 (95% CI: 0.36-1.01)] (p=0.0559). Patients with lower methylation levels at CpG2 in the *CD95L* promoter in the tumour tissue had a stronger risk reduction (HR=0.13 95% CI: 0.03-0.52) when treated with APG101. **Conclusions:** CD95 pathway inhibition in combination with rRT is an innovative concept with clinical efficacy. It warrants further clinical development. *CD95L* promoter methylation in the tumour may be developed as a biomarker. Clinical trial information: NCT01071837.

**2007** **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Validation of rano criteria: Contribution of T2/FLAIR assessment in patients with recurrent glioblastoma treated with bevacizumab.** *Presenting Author: Raymond Yi-kun Huang, Dana-Farber Cancer Institute/Brigham and Women's Cancer Center, Boston, MA*

**Background:** Since its introduction, the RANO criteria have been widely adopted in clinical trials for evaluating treatment response in high-grade gliomas. To date, the criteria have not been validated using outcome data from prospective trials. We examined the radiologic data of patients with recurrent glioblastoma treated with bevacizumab from the randomized phase II BRAIN trial (AVF3708g) to determine the effect of including T2/FLAIR evaluation in the RANO criteria on measurements of objective response rates (ORR) and progression free survival (PFS). **Methods:** The imaging data of 163 patients with recurrent glioblastoma from the BRAIN trial were evaluated by 6 readers blinded to clinical information. The ORR and median PFS were determined using the RANO criteria and compared to those obtained without evaluating the T2/FLAIR abnormality (Macdonald criteria). Landmark analyses were performed at 2, 4 and 6 months, and Cox proportional hazard models were used to determine the associations between OR and progression with subsequent survival. **Results:** The ORRs were 0.433 (95% CI: 0.373 - 0.494) and 0.451 (95% CI: 0.391 – 0.513) by RANO and Macdonald criteria, respectively (p = 0.78). The median PFS was 4.21 months (95% CI: 3.68-5.49) using RANO criteria, compared to 5.52 months (95% CI: 4.27-6.83) as determined by Macdonald criteria (p=0.04). At 2-, 4-, and 6-month landmarks, both OR status and PFS determined by RANO criteria were predictive of overall survival (OS) (hazard ratios for 4-month landmark; OR HR= 2.12, p = 0.0003, PFS HR=4.08, p<0.0001). **Conclusions:** The inclusion of T2/FLAIR assessment in the RANO criteria results in a small difference in median PFS but no significant difference in ORR. The associations of OR and PFS with survival using the RANO criteria at 6 months and earlier time points following therapy potentially support their possible roles as surrogates for OS.

**2008^ Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

**Contrast-enhanced T1-weighted digital subtraction maps combined with diffusion MRI to identify recurrent glioblastoma patients that benefit from bevacizumab therapy.** *Presenting Author: Benjamin M. Ellingson, Department of Radiological Sciences, Biomedical Physics, and Bioengineering; University of California, Los Angeles, Los Angeles, CA*

**Background:** Bevacizumab is an anti-angiogenic therapy approved for recurrent glioblastoma (GBM); however, use of bevacizumab remains controversial. In the current study we demonstrate that recurrent GBM patients with a particular imaging phenotype identified on diffusion MRI who also show an early response on contast-enhanced T1-weighted digital subtraction maps (delta T1) have a significant survival advantage when treated with bevacizumab. **Methods:** A total of 105 patients with recurrent GBM enrolled in a multicenter clinical trial (BRAIN Trial, AVF3708g) with apparent diffusion coefficient (ADC) data from diffusion MRI available were included. Delta T1 maps were calculated by subtracting post-contrast from pre-contrast T1-weighted images, leaving only areas of enhancement visible. ADC histogram analysis was performed prior to therapy by fitting a double mixed Gaussian model to ADC histograms in contrast-enhancing areas. Patients were stratified into three groups based on their imaging phenotype: (1) Pro-Bev – patients with a high pre-treatment ADC in the lower Gaussian curve who show more than a 25% reduction in enhancement after therapy; (2) Anti-Bev – a low pre-treatment ADC who also do not show a change in contrast enhancement after therapy; and (3) Mixed Response – patients with only a single prognostic factor, either by diffusion MRI or delta T1. **Results:** Patients with both a favorable pre-treatment diffusion MRI phenotype and an early response after bevacizumab therapy demonstrated a significantly longer PFS (Cox, P=0.01; c-index = 0.61) and OS (P=0.001; c=index=0.60) compared with the other groups. Patients with an unfavorable pre-treatment diffusion MRI phenotype who do not have an early response were more likely to progress and expire early. **Conclusions:** A combination of pre-treatment diffusion MRI analysis and response assessment using delta T1 maps can be used as an early indicator of GBM patients that will benefit from bevacizumab therapy at recurrence. Such a combination technique may be useful for patient stratification for clinical trials involving bevacizumab combination therapies. Clinical trial information: NCT00345163.

**2009 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

**Prospective analysis of serial FLT-PET scanning to discriminate between true and pseudoprogression in glioblastoma.** *Presenting Author: Martha W. den Hollander, Department of Medical Oncology, University Medical Center Groningen, Groningen, Netherlands*

**Background:** Response evaluation in glioblastoma (GBM) patients after concomitant radiotherapy and temozolomide (TMZ) is hampered by the occurrence of progressive contrast enhancing lesions on MRI that do not reflect true tumor progression. $^{18}$F-fluorothymidine (FLT) is a Positron Emission Tomography (PET) tracer that is taken up by proliferating cells. The goal of this study was to prospectively assess the value of FLT-PET in discriminating between true progression and pseudoprogression in patients with primary GBM treated with radiotherapy and TMZ (NTR3680). **Methods:** FLT-PET scans were performed before start and 4 weeks after radiochemotherapy. MRI scans were performed at these time points and after 3 cycles of adjuvant TMZ. Macdonald criteria were used for response evaluation on MRI. Pseudoprogression was defined as progressive disease on MRI after radiochemotherapy, with stabilization or improvement of enhancing lesions after 3 cycles of adjuvant TMZ. Changes in $SUV_{max}$ and tumor to normal brain tissue ratios were calculated for FLT-PET and compared between patients with true progression and pseudoprogression. In case of multiple lesions, the mean of the $SUV_{max}$of lesions was calculated. Ki67 staining in the primary tumor and overall survival data were analyzed. **Results:** Thirty patients, 28 patients with GBM and two with gliosarcoma (WHO grade IV), were included. Of the 19 patients assessed for pseudoprogression, 6 showed pseudoprogression and 6 showed true progression. There was no difference in (changes in) $SUV_{max}$ and tumor to normal brain tissue ratios on FLT-PET between patients with true progression and pseudoprogression. Baseline FLT uptake correlated with overall survival ($P = 0.002$) but not with Ki67. **Conclusions:** FLT-PET scans do not discriminate between true progression and pseudoprogression in patients with GBM, but baseline FLT uptake does correlate with overall survival. Clinical trial information: NTR3680.

**2010 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

**Diagnosis of pseudoprogression using ferumoxytol perfusion MRI in patients with glioblastoma to predict better outcome.** *Presenting Author: Edward A. Neuwelt, Oregon Health & Science University, Portland, OR*

**Background:** This retrospective IRB approved study determined the survival of GBM patients with or without pseudoprogression. **Methods:** Patients with histologically-proven newly diagnosed GBM at Oregon Health and Science University from January 2006 to June 2012 after standard CRT received adjuvant temozolomide (TMZ) until tumor progression. Diagnosis of pseudoprogression was made by perfusion MRI with ferumoxytol (an iron oxide nanoparticle) and updated Response Assessment in Neuro-Oncology Working Group (RANO) criteria. Survival was determined using Kaplan-Meier product limit analysis and Cox regression model. **Results:** A total of 68 patients were included. The overall median survival was 19.9 months (95% CI 15.1-22.5). Median survival in 24 (35.3%) patients with pseudoprogression was 34.7 months (95% CI 20.3-54.1), significantly longer than the 13.4 months (95% CI 11.1-19.5) in 44 (64.7%) patients without pseudoprogression ($P<0.0001$). The longest survival was seen in patients with combination of pseudoprogression and MGMT promoter methylation, 54.1 months (Table). **Conclusions:** Pseudoprogression is associated with better survival, especially if concurs with MGMT promoter methylation. The patients that experienced true tumor progression had poor survival. This study emphasizes the importance of differentiating tumor progression and pseudoprogression using ferumoxytol to assess perfusion.

| | Death/patients | Hazard ratio (95% CI) | Median survival (months; 95% CI) |
|---|---|---|---|
| **Overall survival** | 56/68 | -- | 19.9 (15.1, 22.5) |
| **Pseudoprogression status** | | | |
| **No** | 43/44 | Reference | 13.4 (11.1, 19.5) |
| **Yes** | 13/24 | 0.24 (0.13, 0.47) | 34.7 (20.3, 54.1) |
| **MGMT status** | | | |
| **Nonhypermethylated** | 6/10 | Reference | 28.2 (19.0, 49.1) |
| **Hypermethylated** | 6/12 | 0.49 (0.15, 1.60) | 54.1 (19.9, 79.9) |

**2011 Poster Highlights Session (Board #1), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**PD1 and PD-L1 expression in glioblastoma.** *Presenting Author: Anna Sophie Berghoff, Institute of Neurology, Medical University of Vienna, Vienna, Austria*

**Background:** We aimed to investigate programmed cell death (PD)1 and PD-ligand (L)1 expression and relevance in glioblastoma. **Methods:** 135 specimens of 117 patients (median age 60); median KPS 90 (range 10-100) with glioblastoma were included. In 18 patients, resection specimens of the first local recurrence in addition to tumor tissue from the initial resection were available. Analyses of PD1, PD-L1, CD3 and CD8 expression were performed by immunohistochemistry and previously published semiquantitative evaluation criteria. *O6-methylguanine DNA methyltransferase* (*MGMT*) promoter methylation was analyzed using pyrosequencing and a cut-off at 8%. **Results:** We found sparse to moderate density of tumor-infiltrating lymphocytes (TILs) in a total of 100/135 (74.1%) cases (CD3+ 92/135, 68.1%; CD8+ 64/135, 47.4%). PD1 expression was found on scattered TILs, both in the perivascular compartment and within the tumor tissue, in 20/135 (14.8%) cases. PD-L1 expression was evident on tumor cells and macrophages/microglial cells throughout the tumor tissue with occasional focal accentuation in 116/135 (85.9%) specimens, with 44.5% showing PD-L1 staining of more than 50% of the viable tumor tissue. *MGMT* methylation was found in 37/99 (37.4%) analyzed samples. There was no significant correlation of expression of PD1 or PD-L1 with the density of TILs or *MGMT* methylation status (p>0.05), respectively. Younger age (p=0.009), high KPS (p=0.035) and *MGMT*hypermethylation (p=0.008) showed a significant correlation with favorable overall survival, while TIL density or expression of PD1 (p=0.783) and PD-L1 (p=0.866) did not associate with patient outcome. Table 1 compares expression of PD1, PD-L1, CD3 and CD8 between matched specimens of the initial tumor and the first local recurrence. **Conclusions:** PD1 and/or PD-L1 are immunohistochemically detectable in a majority of glioblastoma samples. A clinical study with specific immune checkpoint inhibitors seems to be warranted in glioblastoma.

| N = 18 | Initial tumor +, ↓ recurrence + | Initial tumor - ↓ recurrence - | Initial tumor + ↓ recurrence - | Initial tumor - ↓ recurrence + |
|---|---|---|---|---|
| **PD-L1** | 12 (66.7%) | 1 (5.6%) | 4 (22.2%) | 1 (5.6%) |
| **PD1** | - | 15 (83.3%) | 3 (16.7%) | - |
| **CD3** | 10 (55.6%) | 3 (16.7%) | 1 (5.6%) | 4 (22.2%) |
| **CD8** | 10 (55.6%) | 2 (11.1%) | 4 (22.2%) | 2 (11.1%) |

**2012 Poster Highlights Session (Board #2), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Association of tumor-infiltrating lymphocytes with brain edema and overall survival in brain metastases.** *Presenting Author: Matthias Preusser, Medical University of Vienna, Vienna, Austria*

**Background:** Density of tumor-infiltrating lymphocytes (TILs) has a prognostic impact in various extracranial solid tumors. We characterized TILs in patients with brain metastases (BM). **Methods:** We immunostained neurosurgical specimens of patients with newly diagnosed single brain metastasis for CD3, CD8, CD45RO and FOXP3 and used previously published semiquantitative evaluation criteria. **Results:** 118 BM specimens of patients with lung cancer (62/118; 52%), breast cancer (17/118; 14%), melanoma (6/118; 5%), kidney cancer (10/118; 8%) or another primary tumor (23/118; 19%) were available for this study. Dense infiltration with CD3+ TILs was observed in 64/118 (54%) specimens, with CD8+ TILs in 70/118 (59%), with CD45RO+ TILs in 72/118 (61%) and with FOXP3+ TILs in 26/118 (22%) specimens. Dense CD3+ TILs infiltration was more frequently observed in lung cancer, melanoma and kidney cancer BM than in breast cancer BM ($p=0.024$; Chi square test). Melanoma BM had more frequently dense infiltration with FOXP3+ TILs ($p=0.003$; Chi square test) than other BM subtypes. Density of CD3+, CD8+, CD45RO+, or FOXP3+ TILs did not correlate with preoperative steroid application ($p>0.05$; Chi Square test). Patients with dense infiltration of CD3+ TIL had significantly improved OS (27 vs. 12 months; $p=0.002$; log rank test). Further, dense infiltration with CD8+ TILs was associated with improved OS (16 vs. 12 months; $p=0.048$; log rank test) and large peritumoral edema on the preoperative MRI ($p=0.03$; Chi Square test). Dense infiltration with CD45RO+ TILs was correlated with improved survival prognosis (18 vs. 8 months; $p=0.01$; log rank test). Patients with dense infiltration of FOXP3+ TILs had an impaired survival prognosis (6 vs. 16 months; $p=0.05$; log rank test). A composite "immuno score" showed a strong association with median OS (27 months for cases CD8+/CD45RO+/FOXP3- infiltrates and 6 for cases with CD8-/CD45RO-/FOXP3+ infiltrates; $p=0.001$ log-rank test). **Conclusions:** Dense TILs infiltrates are common in BM and correlate with the amount of peritumoral brain edema and improved survival prognosis. Further studies should investigate the therapeutic impact of immunomodulatory agents in patients with BM.

**2013 Poster Highlights Session (Board #3), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Results of comprehensive molecular profiling of gliomas and the potential therapeutic implications.** *Presenting Author: Santosh Kesari, University of California, San Diego, La Jolla, CA*

**Background:** Gliomas are the most common type of primary brain tumors with underlying molecular heterogeneity contributing to differential treatment response. Our retrospective study was designed to interrogate biomarkers from a large cohort of glioma patients to identify alterations with therapeutic implications. **Methods:** 871 glioma tumor samples (79% WHO grade IV glioblastoma, GBM) were analyzed with a multi-platform approach including sequencing, IHC, FISH/CISH and methylation assay to investigate actionable biomarker aberrations. Retrospective data analysis was performed on the complete cohort and molecular subgroups of patients. **Results:** In the 871 patient samples, mutations in 27 genes were seen. Both common TP53 (39%), IDH1 (22%), PTEN (13%) and previously unreported mutations in gliomas were observed, including JAK3, SMO and ABL1. Co-mutation of 2 or more genes occurred in 37% of cases. TP53 mutation was suggestive of genetic instability and was frequently associated with other concurrent mutations ($p=0.0006$). IDH1 mutations were associated with MGMT promoter methylation, low expression of TS, RRM1 and TOP2A (p from $<0.0001$ to 0.0036), suggesting different responses to temozolomide, fluoropyrimidine, gemcitabine and etoposide. IDH1 mutation was also associated with TP53 mutation; whereas wild type IDH1 was associated with PTEN mutation ($p=0.0309$) and showed some association with EGFR mutations ($p=0.0543$). Distinct biomarker profiles by IHC, FISH and sequencing were also observed when comparing GBM to grade II/III gliomas, suggesting different biology from GBM and thus different treatment implications. 20 GBM patients were identified with pre and post treatment analyses performed (comparative analysis ongoing). **Conclusions:** Gliomas exhibit a high degree of molecular heterogeneity as revealed by multi-platform profiling. IDH1 mutation identifies molecular subgroups of patients with different responses to therapeutic agents; while TP53 mutation suggests increased genetic instability. These results highlight the benefits of profiling in consideration of treatment options for glioma patients.

**2014 Poster Highlights Session (Board #4), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Do host factors determine long-term survival in glioblastoma? A genome/transcriptome profiling study by the German Glioma Network.** *Presenting Author: Michael Weller, Department of Neurology, University Hospital Zurich, Zurich, Switzerland*

**Background:** The prognosis of glioblastoma remains poor: only a minority of patients experience long-term survival beyond three years after diagnosis. Previously identified predictors of long-term survival include younger age, gross total surgical resection, $O^6$-methylguanine DNA methyltransferase (MGMT) promoter methylation and isocitrate dehydrogenase (IDH) 1 or 2 mutation (Hartmann et al. Clin Cancer Res 2013; 19:5146-5157), but these parameters do by no means fully account for long-term survival. **Methods:** Accordingly, to identify specific molecular signatures of glioblastomas with long-term survival, we performed genome- and transcriptome-wide molecular profiling of 94 glioblastoma samples, including 28 long-term survivors with >36 months overall survival (OS), 20 short-term survivors with <12 months OS, and 46 patients with intermediate OS. Integrative bioinformatic analyses were used to characterize molecular aberrations in the distinct survival groups stratified by MGMT and IDH1/2 status. **Results:** Glioblastoma patients with long-term survival were younger and more often had *IDH1/2*-mutant and *MGMT*-methylated tumors. Gene expression profiling revealed over-representation of a distinct (proneural-like) expression signature in long-term survivors that was linked to *IDH1/2* mutation. However, *IDH1/2*-wildtype glioblastomas from long-term survivors did not show distinct gene expression profiles and included proneural, classical and mesenchymal glioblastoma subtypes. Genomic imbalances differed between *IDH1/2*-mutant and *IDH1/2*-wildtype tumors, too, but not between survival groups of *IDH1/2*-wildtype patients. **Conclusions:** These data strongly suggest that host-derived rather than tumor-derived factors allow for long survival in glioblastoma. Ongoing studies on long-term survival in glioblastoma of the German Glioma Network therefore focus on immune responses, notably autoantibody profiling, to corroborate the hypothesis that immune control of glioblastoma may contribute to long-term survival.

**2015 Poster Highlights Session (Board #5), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

***MGMT* promoter methylation as a prognostic biomarker for benefit from dose-intensified temozolomide rechallenge in progressive glioblastoma: First results from the randomized phase II DIRECTOR trial.** *Presenting Author: Ghazaleh Tabatabai, Department of Neurology, University Hospital Zurich, Zurich, Switzerland*

**Background:** Rechallenge with temozolomide (TMZ) at first progression of glioblastoma after radiotherapy with concomitant and maintenance temozolomide (TMZ/RT→TMZ) has been studied in retrospective and single-arm prospective studies, applying TMZ continuously or using 7/14 or 21/28 days schedules. Progression-free survival rates have been in the range of 10-30% without any major prognostic impact of $O^6$-methylguanine DNA methyltransferase *(MGMT)*. **Methods:** Glioblastoma patients at first progression after TMZ/RT→TMZ and at least 2 maintenance TMZ cycles were randomized to Arm A (one week on (150 mg/sqm TMZ per day) / one week off) or to Arm B (three weeks on (100 mg/sqm TMZ per day) / one week off). The primary end point was median time to treatment failure defined as progression, premature (< 12 months) TMZ discontinuation for toxicity, or death from any cause; 166 patients were deemed necessary to show a meaningful difference between arms. **Results:** Because of withdrawal of support, the trial was prematurely closed to accrual after 105 patients.The outcomes in Arm A and Arm B for the primary endpoint of median time to treatment failure (56 days [95% CI 55-98] vs. 59.5 days [95% CI 56-105]) and for overall survival (OS) (298 days [95% CI 202-395] vs. 322 days, [95% CI 246-356]) were similar. These endpoints differed, however, by *MGMT* promoter methylation status, which was informative for all patients. Median time to treatment failure in patients with *MGMT*-methylated tumors was 98 days [95% CI 56-223] vs. 56 days [95% CI 56-60] in *MGMT*-unmethylated glioblastoma. PFS-6 was 39.7% vs. 6.9% with vs. without *MGMT* promoter methylation; OS with *MGMT*-methylated glioblastoma was 382 days [95% CI 300-531] vs. 241 days [95% CI 191-313] in *MGMT*-unmethylated glioblastoma. Hematological toxicity > grade 3 was similar (27% Arm A vs. 30.7% Arm B). **Conclusions:** TMZ rechallenge is an active treatment for *MGMT* promoter-methylated glioblastoma progressive after standard therapy. The best TMZ regimen remains to be defined. Alternative strategies are warranted for patients with progressive *MGMT*-unmethylated glioblastoma. Clinical trial information: NCT00941460.

**2016 Poster Highlights Session (Board #6), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**MGMT gene promoter methylation in plasma of glioma patients receiving temozolomide.** *Presenting Author: Riccardo Soffietti, Department of Neuro-Oncology, University and City of Health and Science Hospital of Turin, Turin, Italy*

**Background:** MGMT gene promoter methylation in tumor tissue of gliomas is now recognized as a predictive biomarker for response to temozolomide. Up to date there is lack of studies investigating MGMT methylation status in the circulating DNA of glioma patients undergoing chemotherapy with temozolomide. In this prospective study on a cohort of patients with gliomas of different grades of malignancy we aimed to: (1) evaluate the concordance between MGMT methylation status in tumor tissue and plasma; (2) monitor MGMT methylation status in plasma before and during temozolomide, and explore its value as a predictive biomarker. **Methods:** We enrolled 58 patients who underwent surgical resection, followed by radiotherapy and/or temozolomide. Blood samples were collected at baseline and every 3 cycles of temozolomide up to 12 months. MGMT promoter methylation status was assessed in both paraffin-embedded tumor tissue and plasma by real-time PCR. **Results:** MGMT promoter methylation status was concordant in tumor tissue and plasma at baseline in 42 out of 48 patients (87.5%, Kappa=0.75, 95%CI: 0.57-0.93). When considering glioblastomas only we obtained a 93.7% concordance and a Kappa of 0.87 (95%CI: 0.70-1.00). Mortality was higher for patients with MGMT unmethylated promoter both in tumor tissue (HR=2.21, 95%CI: 0.99-4-95) and plasma (HR=2.19, 95%CI: 1.02-4.68). Progression-free survival was shorter for patients with unmethylated MGMT promoter both in tumor tissue (HR=2.30, 95%CI: 1.19-4.45) and plasma (HR=1.77, 95%CI: 0.95-3.30). The cumulative incidence of unmethylated MGMT promoter in plasma was 58% at baseline and reached virtually 100% at 12 months. **Conclusions:** The assessment of MGMT promoter methylation in plasma can be useful when adequate tumor tissue (i.e. in stereotactic biopsy or in inoperable tumors) is not available. Moreover, the analysis of MGMT promoter methylation in plasma could be particularly useful to monitor methylated patients, helping to establish when the tumor switches from a methylated to an unmethylated status, thus predicting the emerging of a treatment resistance.

**2017 Poster Highlights Session (Board #7), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Determining the glioma CpG island methylator phenotype, 1p/19q codeletion, and *MGMT* promoter methylation from epigenome-wide methylation data in the biomarker cohort of the NOA-04 trial.** *Presenting Author: Benedikt Wiestler, Neurooncology, University of Heidelberg Medical Center, Heidelberg, Germany*

**Background:** Molecular biomarkers, including *isocitrate dehydrogenase 1* or *2* (*IDH1/2*) mutation, 1p/19q codeletion and *$O^6$-methylguanine-DNA-methyltransferase* (*MGMT)* promoter methylation, improve prognostication and may even guide treatment decisions in patients with World Health Organization (WHO) grade III gliomas. At present, each marker is individually tested by distinct assays. Illumina Infinium HumanMethylation450 BeadChip arrays (HM450) allow the determination of large-scale methylation profiles and genome-wide DNA copy number changes, enabling molecular subgrouping of tumors. Algorithms have been developed to detect the glioma CpG island methylator phenotype (G-CIMP) associated with *IDH1/2* mutation, as well as 1p/19q codeletion and *MGMT*promoter methylation, using this assay. **Methods:** Here, we investigated the diagnostic and prognostic performance of these algorithms in the biomarker cohort (n=115 patients) of the NOA-04 trial, which centrally assessed *IDH*, 1p/19q and *MGMT*status using established single marker tests. **Results:** Concordance for *IDH* and 1p/19q status was very high: In 92% of cases, the HM450 and the reference data agreed. In discordant cases, survival analysis by Kaplan-Meier and Cox regression analyses suggested a more accurate assessment of the biological phenotype by HM450 analysis. The HM450-derived MGMT-STP27 model to calculate *MGMT* promoter methylation probability revealed this aberration in a significantly higher fraction of cases than conventional methylation-specific PCR (MSP), with 87/91 G-CIMP positive tumors predicted as *MGMT*promoter-methylated. Fitting a new model for these tumors resulted in an area under the curve of 0.84. **Conclusions:** G-CIMP and 1p/19q codeletion are reliably detectable by HM450 analysis and associated with prognosis in the NOA-04 trial. Efforts are required to resolve the discrepancy between the MGMT-STP27 and MSP data for *MGMT* promoter methylation status. Overall, our data suggests that HM450 analysis may be able to replace individual marker tests for routine assessment of anaplastic gliomas.

**2018 Poster Highlights Session (Board #8), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Randomized phase II study of axitinib versus standard of care in patients with recurrent glioblastoma.** *Presenting Author: Bart Neyns, Universitair Ziekenhuis Brussels, Brussels, Belgium*

**Background:** Vascular endothelial growth factor receptor (VEGFR) signal transduction mediates glioblastoma (GB) associated neo-angiogenesis. Axitinib is an oral small molecule tyrosine kinase inhibitor with high affinity and specificity for the VEGF-receptors, approved for the treatment of metastatic renal cell carcinoma. **Methods:** Axitinib (5 mg BID starting dose) vs. best alternative choice of therapy was studied in an open label, randomized, phase II clinical trial in patients (pts) with recurrent GB. Six-month progression-free survival (6mPFS) was the primary endpoint. **Results:** Between Sep 2011 and Oct 2013, 44 pts who failed surgery, RT and temozolomide were randomized 1:1 at 3 sites. Median age 54y (range 20-79), 33M/11F, WHO-PS 0/1/2/3: 6, 26, 11, and 1 pt. In the control arm 20 pts received bevacizumab and 2 pts received lomustine at standard doses. Axitinib (n=22) was generally well tolerated. Most common axitinib related AEs consisted of dysphonia (3x G2), fatigue (6x G2, 2x G3), hypertension (5x G2), oral hyperesthesia (7x G2, 1x G3), diarrhea (2x G2, 2x G3), and hypothyroidism (3x G2). In 4 pts axitinib dosing was interrupted and subsequently dose reduced because of toxicity; in 4 other pts axitinib was dose escalated to 7 or 10 mg BID (2 pts each). Tumor response by RANO criteria was 28% in the axitinib arm vs. 23% in the control arm (Table). All pts had an increased uptake on 18F-FET PET at baseline. A decrease (-26 to -100%) of SUVmax/background was documented in 6/7 pts on axitinib at the time of response on MRI. Corticosteroids could be stopped in 4/12 and tapered in an additional 5/12 pts in the axitinib arm. After a median follow-up of 10.5 mths, the 6mPFS for axitinib was 22% (95% CI 5-40) vs. 19% (95% CI 2-36) for the control arm. Median PFS and OS were respectively 2.9 vs. 2.6 mths, and 10.3 vs. 7.4 mths for pts treated in the axitinib vs. control arm. **Conclusions:** Axitinib has single-agent activity and manageable toxicity in pts with recurrent GB. The survival on the axitinib arm was comparable to that on the contemporary control arm. Further evaluation of axitinib for recurrent GB is warranted. Clinical trial information: NCT01562197.

| | Axitinib | | Control | |
|---|---|---|---|---|
| | BOR | Confirmed BOR | BOR | Confirmed BOR |
| **CR** | 5 | 2 | 1 | 1 |
| **PR** | 6 | 4 | 5 | 4 |
| **SD** | 5 | | 7 | |
| **PD** | 5 | | 8 | |
| **NE** | 1 | | 1 | |

Abbreviations: BOR, best overall tumor response; NE: not evaluable.

**2019 Poster Highlights Session (Board #9), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Phase II trial of the phosphatidyinositol-3 kinase (PI3K) inhibitor buparlisib (BKM120) in recurrent glioblastoma.** *Presenting Author: Patrick Y. Wen, Dana-Farber Cancer Institute, Boston, MA*

**Background:** The PI3K pathway is activated in most GBMs and represents a potential therapeutic target. Buparlisib is an oral, pan-Class I PI3K inhibitor that enters the brain at therapeutic concentrations and inhibits the growth of U87 and GBM PDX models. **Methods:** The Ivy Consortium conducted a phase II study of buparlisib in recurrent GBM patients with activation of the PI3K pathway (mutation, homozygous deletion or loss of immunohistochemistry (IHC) of PTEN, PIK3CA or PIK3RI mutations, or detectable pAKT). Additional eligibility criteria included radiologic progression, 1st or 2nd relapse, > 18 yrs, KPS > 60, adequate bone marrow and organ function, no prior bevacizumab or enzyme-inducing antiepileptic drugs. Patients received buparlisib 100mg daily. The study consisted of 2 concurrent cohorts. In Cohort 1 (up to 15 patients) buparlisib was given for 8-12 days prior to surgery for recurrent disease. Patients underwent FDG PET, pharmacokinetic studies, and tumor obtained for drug concentrations and pharmacodynamic effects. In Cohort 2, 50 patients with unresectable GBM received buparlisib with a . primary endpoint of PFS6. **Results:** 13 patients have been enrolled into cohort 1, 50 into cohort 2. Treatment was well-tolerated with no grade 4 toxicities. Grade 3 toxicities were asymptomatic lipase elevation (6), rash (4), hyperglycemia (3), fatigue (4), elevated ALT/AST (2), and 1 each of depression, anxiety, hypophosphatemia, thrombocytopenia and lymphopenia. Analysis of tumor specimens from Cohort 1 showed reduction of pAKTS473 by IHC in 4/6 (67%) of evaluable patients. The combined cohorts showed minimal efficacy with median PFS of 1.8 months and median OS of 10.9 months. Best response was stable disease. Only 1 patient in each cohort achieved PFS6. Of the first 40 patients who underwent exome sequencing, there were 4 PIK3CA (10%), 2 PIK3R1 (5%), and 13 PTEN (33%) mutations. Patients with PTEN loss and or PI3K mutations paradoxically had a worse outcome. **Conclusions:** Buparlisib is well-tolerated in patients with recurrent GBM and achieves adequate tumor concentration to inhibit pAKTS473. However, single agent efficacy was minimal. Final correlation of tumor genotype with outcome will be presented.

**2020 Poster Highlights Session (Board #10), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Panobinostat in combination with bevacizumab for recurrent glioblastoma and anaplastic glioma.** *Presenting Author: Eudocia Quant Lee, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Bevacizumab is frequently used to treat recurrent high-grade gliomas, but responses are generally not durable. Panobinostat is a histone deacetylase inhibitor with anti-neoplastic and anti-angiogenic effects in glioma and may work synergistically with bevacizumab. We conducted a multicenter phase II trial of panobinostat in combination with bevacizumab in patients with recurrent grade III and IV gliomas. **Methods:** Two cohorts were enrolled: one with recurrent glioblastoma (GBM) as the primary study and one with recurrent anaplastic glioma (AG) as the exploratory study. Patients were treated with oral panobinostat 30 mg 3 x per week, every other week, in combination with bevacizumab 10 mg/kg every other week. The primary endpoint was 6-month progression-free survival (PFS6) in the GBM cohort and the study was powered to discriminate between a 35% and 55% PFS6 rate (85% power at an alpha level of 0.07). **Results:** At planned interim analysis, 13 of the first 21 patients accrued to the GBM cohort had progressed within 6 months of initiating study treatment. The GBM cohort did not meet criteria for continued accrual and was closed early. In the GBM cohort, PFS6 rate was 30.4% [95% confidence interval: 12%, 51%], median PFS was 5 months [3, 9], and median OS was 9 months [6, 19]. Accrual in the AG cohort continued to completion and a total of 15 patients were enrolled. In the AG cohort, PFS6 was 46.67% [21%, 73%], median PFS was 7 months [2, 10], and median OS was 17 months [5, 27]. The most common grade 3 or 4 toxicities related to treatment in the GBM arm were hypophosphatemia (12.5%), thrombocytopenia (12.5%), lymphopenia (8.3%), neutropenia (8.3%), and ALT elevation (8.3%). In the AG arm, the most common grade 3 or 4 toxicities were thrombocytopenia (20.0%) and hypophosphatemia (13.3%). There were no deaths related to study treatment. **Conclusions:** Although reasonably well-tolerated, this phase II study of panobinostat and bevacizumab in recurrent GBM did not meet criteria for continued accrual and the GBM cohort of the study was closed. However, in the recurrent AG cohort, bevacizumab in combination with LBH589 may delay progression. Updated outcome and safety data will be presented. Study supported by Novartis and Genentech. Clinical trial information: NCT00859222.

**2021 Poster Highlights Session (Board #11), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**A phase 1 study evaluating ABT-414 in combination with temozolomide (TMZ) for subjects with recurrent or unresectable glioblastoma (GBM).** *Presenting Author: Hui Kong Gan, Austin Health and Ludwig Institute for Cancer Research, Melbourne, Australia*

**Background:** Patients (pts) with recurrent GBM have few treatment options and a very poor prognosis. GBM tumors often exhibit aberrant epidermal growth factor receptor (EGFR) proliferative signaling. ABT-414 is an antibody drug conjugate consisting of a unique antibody targeting active EGFR or mutant EGFRvIII linked to a potent, toxic anti-microtubule agent monomethylauristatin F (MMAF). ABT-414 has demonstrated high antitumor activity in preclinical GBM tumor models harboring either wild type EGFR or EGFRvIII. **Methods:** Objectives were to evaluate the toxicities, pharmacokinetics (PK), and the recommended phase 2 dose of ABT-414 when administered every other week (QOW) in combination with TMZ in pts with recurrent or unresectable GBM. Assessments include adverse events (AEs, NCI-CTCAE), PK parameters, objective response (RANO criteria) and tumor tissue EGFR biomarkers. **Results:** As of Jan 1, 2014, safety data was compiled for 12 pts (6/6, Male/Female, median age 48). Common ($\geq$ 3 pts) adverse events include blurred vision (n=5), corneal deposits (n=4), foreign body sensation in the eye, nausea, pyrexia, and headache (n=3 each). Grade 3/4 AEs include lymphopenia, corneal deposits, skin infection, and blood cholesterol increase (n=1 each). Three cohorts have been treated to date (0.5, 1.0, 1.5 mg/kg). One dose limiting toxicity of grade 3 corneal deposits was reported at 1.0 mg/kg with improvement of symptoms after a dose reduction. ABT-414 PK results in 7 pts appeared to be dose proportional from 0.5-1.0 mg/kg, with mild accumulation using QOW dosing, and a half-life of 7-8 days. As of Jan 9, best responses for 9 pts with measurable disease at baseline include 1 complete response (CR) and 2 partial responses (33%). Patient samples are being evaluated for EGFR amplification, EGFR VIII status and expression of EGFR mRNA to determine which marker best associates with clinical response. **Conclusions:** Preliminary safety data demonstrate a unique toxicity pattern related to MMAF-induced corneal epithelial microcysts. Preliminary responses in 3/9 pts with TMZ refractory GBM, including 1 CR, warrant further study. Phase 2 studies with ABT-414 in GBM are being planned. Clinical trial information: NCT01800695.

**2022 Poster Highlights Session (Board #12), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Can average-risk medulloblastoma adult patients be treated with radiotherapy and plus chemotherapy?** *Presenting Author: Enrico Franceschi, Medical Oncology Department, Bellaria-Maggiore Hospital, Azienda USL of Bologna - IRCCS Institute of Neurological Sciences, Bologna, Italy*

**Background**: The standard treatment in children with average-risk medulloblastoma (MB) is chemotherapy after reduced-dose radiotherapy (23.4 Gy of craniospinal irradiation and a posterior fossa boost to 55.8 Gy). However, in adults, there is no agreement on the use of adjuvant chemotherapy in this setting. **Methods**: We performed a retrospective analysis of adult MB pts with average-risk disease, defined as no postsurgical residual (or $<1.5$ $cm^2$) and no metastatic disease (M0). Main inclusion criteria were: age $>$ 16 years, post-surgical treatment with standard craniospinal irradiation with or without adjuvant chemotherapy (cisplatin and etoposide $\pm$ cyclophosphamide). **Results**: From 1988 to 2012 were accrued 43 average-risk MB pts treated with surgery and adjuvant radiotherapy. Fifteen (34.9%) pts received also chemotherapy: 7 before radiotherapy (RT), 5 after RT, and 3 before and after RT. Median age was 31 years (range: 16-57), M/F ratio 27 (62.8%)/16 (37.2%). Histology was classic in 24 pts (55.8%), desmoplastic in 12 pts (27.9%), extensive nodularity in 5 pts (11.6%), large cell/anaplastic in 2 pts (4.7%). Reasons to administer chemotherapy were residual disease $<1.5$ cm in 9 pts (60.0%), delay in RT start in 6 pts (40.0%). After a median follow up time of 10 years (range: 8-13), median overall survival (OS) was 18 years (95%CI: 9 – 28) in pts who receive RT alone, and was not reached in pts treated with radiotherapy plus chemotherapy. The survival rates at 5,10 and 15 years were 100%, 78.6% (95% CI: 60.0-97.2%) and 60.2% (95%CI: 36.9-83.5%), in pts treated with RT alone, and 100%, 100% and 100%, in pts treated with RT plus chemotherapy (p=0.079). To date, all pts receiving adjuvant chemotherapy are alive. Univariate analyses did not show significant differences in survival by gender (P=1.000), age (P=0.070) and T stage (T1-Ta vs T3b-T4, P=0.881) between groups. **Conclusions**: Our findings suggest a role for adjuvant chemotherapy in the treatment of average-risk MB adult pts. Due to the extreme rarity of MB in adults, prospective trials remain a challenge. Further improvements might drive to add chemotherapy in average-risk setting with less favorable biological signatures (large cell/anaplastic MB and non-WNT group).

**2023 Poster Highlights Session (Board #14), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**A phase 2 study of orally administered PLX3397 in patients with recurrent glioblastoma.** *Presenting Author: Nicholas A. Butowski, University of California, San Francisco, San Francisco, CA*

**Background:** PLX3397 is an oral, small molecule that potently and selectively inhibits CSF1R, Kit, and Flt3-ITD kinases. CSF1R is expressed on microglia/macrophages and tumor cells within glioblastoma (GB). Many glioma cell lines express the CSF1R ligands, CSF-1 and IL-34 and the KIT ligand, SCF, and depletion of microglia in preclinical GB models reduces tumor burden and spread. **Methods:** This study of recurrent GB measured the 6-month PFS rate (PFS6), median duration of response, overall response rate (ORR), overall survival (OS), safety, and plasma and tumor pharmacokinetics (PK) and pharmacodynamics (PD) during PLX3397 treatment. **Results**: 38 recurrent GB patients were treated with PLX3397 at 1000 mg daily, with Cohort 1 (14 patients) treated 7 days in advance of recurrent surgery and Cohort 2 (24 patients) without surgery. PLX3397 was well tolerated; common (>10%) treatment-related adverse events included fatigue, constipation, nausea, hair color change, elevation in AST/ALT, anorexia, and headache. The primary endpoint of PFS6 was 11.4% with no complete or partial responses. 7/38 (18%) of patients experienced stable disease.Plasma PK Cmax was median 8090 ng/mL (range 3100-13400) with Tmax of 2 hr. Cohort 1 tumor tissue PK was median 5500 ng/g (range 1320-69400). PD effects observed in blood in both Cohorts included elevated plasma CSF-1 and reduced $CD14^{dim}/CD16^{+}$ monocytes. In pre-surgical patients (Cohort 1), tissue PD effects observed included possible changes in tumor macrophage/microglia morphology, IBA1 IHC, FACS, and pERK IHC compared to control patient tissues. PDGFRA amplification was seen in 13/36 archival samples. **Conclusions**: PLX3397 is a potent inhibitor of tumor-associated macrophages and microglia, readily entered GB tissue, and demonstrated expected PD effects. As a single agent, PLX3397 showed no significant improvement in PFS, although further research toward identifying a responsive subset of GB patients is ongoing. PLX3397 is well-tolerated and its safety profile is conducive to testing its combination with other treatments; A Phase 2 trial combining PLX3397 with RT and Temodar in newly diagnosed GB has been initiated. Clinical trial information: NCT01349036.

**2024 Poster Highlights Session (Board #15), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Primary malignant brain tumours (PMBT) in phase I studies: Barriers to treatment and patient outcomes.** *Presenting Author: Scheryll Paula Alken, Departments of Neuro Oncology/Drug Development, Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*

**Background:** Primary malignant brain tumours (PMBT) are a rare tumour group with a poor outcome and limited options at relapse. Despite recent incremental gains from multimodal therapy and an emerging understanding of underlying genetic alterations, patients (pts) with PMBT have traditionally been excluded from phase I trials due to a number of concerns including blood-brain barrier penetration; it is recognised that such concerns are less relevant in the molecular era. We examined the outcomes of and barriers to participation of these pts on phase I studies. **Methods:** We reviewed the case records of pts with PMBT referred to the Neuro Oncology and Clinical Pharmacology Units of the Royal Marsden Hospital between 2004 and 2013 for consideration of a phase I study. Pt characteristics including demographics and details of prior treatment were examined. Kaplan-Meier estimator and Cox regression were used to evaluate progression free survival (PFS) and overall survival (OS). All tests performed were two-sided with an alpha of 0.05, and a power of 80% was used. Surviving patients were censored at date of last follow-up. **Results:** Seventy three pts with PMBT were identified. Of these, 50 (68.5%) were allocated to a phase I trial and 38 (52%) of these patients received at least one dose of the study drug. 9 pts (18%) failed screening, 3 pts (6%) withdrew consent. 11 pts (15%) were not allocated to a study due to a lack of suitable trials, 9 (12%) were not allocated due to poor performance status (PS). Factors influencing enrolment were examined; only Karnofsky PS (KPS) was statistically significant (HR 1.09, 95% CI 1.04 – 1.15, p=0.001). The median PFS of pts dosed was 7.3 months. The median OS of these pts was 7.9 months versus 4.2 months in those not dosed (p=0.024). Grade 3 drug related toxicities were seen in 9.6% of patients. **Conclusions:** Patients with PMBT can be safely treated in phase I trials. A lack of suitable trials remains the main barrier to enrolment, as does KPS, which is similar to other rare malignancies. Based on our results these patients tolerate investigational agents similar to other groups. This study adds to the growing body of evidence encouraging investigators to enrol such patients.

**2025 Poster Highlights Session (Board #16), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Results of stage 1 of the oparatic trial: A phase I study of olaparib in combination with temozolomide in patients with relapsed glioblastoma.** *Presenting Author: Anthony J. Chalmers, University of Glasgow, Glasgow, United Kingdom*

**Background:** Drug delivery is a major problem in the treatment of glioblastoma (GBM). Tumour pharmacokinetics (PK) of small molecule targeted agents in GBM are not well understood, and poor activity may result from lack of biological efficacy or adverse PK. Olaparib, a small molecule inhibitor of the DNA repair enzyme poly(ADP-ribose) polymerase (PARP), has potential to overcome treatment resistance of GBM. Despite radiological responses in brain metastases, GBM penetration by olaparib has not been studied. **Methods:** Preclinically, blood-brain barrier penetration was assessed by directional transport of [$^{14}$C]-olaparib across MDCKII cells expressing MDR1 and autoradiography of rats and mice treated with [$^{14}$C]-olaparib. Clinically, 8 patients with recurrent GBM underwent dynamic contrast enhanced (DCE) MRI at baseline followed by tumour resection after 4 days of oral olaparib (tablet: 100 mg QD, n=5; 200 mg BID, n=3). Olaparib levels were measured in tumour and plasma by LC-MS. **Results:** Olaparib was a substrate for MDR1 and efflux was blocked by the MDR1 inhibitor ketoconazole. Radioactivity was not detected in the central nervous systems (CNS) of rats or mice after single dose [$^{14}$C]-olaparib, but significant levels were measured in subcutaneous HCT-116 tumour xenografts up to 96 hrs. Olaparib was detected in 24/24 resected GBM specimens from 8 patients (Table) at concentrations similar to those in previous breast cancer studies in which PARP inhibition and tumour responses were observed. Pre-treatment DCE-MRI showed increased vascular permeability in tumours, and tumour cellularity parameters correlated with olaparib levels. **Conclusions:** Olaparib is excluded from the CNS under normal conditions but reliably penetrates recurrent GBM at therapeutic levels. Small molecule PK in GBM are poorly predicted by standard pre-clinical models. Clinical trial information: NCT01390571.

| | | Olaparib concentration (day 4) | | |
|---|---|---|---|---|
| Subject | Daily olaparib dose (mg) | Tumor section (ng/g) | Mean tumor (ng/g) | Plasma (ng/ml) |
| 1 | 400 | 137<br>210 | 238 | 5290 |
| 2 | 400 | 367<br>71.2<br>72.9 | 94.7 | 3840 |
| 3 | 400 | 140<br>431<br>133 | 282 | 1330 |
| 4 | 100 | 281<br>177<br>105 | 112 | 876 |
| 5 | 100 | 55.0<br>324<br>354 | 364 | 773 |
| 6 | 100 | 413<br>494<br>345 | 413 | 617 |
| 7 | 100 | 401<br>53.1<br>65.8 | 59.8 | 1290 |
| 8 | 100 | 60.6<br>203<br>156<br>166 | 175 | 1460 |

**2026 Poster Highlights Session (Board #17), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Targeting glioma-initiating cells in GBM: ABTC-0904, a randomized phase 0/II study targeting the Sonic Hedgehog-signaling pathway.** *Presenting Author: Andrew E. Sloan, University Hospital Case Medical Center, Cleveland, OH*

**Background:** The prognosis for GBM, which appears to be driven by glioma initiating cells (GIC), remains poor. Our hypothesis was that interrupting sonic hedgehog signaling (SHh) would inhibit GIC activity and improve PFS (PFS6). **Methods:** A two armed, randomized phase 0/II study of Vismodegib, an inhibitor of SMO, was performed in 40 patients undergoing resection for recurrent GBM (rGBM). The trial hypothesis was to achieve 25% PFS6 rate compared to a null of 10 % with a 90% power and a 10% type I error rate (1-sided). Arm I received Vismodegib for 7 days pre-operatively; Arm II was not treated pre-operatively. All patients were treated with Vismodegib post-operatively. Primary objective was to assess PFS6, with secondary endpoints of median overall survival, response and toxicity. Secondary objectives included determination of: intra-tumoral PK and PD; inhibition of SHh signaling by RT-PCR and immunohistochemistry; and inhibition of GIC proliferation and self-renewal by neurosphere proliferation and limited dilution assay. **Results:** PK/PD data and tumor specimens were obtained from 39 of the 40 patients. Median drug levels in plasma and tissue were7638 and 3270 ng/ml respectively for patients in Arm I. SHh signaling intermediates (Gli-1, Gli-2, PTCH-1b) were 3.3 to 110-fold decreased in Arm I vs. Arm II (p<0.0002). Finally, proliferating CD133$^+$ neurospheres were derived from 14 of the 39 cultures assessed and array CGH suggested GIC (vs. NSC) as the cells of origin. The proportion of tumor-derived CD133$^+$neurospheres undergoing proliferation and self-renewal was decreased in Arm I vs. II (p <0.005 and p < 0.003 respectively). PFS6 and OS were 1.8m and 8.3m respectively; but there was no difference between the two arms. **Conclusions:** Vismodegib was well tolerated but not efficacious as a single agent in rGBM. However, this agent achieved therapeutic intra-tumoral concentration in rGBM and had biological activity on proliferation and self-renewal of GBM derived CD133$^+$neurospheres. Combinatorial therapy targeting SHh pathway in GBM should be pursued. Clinical trial information: NCT00980343.

**Incidence of CD133$^+$ neurospheres by arm.**

| Arm | # Evaluable specimens | # (%) which made CD133$^+$NS (p = 0.005 Fisher exact test) |
|---|---|---|
| I | 20 | 3 |
| II | 19 | 11 |

**2027 Poster Highlights Session (Board #18), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Phase II study of monthly pasireotide LAR (SOM230C) for recurrent or progressive meningioma: Final results.** *Presenting Author: Andrew David Norden, Dana-Farber Cancer Institute, Boston, MA*

**Background:** No medical therapy for recurrent meningioma has proven effective, yet a subset of these tumors recur after surgery and radiation. A pilot study of sustained-release somatostatin yielded promising results. Pasireotide LAR is a long-acting somatostatin analog with higher affinity for most somatostatin receptor subtypes than octreotide. **Methods:** This was a phase II trial of monthly pasireotide LAR 60 mg IM in patients with recurrent or progressive meningioma. Patients were stratified by histology (cohort A: atypical [grade 2] and malignant [grade 3] meningiomas; cohort B: benign [WHO grade 1] meningiomas). Treatment cycles were 28 days. Restaging MRIs were performed every 3 cycles and response was assessed using Macdonald criteria. Octreotide scanning was performed at baseline. Tumor tissue was obtained for somatostatin receptor immunohistochemistry. Serum IGF-1 levels were checked serially. **Results:** 18 patients in cohort A and 16 in cohort B were accrued. Cohort A had median age 59 (range 39-74), 8 men (44%), median KPS 80 (range 60-100), 17 (94%) with previous radiation therapy. Cohort B had median age 52 (range 36-81), 9 men (56%), median KPS 90 (range 70-100), 11 (69%) with previous radiation therapy. There were no responses. Twelve patients in cohort A (67%) achieved stable disease for a median of 4 cycles, and 13 patients in Cohort B (81%) achieved stable disease for a median of 7 cycles. In Cohort A, PFS6 was 17% and median PFS 15 weeks (95% CI: 8-20). In Cohort B, PFS6 was 50% and median PFS 26 weeks (12-43). Toxicity was mild except for grade 3 hyperglycemia in 5 (15%) patients, grade 4 hyperglycemia in 1 (3%) patient, grade 4 hypoglycemia in 1 (3%) patient, grade 3 hypokalemia in 1 (3%) patient, grade 3 fatigue in 2 (6%) patients, grade 3 amylase elevation in 1 (3%) patient, and grade 3 lipase elevation in 2 (6%) patients. Neither octreotide uptake nor IGF-1 levels predicted outcome. Staining for sst3 was predictive of favorable OS (HR 0.44, p=0.02) and PFS (HR 0.64, p=0.04). **Conclusions:** Pasireotide LAR is inactive in most recurrent meningiomas. Tumors with increased sst3 expression may be particularly sensitive to pasireotide, for reasons that remain to be determined. Clinical trial information: NCT00813592.

**2028 Poster Highlights Session (Board #19), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**A multicenter randomized study comparing temozolomide (TMZ) versus TMZ-plus-bevacizumab (BEV) before standard treatment in unresectable glioblastoma (GBM) patients (p): The GENOM 009 study by the GEINO group.** *Presenting Author: Carmen Balana, Catalan Institute of Oncology Hospital Germans Trias i Pujol, Barcelona, Spain*

**Background:** We compared the efficacy and safety of treatment with TMZ or TMZ+BEVprior to and concomitant with radiotherapy in unresectable(GBM) patients. **Methods:** Between December 2009 and April 2013, p with unresectable GBM, PS<3 and MMS ≥25 were randomly assigned to receive eitherTMZ (85 mg/m², days 1–21, for 2, 28-day cycles), followed by standard TMZ with concomitant radiotherapy (60Gy) and then adjuvant TMZ for 6 cycles (TMZ Arm), or the same regimen but with the addition of BEV (10mg/kg /15 days) during pre-radiotherapy and concomitant treatment (BEV Arm). The primary endpoint was response according to RANO criteria after the 2 pre-radiotherapy cycles.The study was powered to detect a 30% difference between arms ($\alpha$ and $\beta$ errors of 0.05 and 0.20). Secondary endpoints included toxicity, neurological deterioration before radiation, progression-free survival (PFS), overall survival (OS) and 1-year survival. **Results:** 103 p were registered and 93 randomized – 45 to the TMZArm and 48 to the BEV Arm.Partial response (PR) was attained in 7.1% of p in the TMZ Arm vs 25.6% in the BEVArm(P=0.001), and clinical benefit (PR + stable disease) in 26.1% vs 65%, respectively Neurological deterioration before radiotherapy was more frequent in the TMZ Arm (48.9% vs 20.8% of p; P=0.004). PFS was 2.2 months (m) in the TMZ Arm vs 4.8 m in the BEV Arm (HR, 0.79; P=0.29). OS was 7.7 m vs 10.8 m (HR, 0.71; P=0.12) and 1-year survival was 29.6% vs 48.9% (HR, 0.60; P=0.06), respectively. MGMT methylation was an independent prognostic factorfor longer PFS (P=0.01), OS (P=0.001) and 1-year survival(P=0.004). More toxicities occurred in the BEV Arm, but a significant difference was observed only for stomatitis (P=0.02). **Conclusions:** The primary endpoint was met. The response rate was significantly higher in the BEV Arm. A tendency towards improved PFS, OS and 1-year survival was also observed in the BEV Arm, but the trial was not powered to detect statistical significance for these outcomes.TMZ+BEV is a feasible and effective option for unresectable GBM p. Clinical trial information: NCT01102595.

**2029 Poster Highlights Session (Board #20), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Phase 1/2 study of investigational hypoxia-targeted drug, TH-302, and bevacizumab (bev) in recurrent glioblastoma (GBM) following bev failure.** *Presenting Author: Andrew Jacob Brenner, Cancer Therapy and Research Center at UT Health Science Center, San Antonio, TX*

**Background:** Despite vascular dependence, GBM is resistant to antiangiogenic therapy. Co-targeting tumor angiogenesis and tumor hypoxia, a key driver of treatment resistance, is one approach to potentially prevent or reverse this mechanism of resistance. An ongoing Phase 1/2 study investigates TH-302 with bev in patients (pts) with recurrent GBM following bev failure. Median PFS and 3-mo PFS (PFS-3) in this pt population has been reported as 37.5 days and ~16% (Quant, Neuro-Onc 2009). **Methods:** Single center, dose-escalation, prospective study (NCT01403610) with 2:1 randomization to TH-302 single dose of 575 mg/m$^2$ or placebo administered pre-surgery (cohorts 1-3 only), followed by post-surgery combination therapy of bev at 10 mg/kg and TH-302 dose escalated 240-670 mg/m$^2$every 2 weeks (4 week cycle) until disease progression. Following the first 5 pts in cohort 3, pts were allowed to proceed directly to TH-302/bev combination therapy without surgery. Resected tumor tissue was evaluated for hypoxia induced pimonidazole (PIMO) adducts, endogenous CA-IX staining, γH2AX and TUNEL DNA damage biomarkers, and by metabolomic profiling. **Results:** 21 pts have been enrolled: 14 randomized in presurgery cohorts 1-3 with 9 proceeding to TH-302/bev after surgery and 7 pts proceeding directly to TH-302/bev. No Gr 4 AEs were observed. Two Gr 3 AEs were observed at 340 mg/m$^2$ (skin ulceration) and 670 mg/m$^2$ (thrombocytopenia). Primary TH-302 related toxicities were mucosal but not dose limiting: rectal mucositis in 2/4 pts at 480 mg/m$^2$ and 4/4 pts at 670 mg/m$^2$. Oral mucositis was limited. Co-localized PIMO and CA-IX staining showed extensive tumor hypoxia. MR-spectra showed significant differences in metabolites before treatment compared to at progression. Best tumor responses in 16 evaluable pts: 1 CR, 2 PRs, 9 SDs. Median PFS is 3.1 mos (95% CI: 2.1 to 4.0 mos) and PFS-3 is 52% (95% CI: 27% to 78%). **Conclusions:** Extensive tumor hypoxia was observed in GBM pts previously treated with bev. The recommended Phase 2 dose of TH-302 is 670 mg/m$^2$ when combined with bev. These preliminary data suggest potential activity of TH-302/bev in GBM pts with poor prognosis. Dose expansion at 670 mg/m$^2$ is ongoing. Clinical trial information: NCT01403610.

**2030 Poster Highlights Session (Board #21), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Phase II trial of vorinostat (VOR) combined with temozolomide (TMZ) and radiation therapy (RT) for newly diagnosed glioblastoma (GBM) (Alliance N0874/ABTC-0902).** *Presenting Author: Evanthia Galanis, Mayo Clinic, Rochester, MN*

**Background:** VOR is a histone deacetylase inhibitor that represents a rational targeted agent in GBM treatment. Given its single agent activity in recurrent disease (Galanis et al 2009) and radiosensitizing properties, this phase II trial was designed to test the addition of VOR to standard chemoradiation in newly diagnosed GBM patients (pts). **Methods:** Pts received vorinostat at 300 mg/day, days 1-5 weekly during RT in combination with temozolomide (75 mg/m$^2$/day). Following a 4-6 week rest period, pts received up to 12 cycles of standard adjuvant TMZ in combination with VOR at a dose of 400 mg/day on days 1-7 and 15-21 of each cycle (Lee et al, 2012). **Results:** A total of 107 patients were accrued to this single arm trial. This preliminary report is based on mature outcome data in 73 patients. Final data analysis will be presented at the meeting. With a median follow up of 11.3 months (range 0.8-21.6 months), OS 15, (survival status at 15 mo, primary trial endpoint) was 39.1% with a median OS of 14.3 months and PFS of 8.1 months. MGMT methylation status is available in 52 pts; OS 15 and PFS were 44.4% vs 11.1% and 8.1 vs 6.4 mo in methylated and unmethylated pts respectively. Most common grade 3/4 toxicities were lymphopenia (32%), thrombocytopenia (28%), neutropenia (22%), fatigue (12.1%), anemia (8.4%) and anorexia (6.5%). There were no treatment related deaths. **Conclusions:** The HDAC inhibitor VOR in combination with TMZ and RT has tolerable toxicity in newly diagnosed GBM patients. Initial analysis based on mature outcome data in 70% of the evaluable patients does not indicate an improvement in outcome; final data will be presented at the meeting. Ongoing RNA sequencing analysis of baseline tumor tissue in 80 pts will assess if a 43 gene VOR responsive signature, identified in preclinical models, can define subgroups of patients deriving benefit from treatment. Clinical trial information: NCT00731731.

**2031 Poster Highlights Session (Board #22), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Phase I study of plerixafor and bevacizumab in recurrent high-grade glioma.** *Presenting Author: Katrina H. Smith, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Although anti-angiogenic therapy for high-grade glioma (HGG) is promising, responses are not durable. The SDF-1/CXCR4 axis may help mediate resistance to VEGFR inhibition. SDF-1 is a known mediator of cancer cell invasion, vasculogenesis and vessel co-option. Plerixafor is a reversible CXCR4 inhibitor that has demonstrated growth inhibition in orthotopic glioblastoma xenografts. **Methods:** We conducted an open-label Phase I study to determine the safety and tolerability of plerixafor in combination with bevacizumab 10 mg/kg every two weeks in patients with recurrent HGG. In Part 1 of the study, plerixafor was dosed on Days 1-21 of each 28 day cycle. A 3 x 3 dose escalation design to a maximum planned dose level of plerixafor 320 $\mu$g/kg on Days 1-21 and bevacizumab 10 mg/kg on Days 1 and 15 of each 28 day cycle was used. Dose limiting toxicities (DLTs) were determined during the initial 4 weeks of therapy and included drug-related Grade ≥ 3 non-hematologic toxicities and Grade ≥ 4 hematologic toxicities. **Results:** 17 patients have been enrolled into Part 1 of the study to date: median age was 54 (23-67), median Karnofsky Performance Status was 90 (70-100), 9 were women (52.9%) , 9 had grade 4 glioma (52.9%), 8 had grade 3 glioma (47.1%), median number of prior therapies 1 (1-3). One DLT (grade 3 rectal fistula) was seen at a dose level of plerixafor 240 $\mu$g/kg + bevacizumab and the cohort was expanded to from 4 to 8 patients. Because no further DLTs were seen at the 240 $\mu$g/kg dose level, the maximum planned dose level of plerixafor 320 $\mu$g/kg + bevacizumb opened and 6 patients have been treated to date. Since no DLTs have been seen, the cohort has now been expanded to 12 patients. There are no other treatment-related grade 3 and no grade 4 toxicities. One grade 1 stroke (attributed to bevacizumab, unrelated to plerixafor) was found incidentally on imaging and the patient was removed from active treatment. **Conclusions:** Combination treatment with bevacizumab and plerixafor is well tolerated in HGG patients. No DLT has been seen in the first 6 patients treated at the maximum planned dose level (plerixafor 320 $\mu$g/kg on Days 1-21 and bevacizumab 10 mg/kg on Days 1 and 15 of each 28 day cycle) and the cohort has been expanded to 12 patients. Updated results will be presented. Clinical trial information: NCT01339039.

**2032 Poster Highlights Session (Board #23), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Predictive factors of bevacizumab efficacy in relapsed glioblastoma patients.** *Presenting Author: Patrizia Farina, Medical Oncology 1, Venetian Institute of Oncology-IRCCS, Padua, Italy*

**Background:** Bevacizumab is widely used in recurrent glioblastoma patients. Despite encouraging response rate, some patients do not respond to this schedule and many develop an early relapse. Predictive biomarkers of response or resistance are thus highly desirable to improve clinical benefit. **Methods:** Seventy patients with recurrent glioblastoma treated with bevacizumab (40 at first recurrence, 30 at > first recurrence) were included in the cohort and sequential plasma samples were collected before and during the treatment. The plasma of 23 healthy volunteers was also collected. Plasma concentrations of VEGF, PlGF, Ang2, TEK/Tie2 receptor (sTie2), BMP9, sFlt1, sRobo4 levels were assessed by ELISA based assays. Response to treatment was evaluated according to RANO criteria. **Results:** Median OS was 28.4 months for responders, 19.1 months for non responders patients ($p$=0.0009). Median PFS was 25.4 weeks for responder patients and 10.1 weeks for non responder patients ($p<$ 0.0001). A median of 10 cycles (range 2-32) per patient was administered. 36 patients were responders (4 complete responses and 32 partial responses) and 34 patients were considered as non responders (15 stable diseases and 19 progressive diseases). Baseline levels of VEGF-A, and PlGF were higher in patients than in healthy volunteers ($p<$0.0001) whereas BMP9 baseline median concentration was reduced in patients ($p=$ 0.003), and no difference was found for Ang2, sTie2, sFlt1 and sRobo4 between patients and healthy volunteers. No biomarker at baseline was associated with response, PFS or OS. During the first two months of bevacizumab treatment, VEGF-A, sTie2, Ang2 and sRobo4 decreased whereas PlGF level strongly increased. Bevacizumab treatment did not affect plasma levels of BMP9 and sFlt1. The evolution of plasma concentrations did not discriminated responder and non responder patients. Finally we found no significant variation for any biomarker at relapse. **Conclusions:** Our study identified plasmatic markers associated with gliomas and level variation associated with bevacizumab treatment but failed to identify any predictor of response, PFS or OS.

**2033 Poster Highlights Session (Board #24), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Venous thromboembolism (VTE) and glioblastoma.** *Presenting Author: Jacob Joseph Mandel, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** The risk of VTE is very high for patients with brain tumors, with Glioblastoma (GB) considered one of the most at risk cancers. The aim of this study is to describe the occurrence and associated risk factors for the development of VTE among GB (patients) pts. **Methods:** In this IRB approved retrospective study, our neuro-oncology longitudinal database was screened for pts with GB, who were treated with concurrent radiation and Temozolomide (TMZ) followed by adjuvant TMZ from 2005-2011. 543 pts were identified. **Results:** 134 (24.6%) pts developed VTE, with 139 documented events. 56 pts (42%) were diagnosed with deep vein thrombosis (DVT) , 27 pts (20%) with pulmonary emboli (PE) with no evidence of DVT, and 51 pts (38%) had both DVT and PE. The majority were diagnosed after starting adjuvant TMZ (61%) with a median time of 6.5 months from starting adjuvant TMZ (range 0.03-120) with only 22 (16%) pts developing VTE before starting post surgery treatment and 32(23%) during chemoradiation. At time of VTE diagnosis, 44 (32%) patients had stable disease, 61 (43%) were clinically or radiographically progressing and the rest were newly diagnosed or during concurrent treatment. 56 (40%) patients were admitted secondary to their VTE. Treatment with anticoagulation alone was given to 68 (52%) pts, IVC filter only was inserted to 6 (5%) pts and 56 (43%)pts were treated with both modalities). 15 pts developed complications secondary to anticoagulation(5 brain haemorrhage , 6 bleeding in other locations and 4 thrombocytopenia). On univariate analysis risk factor associated with development of VTE after starting adjuvant TMZ treatment were: sex, prior history of venous thrombosis, poor KPS, requiring assistive device for ambulation, paresis, high BMI, pre chemotherapy WBC counts, and various medications (including anticoagulation, blood pressure drugs, anti-acid drugs and corticosteroids) ($p<0.05$). On multivariate analysis sex, poor KPS, high BMI, history of VTE and use of corticosteroids were significant risk factors for the development of VTE ($P<0.05$). **Conclusions:** VTE is a common complication of GB and can occur during the course of the disease. Factors associated with increased risk have been identified and will be useful in developing risk models in this patient population.

**2034 Poster Highlights Session (Board #25), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Joint modeling of longitudinal health-related quality of life (HRQoL) data and survival.** *Presenting Author: Divine Ewane Ediebah, European Organisation for Research and Treatment of Cancer Headquarters, Brussels, Belgium*

**Background:** In cancer clinical trials, several outcome measures may co-vary. Both treatment itself and treatment-related impairment of health-related quality of life (HRQoL) may affect survival. When these effects are analyzed separately, bias may arise. Therefore, our aim is to investigate the combined effect of treatment and longitudinally measured HRQoL on survival. **Methods:** We analyzed data from an EORTC randomized clinical trial (RCT) of 288 patients with anaplastic oligodendrogliomas who received radiotherapy (RT) alone or RT plus procarbazine, lomustine and vincristine (PCV) chemotherapy. HRQoL was assessed with the EORTC QLQ-C30 and Brain Cancer Module, at baseline, at the end of RT, and then every 3 to 6 months until progression. The appetite loss (AP) scale was pre-selected as the primary HRQoL endpoint, because this scale was previously found to be significantly different between the two treatment arms. Joint modeling was used to assess the combined effect of treatment and treatment-related AP on survival. The hazard ratios (HRs) for treatment effect were calculated using three different modeling strategies: Cox model with treatment only (model 1 [M1]), Cox model with treatment and time-dependent AP score (model 2 [M2]) and the joint model (model 3 [M3]). **Results:** In general, treatment with RT plus PCV chemotherapy resulted in decreased risk of death compared to RT alone. Estimated HR for treatment was 0.76 (95% CI 0.58–1.00) for M1, 0.72 (0.55–0.96) for M2 and 0.69 (0.52–0.92) for M3. This corresponds to a lower risk of death of 24% in M1, 28% in M2 and 31% in M3, for patients treated with RT plus PCV chemotherapy. Treatment-related AP resulted in increased risk of death, with estimated HR of 1.06 (1.01–1.12) for M2 and 1.13 (1.03–1.23) for M3. This translates to a 13% increased risk of death in M3 as compared to 6% increased risk of death in M2 for every 10-points increase of AP. **Conclusions:** Our findings suggest that part of the survival benefit of treatment with RT plus PCV chemotherapy can be masked by the negative effect that this treatment has on patients' HRQoL. In our study, up to 7% of the theoretical treatment efficacy was lost through increased AP affecting survival. Clinical trial information: NCT00002840.

**2035 Poster Highlights Session (Board #26), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Prospective assessment of neurocognitive outcomes in children and young adults with progressive/residual benign and low-grade brain tumors treated with high-precision conformal or conventional radiotherapy: Results of a randomized clinical trial.** *Presenting Author: Rakesh Jalali, Tata Memorial Hospital, Mumbai, India*

**Background:** Evidence for modern conformal partial brain radiotherapy is largely on retrospective or small case-series. We report longitudinal detailed neuropsychological outcomes from a prospective randomized trial comparing high-precision conformal radiotherapy (CRT) versus conventional radiotherapy (Conv RT) in children and young adults with progressive/residual benign and low-grade brain tumors (NCT00517959). **Methods:** Between 2001-10, 200 patients (132 males, 68 females; median age 13 years) were randomized to receive CRT (n=105; multiple non-coplanar fields using micromultileaf collimators under stereotactic guidance) or Conv RT (n=95; 2-4 open fields and beam modification) by 6 MV to dose of 54 Gy/30 fractions. Age-appropriate battery included full-scale IQ (FSIQ), verbal quotient (VQ), performance quotient (PQ), memory quotient (MQ>16 years of age) by Wechsler scores, LOTCA and anxiety-depression tests. Serial evaluations were done at pre-RT, 6-months and 2, 3 and 5 years and analyzed using generalized linear-mixed model (GLMM). **Results:** The most common histology was craniopharyngioma and low-grade astrocytoma. Baseline characteristics were well balanced between two arms. A substantial proportion of patients had low intelligence (FSIQ <69) in both arms (CRT-17%; Conv RT-16%) before RT. GLMM for repeated measures demonstrated significantly better preservation of FSIQ over time in patients treated with CRT compared to Conv RT at 3 year (p=0.003) and 5 year post-RT evaluation (p=0.012,Hyunh-Feldt test), as also in VQ (p=0.047) and MQ (p=0.049). Decline in LOTCA scores at 5-years (mainly in visuo-motor organization and attention-concentration) was significantly higher in Conv RT than CRT (p=0.019). Children <16 years had lesser depression in conformal arm (p=0.01) with no differences in anxiety between two arms. **Conclusions:** Our randomized trial provides high-quality evidence supporting use of high-precision conformal radiotherapy in children and young adults with progressive and residual benign and/or low-grade brain tumors. Clinical trial information: NCT00517959.

**2036 General Poster Session (Board #1), Sat, 1:15 PM-5:00 PM**

**Keeping GBM in check by targeting CHK1-CIP2A axis.** *Presenting Author: Anchit Khanna, Adult Cancer Program, Lowy Cancer Research Centre, UNSW Medicine, The University of New South Wales, Sydney, Australia*

**Background:** Checkpoint kinase1 (CHK1) is constitutively active in many human cancers including Glioblastoma (GBM). Unfortunately CHK1 inhibitors, currently in clinical trials, have shown deleterious effects on normal cells, thus limiting their clinical utility. Therefore, identification and targeting of cancer specific effectors of CHK1 signaling, emerges as an attractive therapeutic alternative. **Methods:** Analysis of 906 gliomapatient samples was done. GBM cell lines (including primary) were used for mechanistic and functional studies. *In vivo* models of GBM were used to verify the findings. **Results:** Meta-analysis of key datasets revealed a strong positive correlation for CHK1 and CIP2A expression. By contrast, a negligible correlation was seen in normal samples. Importantly, high mRNA expression of both proteins associated with reduced overall survival in glioma patients and marked for a more aggressive form of the disease. CIP2A amplification, found in 14.72% cases in the REMBRANDT study, was associated with worse overall survival in GBM patients. Inhibition of CHK1, by siRNA and chemicals, resulted in decreased CIP2A expression both *in vitro* and *in vivo*. Functionally, both CHK1 and CIP2A promoted viability, clonogenicity and anchorage-independent growth of GBM cells. Strikingly, the CHK1-mediated reduction in the clonogenic potential was partially rescued by exogenous CIP2A expression in GBM cells. Mechanistically, we identify STAT3 as the transcriptional mediator for CHK1-mediated CIP2A regulation. Depletion of STAT3 resulted in decreased CIP2A expression in both, U251MG and primary GBM cells. Further, CHK1 promoted STAT3 phosphorylation *in vitro* and *in vivo*. Accordingly, higher CIP2A, pCHK1 and pSTAT3 levels were observed in *de novo* and patient-derived GBM samples, relative to normal human astrocytes. Analogously, 10- to 15-fold higher CHK1 and CIP2A mRNA expression was seen in the genetically engineered mouse models of human GBM. Finally, using xenograft mouse models we show that both CHK1 inhibitor and CIP2A depletion inhibit GBM growth. **Conclusions:** These results highlight CHK1 and CIP2A expression as potential diagnostic and prognostic markers in human GBMs and identify CIP2A as a relevant cancer specific therapeutic target.

**2037 General Poster Session (Board #2), Sat, 1:15 PM-5:00 PM**

**Diagnostic value of plasma and urinary 2-hydroxyglutarate to identify patients with IDH-mutated glioma.** *Presenting Author: Giuseppe Lombardi, Medical Oncology 1, Venetian Institute of Oncology-IRCCS, Padua, Italy*

**Background:** Mutation of IDH1 gene is a prognostic factor and a diagnostic hallmark of gliomas. Mutant IDH1 enzyme can convert $\alpha$-KG into 2-Hydroxyglutarate(2HG); mutated gliomas have elevated amounts of intracellular 2HG. We analyzed 2HG concentration in plasma and urine in glioma patients(PTS) to identify a biomarker of IDH1 gene mutation **Methods:** All PTS had a prior histological confirmation of glioma, a recent brain MRI (within 2 weeks) showing the neoplastic lesions. The exclusion criteria were any chemotherapy performed within 28 days prior, other neoplastic and metabolic diseases. Plasma and urine samples were taken from all PTS and 2HG concentrations determined by liquid chromatography tandem mass spectrometry; Mann-Whitney test was used to test for differences in metabolite concentrations. ROC curve was used to evaluate the cut off value of 2HG biomarker. **Results:** 84 PTS were enrolled: 38 with IDH1 mutated and 46 IDH1 wild-type. Among PTS with mutant IDH1 we had 21 high-grade gliomas (HGG) and 17 low-grade gliomas (LGG); among PTS with IDH1 wild-type we had 35 HGG and 11 LGG. In all PTS we analyzed the mean 2HG concentration in plasma (P_2HG), in urine (U_2HG) and the ratio between P_2HG and U_2HG (R_2HG). The results are shown in Table. We found an important significant difference in R_2HG between PTS with and without IDH1 mutation. The optimal cut-off value of R_2HG to identify glioma PTS with and without IDH1 mutation was 19 with sensitivity (S) 63%, specificity (SP) 76% and accuracy (A) 70%.; in only PTS with HGG the optimal cut-off value was 20 (S 76%, SP 89%, A 84%, PPV 80%, NPV 86%). No association between the grade or size of tumor and R_2HG were found. In 7 out of 7 HGG PTS, we found a correlation between R_2HG value and response to treatment. **Conclusions:** By analyzing the R_2HG derived from individual plasma and urine 2HG levels is possible discriminate glioma PTS with and without IDH1 mutation. A larger samples need to be analyzed to investigate this method to monitor treatment efficacy.

| | IDH1 wt | IDH1 mut | P |
|---|---|---|---|
| **P_2HG (ng/mL)** | 97.0 | 97.2 | 0.9 |
| **U_2HG(mg/mg)*** | 7.3 | 4.6 | 0.002 |
| **R_2HG (all gliomas)** | 15.6 | 22.2 | <0.0001 |
| **R_2HG (only HGGs)** | 15.3 | 24.9 | <0.0001 |

* Concentration of 2HG (mg/mL) normalized by creatinine concentration (mg/mL).

**2038 General Poster Session (Board #3), Sat, 1:15 PM-5:00 PM**

**Features of adult clinical trial participants with glioblastoma (GB) at The University of Texas MD Anderson Cancer Center (MDACC).** *Presenting Author: Mark Daniel Anderson, University of Mississippi Medical Center, Jackson, MS*

**Background:** GB is the most common primary brain tumor in adults and has a poor prognosis. Less than 10% of pts are treated on clinical trials. **Methods:** In this IRB-approved retrospective study, our database was screened for GB pts from 2007-2012. 510 adult patients (pts) with primary GB were identified who participated on a clinical trial. 112 adult pts with primary GB were identified who were clinical trial eligible, but elected not to enroll in a clinical trial. **Results:** Median age was 54 years (18-83). 307 pts with a primary GB were consented for a newly diagnosed protocol (NDP) and their median OS was 25 months and their median PFS was 12.6 months. Median OS for pts who only enrolled on a recurrent GB protocol (RP) was 19 months from time of diagnosis. These 2 groups had differences in employment, education, symptoms, tumor location, performance status, extent of resection and location of therapy. Pts that were eligible for a clinical trial, but did not enroll, tended to be older, have a lower KPS, live farther away, but had no differences in outcome. Active smokers were less likely to participate in clinical trials. Many pts who enrolled on a clinical trial enrolled in more than one, but receiving dose dense TMZ reduced clinical trial enrollment at recurrence. Age, KPS at presentation, and extent of resection were confirmed as prognostic factors associated with OS. Also, location of radiation therapy (MDACC versus community facility; p=0.02) was associated with OS. 383 pts were identified who either did not follow up for enrollment (n=161, due to distance, evaluation as a second opinion, unknown) or were ineligible for clinical protocols (n=221, prior therapy, early progression or death, treatment toxicity/medical comorbidities, tumor location, insurance denial). **Conclusions:** Clinical trial eligible GB pts at MDACC have overall better prognoses than historical controls, consistent with other studies. Caution should be taken when interpreting efficacy from single institution, single arm clinical trials. Location of radiation therapy may represent an important variable associated with survival and requires additional investigation. Travel is a significant barrier to clinical trial enrollment.

**2039 General Poster Session (Board #4), Sat, 1:15 PM-5:00 PM**

**Recurrent glioblastoma: Does the timing of bevacizumab treatment impact survival?** *Presenting Author: Susmita Sakruti, Cleveland Clinic, Cleveland, OH*

**Background:** Bevacizumab (Bev) is FDA approved for use in recurrent glioblastoma (rGBM). There is limited literature on outcomes in rGBM depending on the time of initiation of Bev therapy. We examined the progression-free survival (PFS) and overall survival (OS) in rGBM patients treated with Bev at our center. **Methods:** With IRB approval, the Cleveland Clinic Brain Tumor database was used to examine 690 rGBM patient charts (2003 to 2013). The patients were stratified into three groups: 1) patients treated with Bev at first recurrence, 2) second recurrence, and 3) $\geq$ 3 recurrences. OS and PFS between the three cohorts were calculated using Kaplan-Meier analysis and compared using Renyi log-rank tests. **Results:** One hundred and fifty patients, median age 56 years (range: 24-83), were included in this analysis. Median KPS prior to Bev treatment was 80 (range: 40-100). Twenty-eight patients had multifocal and 122 had unifocal GBM at time of starting Bev therapy. The median number of comorbidities at diagnosis were 1 (range: 0-4). Seventy five patients (50%) received Bev at first recurrence, 50 patients (33%) started Bev at second recurrence, and 25 patients (17%) were treated with Bev at third or later recurrences. Median OS from start of Bev was 12.2 months (95% CI: 10.0, 14.3) and median PFS was 8.3 months (95% CI: 6.2, 10.2). Stratified by recurrence and initiation of Bev, median PFS was 7.1 months (95% CI: 5.9, 10.1) for the first recurrence, 9.9 months (95% CI: 6.3, 25.2) for second recurrence, and 9.4 months (95% CI: 3.8, 16.8) for the third recurrence (p=0.09). Median OS was 11.7 months (95% CI: 10.3, 14.3) for first recurrence, 10.0 months (95% CI: 8.1, 39.3) for second recurrence, and 13.9 months (95% CI: 8.2, 18.4) for the third recurrence (p=0.26). **Conclusions:** There was no significant difference in median OS or PFS in the three rGBM groups treated with Bev.

| GBM | N | OS [months] (p=0.26) | PFS [months] (p=0.09) |
|---|---|---|---|
| **1st recurrence** | 75 | 11.7 | 7.1 |
| **2nd recurrence** | 50 | 10.0 | 9.9 |
| **≥3rd recurrence** | 25 | 13.9 | 9.4 |

**2040 General Poster Session (Board #5), Sat, 1:15 PM-5:00 PM**

**A model to predict the feasibility of concurrent chemoradiotherapy with temozolomide in glioblastoma multiforme patients over age 65.** *Presenting Author: Florian Putz, Department of Radiation Oncology, University of Erlangen-Nuremberg, Erlangen, Germany*

**Background:** It is controversial whether concurrent chemoradiotherapy (CRT) with temozolomide is feasible and beneficial in elderly patients with glioblastoma (GBM). **Methods:** Retrospective analysis of 76 elderly GBM patients (≥ 65 years) treated with concurrent CRT with temozolomide. Factors influencing prognosis and feasibility of CRT were investigated. **Results:** Median overall survival (mOS) was 11.3 months. Univariate analysis showed a significant difference in mOS for cumulative dose of concurrent temozolomide (optimal cutoff, 2655 mg/m$^2$; 13.9 months for > 2655 mg/m$^2$ v 4.9 months for ≤ 2655 mg/m$^2$; P = .0103). Significant independent prognostic parameters in multivariate analysis were: a cumulative dose of concurrent temozolomide > 2655 mg/m$^2$ (hazard ratio [HR], 0.41; P = .008), thrombocytopenia grade III/IV (HR, 3.05; P = .034), and biopsy only (HR, 2.10; P = .022). Hematotoxicity was the most common cause of treatment interruption or discontinuation in patients with an insufficient cumulative temozolomide dose. Prognostic factors for successful performance of CRT with a cumulative dose of concurrent temozolomide > 2655 mg/m$^2$ were: female gender (odds ratio [OR], 0.208; P = .0103), age (OR, 0.849 per year; P = .0178), and pretreatment platelet count (OR, 1.010 per 1000 platelets/$\mu$l; P = .0057). **Conclusions:** The probability of successful performance of concurrent chemoradiotherapy with temozolomide can be estimated based on the patient's age, sex and pretreatment platelet count using the model developed in this study. Thus, a subgroup of elderly patients with GBM can be identified in whom concurrent chemoradiotherapy with temozolomide is feasible and who have a favorable prognosis.

**2041 General Poster Session (Board #6), Sat, 1:15 PM-5:00 PM**

**Predicting GBM response to targeted therapeutics using simulation with ex vivo validations.** *Presenting Author: Sandeep C. Pingle, University of California San Diego, La Jolla, CA*

**Background:** The unique signature of a patient's tumor implies that a one-size-fits-all treatment approach will likely fail. This necessitates a rationally designed personalized therapeutic approach employing N=1 segmentation. To predict clinical responses to targeted drugs, we (1) employed predictive modeling and validated this retrospectively (2) used patient tumor profiling data to create simulation avatars (3) screened drugs prospectively and predicted response for patient-derived cell lines (4) validated outcomes ex-vivo in patient lines. **Methods:** Human patient-derived glioblastoma (GBM) samples were cultured and characterized using histopathologic and integrated genomic analyses. Using these data, we created simulation avatars of patient lines. Responses of patient-derived GBM lines to erlotinib, sorafenib and dasatinib were used as alignment datasets. The predictive simulation-based approach from Cellworks provides a comprehensive representation of GBM disease physiology, incorporating signaling and metabolic networks with an integrated phenotype view. This model predicts clinical outcomes based on phenotype and biomarker assays. We prospectively screened ten drugs across eight patient profiles and validated their responses ex vivo. **Results:** We evaluated the ability of the simulation model to predict drug responses, using results from a recent study by Garnett et al. Of the gene mutation-drug response associations reported in this study, we predicted 22 of the 25 associations tested (>85% correlation). Importantly, we predicted the sensitivity of patient-derived GBM lines to various targeted therapeutic agents; more than 75% predictions matched our experimental ex vivo results. **Conclusions:** There is an unmet need for individualization of cancer treatment. Use of innovative simulation technology to predict responses to drugs may provide a way to stratify patients for clinical trials. This study validates our *in silico* model for predicting sensitivity of patient cells to targeted therapeutics. By accurately predicting responses *a priori*, the *in silico* model enables personalizing cancer therapy and promises to improve clinical management.

**2042^ General Poster Session (Board #7), Sat, 1:15 PM-5:00 PM**

**Survival and quality of life in the randomized, multicenter GLARIUS trial investigating bevacizumab/irinotecan versus standard temozolomide in newly diagnosed, MGMT-non-methylated glioblastoma patients.** *Presenting Author: Ulrich Herrlinger, Division of Clinical Neurooncology, Department of Neurology and Center of Integrated Oncology Cologne/Bonn, University of Bonn, Bonn, Germany*

**Background:** There is a need for more effective therapies in newly diagnosed glioblastoma (GBM) patients with an MGMT-non-methylated tumor. The GLARIUS trial explored the efficacy of bevacizumab (BEV) + Irinotecan (IRI) as compared to standard TMZ in the first-line therapy of MGMT-non-methylated GBM. The primary endpoint progression-free survival after 6 months (PFS-6) has already been reported as being markedly increased in the BEV/IRI arm (Herrlinger et al., ASCO 2013, LBA 2000). The present report focuses on progression-free survival, overall survival (OS) and quality of life (QoL). OS and QoL are particularly important parameters since previous randomized trials investigating BEV in primary therapy of GBM have not been able to demonstrate an OS benefit and have yielded conflicting results regarding QoL. **Methods:** Patients (n=170) with newly diagnosed, MGMT-non-methylated glioblastoma received local radiotherapy (RT, 30 x 2 Gy) and were randomized (2:1) for experimental therapy with BEV (10 mg/kg q2w) during RT followed by maintenance BEV (10 mg/kg q2w) + IRI (125 mg/m$^2$ q2w) or standard therapy with daily TMZ (75 mg/m$^2$) during RT followed by 6 courses of TMZ (150-200 mg/m$^2$/day for 5 days q4w). For 5 prespecified domaines of the EORTC-QLQ C30 and BN20 questionnaires (global health status, physical functioning, social functioning, motor dysfunction, communication deficit as prespecified domaines), the time to deterioration by at least 10 points was analyzed using Kaplan-Meier statistics. **Results:** With BEV/IRI, PFS was significantly prolonged from a median of 5.9 months (95%CI 2.7-6.2 months) to 9.7 months (95%CI 8.7-10.5 months, p=0.0004; hazard ratio 0.56, 95%CI 0.4-0.79). At progression, the crossover rate was similar in both arms (60.8 and 61.9%). Final OS results will be presented. In all prespecified dimensions of QoL, the time to deterioration was not significantly different between the treatment arms. Data of post-progression QoL will be presented. **Conclusions:** BEV/IRI therapy was superior to TMZ regarding PFS. BEV/IRI therapy did not alter QoL as compared to TMZ therapy. Clinical trial information: No.: 2009-010390-21.

**2043 General Poster Session (Board #8), Sat, 1:15 PM-5:00 PM**

**An update on high-dose chemotherapy with autologous stem cell transplantation in adults with recurrent embryonal tumors of the central nervous system.** *Presenting Author: Ryan Eldredge Wilcox, Mayo Clinic, Rochester, MN*

**Background:** Recurrent embryonal tumors of the central nervous system (CNS) in adults are rare and have a poor prognosis. High-dose chemotherapy followed by autologous stem cell transplant (HDC/ASCT) in our previous experience has shown to result in durable responses. (Gill; Cancer 2008; Apr 15;112(8):1805-11). We present an updated report of the Mayo Clinic experience. **Methods:** We performed a retrospective review of adults (age ≥18) with recurrent embryonal tumors at our institution treated with HDC/ASCT between 1998 and 2012. Kaplan-Meier method was used to calculate time to event and survival analysis. **Results:** 19 patients were identified: 14 medulloblastoma, 4 PNET/cerebral neuroblastoma, and 1 pineoblastoma. Median follow up was 120 mo. (95% CI: 74-157). At initial diagnosis, median age was 28 yrs. (18-64); 58% were male; 63%, 32% and 5% had gross total, subtotal, and no resection; 95 % had radiation therapy, and 53% had chemotherapy. Median time to first relapse was 58 mo. (12 - 146) and median time from relapse to transplant was 5 mo. (3 - 17). At first recurrence, median age was 35 yrs (21 - 65); M-stage was: M0 in 42%, M1 in 0%, M2 in 5%, M3 in 32%, and M4 in 21%, 11 pts had gross total, and 4 had subtotal resection; 2 had radiation, and 15 were treated with induction chemotherapy, with 87% receiving a platinum containing regimen. Prior treatment response status at transplant was CR in 37%, PR in 47%, and PROG in 16%. Most patients had tandem peripheral blood stem cell transplant following conditioning with ThioTEPA/BCNU then ThioTEPA/Carboplatin, (completed in 95% and 79% respectively). From first recurrence, mTTP was 23 mo. (95% CI: 15 - 49), and mOS was 35 mo. (95% CI: 24 - 50). 2-, 5-, and 10- year survival were 68%, 38%, and 14% respectively. There were no treatment related mortalities. **Conclusions:** These data in 19 adult patients confirm earlier observations in smaller patient cohorts, compare favorably with historic controls treated with standard dose chemotherapy in our institution, and support HDC/ASCT in adults with recurrent embryonal tumors of the CNS as a viable therapeutic option in appropriate patients.

**2044 General Poster Session (Board #9), Sat, 1:15 PM-5:00 PM**

**Primary central nervous system lymphoma: The influence of radiotherapy on patient outcome in an unselected population.** *Presenting Author: Scheryll Paula Alken, Departments of Neuro Oncology/Drug Development, Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*

**Background:** Treatment strategies for newly diagnosed PCNSL typically combine high dose methotrexate with whole-brain radiotherapy (WBRT). However, although WBRT is associated with neurotoxicity, its omission may compromise disease control. To address these issues, we report a retrospective, population-based study of high dose methotrexate with or without WBRT. **Methods:** We included patients (pts) with newly diagnosed PCNSL treated in three major medical oncology centers in Ireland between 2001 and 2011, which included 57% of cases diagnosed in Ireland over the same period. Medical records were examined for clinicopathologic characteristics, administered treatment and survival. Progression-free survival (PFS) and overall survival (OS) were estimated with the Kaplan-Meier method. For the primary endpoint, PFS was compared by receipt of WBRT using the log-rank test and Cox proportional hazard test. **Results:** A total of 70 pts were included in the study, median age of 60 years (range 17–78); 39 (53%) were male. In total, 66 (94%) received high dose methotrexate and 25 (36%) received WBRT. Distribution of demographics and clinical features including MSKCC RPA were comparable by receipt of WBRT (table). At a median follow up of 25 months for survivors, 33% have no evidence of disease and 46% are alive. For the primary endpoint, PFS was similar for pts who received WBRT or not (HR 0.95, 95%CI 0.39–2.32) (Table). Similarly, there were no differences in OS by receipt of WBRT (HR 0.92, 95%CI 0.44 – 1.51). **Conclusions:** In this retrospective study of older patients with newly diagnosed PCNSL the omission of WBRT did not adversely affect patient outcomes though selection bias cannot be outruled. Randomized studies are ongoing to examine if WBRT can be omitted from first line treatment without compromising outcome.

| | WBRT | | No WBRT | | |
|---|---|---|---|---|---|
| | N | % | N | % | P |
| Age (Median) | 56 | | 64 | | 0.35 |
| Range | 25 - 78 | | 17 - 76 | | |
| Gender (males) | 15 | 52 | 24 | 59 | 0.63 |
| ECOG PS | | | | | |
| 0 - 1 | 15 | 52 | 27 | 66 | 0.88 |
| ≥2 | 12 | 41 | 12 | 29 | |
| Unknown | 2 | 7 | 2 | 5 | |
| MSKCC RPA | | | | | |
| I | 9 | 31 | 10 | 24 | 0.71 |
| II | 12 | 41 | 15 | 37 | |
| III | 6 | 21 | 10 | 24 | |
| Unknown | 2 | 7 | 6 | 15 | |
| PFS (months) | | | | | |
| Median | 20.8 | | 22.3 | | 0.91 |
| OS (months) | | | | | |
| Median | 33.7 | | 32.1 | | 0.42 |

**2045 General Poster Session (Board #10), Sat, 1:15 PM-5:00 PM**

**Pilot study of pulse high-dose lapatinib in combination with temozolomide (TMZ) and radiotherapy (RT) for upfront treatment of glioblastoma (GBM).** *Presenting Author: Phioanh Leia Nghiemphu, Department of Neurology, University of California, Los Angeles, Los Angeles, CA*

**Background:** The Epidermal Growth Factor Receptor (EGFR) is a potentially important therapeutic target for GBM since 45% of GBM tumors harbor either amplification, mutations, or both, of the EGFR gene (Cancer Genome Atlas Research Network, Nature, 2008).Lapatinibis a kinase inhibitor that potently targets the inactive conformation of EGFR. However, conventional, daily dosing of lapatinib is not sufficient to achieve a high intratumoral concentration for brain tumors and has proven ineffective in the treatment of recurrent GBM (Vivanco et al, Cancer Discov, 2012). High dosages of lapatinib given in pulses may be more effective at inhibiting brain tumor growth and enhancing the effect of chemotherapy and RT. We performed a pilot study of pulse high dose lapatinib to assess the safety of this novel dosage given in combination with TMZ and RT. **Methods:** After informed consent, adult patients with newly diagnosed GBM received lapatinib at 2500 mg twice a day, for 2 consecutive days per week, in combination with standard dosing of RT + TMZ. After RT, patients continued high dose lapatinib 2-day weekly pulses until progression and also received 12-24 cycles of adjuvant TMZ. **Results:** 10 patients were enrolled in this pilot study. At the time of this report, all patients had completed treatments in the Concurrent Period with RT + TMZ + pulse high dose lapatinib. Median follow-up was 16.6 weeks (range 8-59). The most common toxicities were lymphopenia (8 patients), diarrhea (7), fatigue (7), and skin rash (4), mostly at grade 1-2. The only grade 3 toxicity related to this combination was lymphopenia in 4 patients. There were no grade 4-5 toxicities. One patient withdrew from study after 10 weeks of treatment after a hospitalization for epigastric pain although no laboratory or imaging abnormalities were found, and patient improved on proton pump inhibitor. One patient had resection of an enhancing growth 6 months after completing RT and pathology was consistent with treatment-induced necrosis. **Conclusions:** High dose lapatinib given in 2-day weekly pulses with TMZ and RT was well tolerated, and this combination will be further evaluated in an expanded phase II trial for upfront treatment of GBM. Clinical trial information: NCT01591577.

**2046 General Poster Session (Board #11), Sat, 1:15 PM-5:00 PM**

**PC or PCV? That is the question: A retrospective review of primary anaplastic oligodendroglial tumors treated with procarbazine and CCNU without or with vincristine.** *Presenting Author: Courtney C. Webre, Texas A&M Health Science Center, Bryan, TX*

**Background:** While procarbazine, CCNU and vincristine (PCV) has been shown to be efficacious in the treatment of anaplastic oligodendroglial tumors (AOT), the question of whether procarbazine and CCNU (PC) alone is sufficient still exists, since vincristine has been argued to add toxicity with little if any clinical benefit. This retrospective study was designed to provide initial insight into the comparison of PC with and without vincristine. **Methods:** Using the Brain Tumor Center historical database, we queried patients diagnosed with (AOT) treated at MD Anderson Cancer Center from June 1, 1993 through October 13, 2009. Patients were eligible if they had been diagnosed with a primary AOT and were subsequently treated with either PC or PCV at some point in the treatment regimen. A total of 120 patients were included in the study population, with 97 patients included in the primary analysis of treatment before first progression. **Results:** Initial treatment included radiation and chemotherapy (80.4%), chemotherapy alone (18.6%), or radiation alone (1.0%). Overall survival did not differ with initial treatment. 21 patients (21.6%) received PC during primary treatment, while 76 patients (78.4%) received PCV. 11 patients reported neurotoxicity in the PCV arm (defined as dysautonomia, peripheral neuropathy and ataxia), compared with none in the PC arm. Of the 97 patients included in the analysis, 45 were alive at last contact with a median follow-up of 9.9 years. The median overall survival (OS) time was 6.5 years (95% CI: 4.8-16.7 years). OS was significantly associated with KPS within one month of diagnosis (p=0.002) but not with age (p=0.26). There were 63 patients with disease progression or death, and the median progression-free survival (PFS) was 2.9 years (95% CI: 2.0-6.3 years). There was no difference between the two groups in OS (p=0.61) or PFS (p=0.28). **Conclusions:** Initial therapy with PC vs. PCV achieved comparable results with a median follow-up of 9.9 years. There was no difference in dose reductions although neurotoxicity was more frequent with vincristine. Further studies with correlative codeletion status are needed.

**2047 General Poster Session (Board #12), Sat, 1:15 PM-5:00 PM**

**A meta-analysis of antiangiogenic therapy for glioblastoma (GBM).** *Presenting Author: Mustafa Khasraw, Andrew Love Cancer Centre, Geelong, Australia*

**Background:** Overall Survival (OS) and Progression Free Survival (PFS) results of randomized controlled trials (RCTs) are available of anti-angiogenic therapy (AAT) in GBM, especially Bevacizumab (Bev). **Methods:** Searches were conducted to identify published and unpublished RCTs starting in 2000 including The Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE and EMBASE. Proceedings of relevant oncology conferences from 2000 to 1/ 2014, were also searched. RCTs with random allocation of the use of AATs to treat GBM were included. Authors screened search results and reviewed abstracts of potentially relevant articles before retrieving the full text of eligible articles. **Results:** Seven eligible RCTs were identified including 3187 patients. There was significant heterogeneity in studies especially in response assessment criteria. Six studies were only available in abstract form. Trials included in this analysis did not show improvement in OS with a pooled hazard ratio (HR) of 0.95 (95% CI 0.87 to 1.04; P = 0.27). They did however demonstrate improvement in PFS with improvement in the HR for PFS at 0.74 (95% CI 0.68 to 081; P= 0.00001). The HRs of the studies containing Bev as the AAT were generally more likely to report favorable results than other AAT, the pooled HR for PFS for Bev studies (n = 1712 patients) was significant at 0.57 (95% CI 0.4 to 0.82; P = 0.002). In the adjuvant setting with 5 RCTs including 2441 patients (AVAGLIO, RTOG 0825, GLARIUS with Bev; CENTRIC and CORE with cilengitide), the HR for OS was 0.90 (P = 0.19). Pooled analysis for PFS in the adjuvant setting (4 studies, n= 2441) showed significant HR at 0.69 (95% CI 0.56, 0.85; P= 0.0006). In the recurrent setting pooling of 2 RCTs (n=576) namely the phase 3 with cediranib (REGAL) and the phase 2 study with Bev (BELOB) showed HR for OS was 1.02 (P = 93). The BELOB study did not report PFS i.e., there is no RCT data to assess PFS with Bev in recurrent GBM. **Conclusions:** Bev appears to prolong PFS in newly diagnosed GBM. Available data does not demonstrate a survival benefit in newly diagnosed patients. In the recurrent setting, there is no adequately powered RCT to address if there is a PFS or survival benefit with Bev. A more detailed analysis is prepared as a Cochrane systematic review.

**2048 General Poster Session (Board #13), Sat, 1:15 PM-5:00 PM**

**Association of high volume center with survival for glioblastoma patients: Results from a prospective population-based registry (PERNO).** *Presenting Author: Alba Ariela Brandes, Bellaria-Maggiore Hospital, Azienda USL of Bologna - IRCCS Institute of Neurological Sciences, Bologna, Italy*

**Background**: The Project of Emilia Romagna in Neuro-Oncology (PERNO) is a prospective registry and it was created to evaluate the incidence and treatment of primary brain tumors (PBTs) in this italian region. In this network, as a subproject, a population-based prospective study was conducted to assess the survival outcome of glioblastoma (GBM) patients, and correlations with potential prognostic factors. **Methods**: Based on the data from this registry, from January 1st 2009 to December 31st 2010, a prospective study was made of the treatment efficacy and outcome in newly diagnosed GBM patients £70 years treated with the worldwide accepted standard treatment according to the EORTC 22981/26981) /NCIC CE.3 trial (temozolomide concomitant with and adjuvant to radiotherapy - RT/TMZ). **Results**: 267 GBM patients were enrolled, 139 patients were £70 years and received RT/TMZ, achieving a median overall survival (OS) of 16.4 months (95%CI: 14.0–18.5). At multivariate analysis, OS was significantly correlated with KPS (HR=0.458, 95%CI: 0.248-0.847, p=0.0127), *MGMT* methylation status (HR=0.612, 95%CI: 0.388-0.966, p=0.0350) and if treatment was received in the high volume center (HR=0.569, 95%CI: 0.328-0.986, p=0.0446). Median overall survival was 24.1 months for patients treated in the referral high volume center and 15.9 months in other centers (HR: 0.533, 95% CI: 0.328 – 0.866, p=0.0110), with no significant differences in KPS and *MGMT* methylation status among the centers. **Conclusions**: For the first time in the field of neuro-oncology, we have investigated the impact of center volume and expertise in post-surgical treatment, as a variable that may influence the outcome of GBM patients < 70 years and treated with RT/TMZ. Our findings may have depended on several factors, such as expertise in neuroradiology interpretation as well as the management of adverse events, and the use of third line treatments or the best supportive care. The amount of OS improvement supports further investigation of center volume and expertise as a prognostic factor.

**2049 General Poster Session (Board #14), Sat, 1:15 PM-5:00 PM**

**Changing trend of HIV-associated PCNSL over 15 years: A single-center experience.** *Presenting Author: Andrew Bayat, The University of Texas Southwestern Medical Center, Dallas, TX*

**Background:** Primary central nervous system lymphoma (PCNSL) is a rare form of extra nodal non Hodgkin lymphoma, accounting for approximately 3-4% of primary brain tumors and approximately 1% of all NHL. HIV is one of the leading risk factors for PCNSL. Though whole brain radiation is used often, there is no standard of care available for HIV associated PCNL. In this single center retrospective study we report the survival data of patients with biopsy-proven PCNSL with and without HIV between 1998-2013. **Methods:** We identified patients with PCNSL between 1998 and 2013 through our institution's tumor registry. After patient identification, the medical records were reviewed for the following patient data: age at diagnosis, ethnicity, sex, HIV status, CD4 cell count, HIV viral load, neuroimaging, treatment (radiation therapy and/or chemotherapy), date of death and date of last contact. Survival data and date of death were obtained from our tumor registry, chart reviews, and social security death index searches. **Results:** A total of 128 patient were identified as having biopsy-proven PCNSL: 41 HIV-positive and 87 HIV-negative. Average age at diagnosis was 60.8 for HIV-negative patients and 38.9 HIV-positive. The HIV-positive cohort was 80% males while only 54% in HIV-negative. Median survival for the two groups was 4.6 and 15.9 months respectively. Amongst HIV-negative patients: those who received MTX + WBRT had median survival of 25.7 months whereas those who received MTX alone had a median survival of 10.9 months although this difference did not meet statistical significance. HIV-positive patients who were diagnosed between 2009 and 2013 had significantly longer median survival than those diagnosed between 2004-2008 as well as 1998-2003 timeframes. **Conclusions:** Our current data confirm that there remains a marked gap in median survival among HIV-negative and HIV-positive patients diagnosed with PCNSL. It would also suggest that there is no significant difference in median survival among HIV-negative patients who receive WBRT versus those who receive MTX alone. We also confirm that median survival for HIV-positive patients has improved over the last decade coinciding with improvements in antiretroviral therapy.

**2050^ General Poster Session (Board #15), Sat, 1:15 PM-5:00 PM**

**Radiotherapy (RT), temozolomide (TMZ), procarbazine (PCB), and the integrin inhibitor cilengitide in patients (pts) with glioblastoma (GBM) without methylation of the MGMT gene promoter (ExCentric): Results of an Australian phase II clinical trial.** *Presenting Author: Mustafa Khasraw, Andrew Love Cancer Centre, Geelong, Australia*

**Background:** Building on our preclinical data, we proposed that combination of low dose TMZ and PCB may overcome TMZ chemoresistance in MGMT unmethylated GBM. We proposed adding Cilengitide, a selective $\alpha v\beta 3$ and $\alpha v\beta 5$ integrin inhibitor, to PCB, TMZ and RT. **Methods:** Newly diagnosed GBM pts with unmethylated MGMT received cilengitide 2000 mg twice weekly over 18 months. On week 2 of cilengitide, RT (60 Gy, 2 Gy per fraction) was started for 6 weeks with daily TMZ (60 mg/m2) and PCB (50 mg if BSA < 1.7; 100 mg if BSA ≥ 1.7) followed by 6 cycles of adjuvant TMZ (50mg/m2 in first cycle, 60 mg/m2in subsequent cycles) and PCB (50 mg if BSA < 1.7; 100 mg if BSA ≥ 1.7) given D1 to 20 every 28 days. The primary endpoint was 12m Overall Survival (12 mOS). The probability of accepting insufficiently active treatment was set to 10% and the probability of rejecting an active treatment was set to 20%. If 16 of 29 pts (55%) or less were alive at one year, the treatment was to be declared inactive. Secondary endpoints include 6-month progression-free survival (6mPFS) and toxicity. **Results:** MGMT was tested in 60 pts to enrol 29 evaluable GBM pts with unmethylated MGMT status (median age: 55 y, range 24-74 y; 11 women and 18 men). ECOG status was 0, 1 and 2 in 16, 11 and 2 pts, respectively. The last pt was enrolled in June 2013 and at time of submission of this abstract 18 of 29 included pts (62%) were alive, 11 (38%) who have been followed-up for a year or more and 7 (24%) less than a year. Current median OS and PFS are 58 (95% CI 44-72) and 30 (95% CI 20-39) weeks respectively. Grade (G) 3 and 4 toxicities included thromboembolism (1 G 4 and 2 G3), seizures (1 G4 and 2 G3), neutropenia without fever (5 G3) and asymptomatic elevated transaminases (1 G4 and 6 G3). **Conclusions:** The safety profile of the combination was confirmed. As of Jan 2014, the 12mOS has not yet been reached. Of the 7 pts still alive, 5 will need to survive 12 months or more after enrolment for the primary endpoint of 12 mOS to be met. Updated endpoints, including 12 mOS, will be available and presented at the ASCO annual meeting. Clinical trial information: NCT01124240.

**2051^ General Poster Session (Board #16), Sat, 1:15 PM-5:00 PM**

**Patterns of tumor progression in a phase 3 study of bevacizumab (Bv) plus radiotherapy (RT) plus temozolomide (T) for newly diagnosed glioblastoma (GB).** *Presenting Author: Wolfgang Wick, Neurooncology, University of Heidelberg Medical Center, Heidelberg, Germany*

**Background:** In the AVAglio study, Bv+RT/T prolonged PFS (co-primary endpoint) in pts with newly diagnosed GB v placebo (P)+RT/T. It has been suggested that antiangiogenic therapy may promote infiltrative tumors at PD, so patterns of tumor progression were prospectively assessed in AVAglio (exploratory endpoint). **Methods:** Randomizedpts (n=921) received: RT/T+Bv or P, 6 wks; 28-day break; maintenance T+Bv or P (x6); Bv or P until PD/unacceptable toxicity. PD was investigator (INV) assessed (adapted Macdonald criteria). Lesion patterns were retrospectively assessed by an independent review facility for each disease assessment (baseline [BL]/during treatment/at INV-assessed PD). Diffuse/infiltrative patterns were defined as extended hypersignal on T2/fluid-attenuated inversion recovery (FLAIR) sequences, and are reported in pts with pattern derived at BL and INV-assessed PD. **Results:** Most pts had similar tumor invasiveness at BL and PD (Table). Among pts with non-diffuse disease at BL (n=100 and 138), numerically more Bv- v P-treated pts changed to diffuse disease at PD; median OS for these pts was similar (17.4 v 15.0 mo for Bv+RT/T v P+RT/T, respectively; HR 0.85, 95% CI 0.51–1.42, p=0.5355), and comparable with the OS of the ITT population. In all pts who had BL non-diffuse tumors, median OS was 20.1 v 18.4 months (Bv+RT/T v P+RT/T, respectively; HR 0.76, 95% CI 0.59–0.98, p=0.0303). In all pts with BL diffuse tumors, median OS was 15.6 v 16.2 months (Bv+RT/T v P+RT/T, respectively; HR 0.99, 95% CI 0.82–1.19, p=0.8882). **Conclusions:** In this exploratory analysis, a change from BL non-diffuse disease to diffuse disease at PD did not affect OS; BL pattern of disease did, suggesting that tumor infiltration at diagnosis is an important prognostic factor. Also, in the subset of pts with newly diagnosed non-diffuse GB, there was an OS benefit from adding Bv to standard of care. Clinical trial information: NCT00943826.

| Tumor pattern, $n_{PD}/n_{BL}$ | | Bv+RT/T | P+RT/T |
|---|---|---|---|
| **BL** | **PD** | n=299 | n=333 |
| **Pts with no changes** | | | |
| **Nondiffuse** | Nondiffuse | 64/100 (64.0%) | 104/138 (75.4%) |
| **Diffuse** | Diffuse | 197/199 (99.0%) | 194/195 (99.5%) |
| **Pts with changes from BL** | | | |
| **Nondiffuse** | Diffuse | 36/100 (36.0%) | 34/138 (24.6%) |
| **Diffuse** | Nondiffuse | 2/199 (1.0%) | 1/195 (0.5%) |

**2052 General Poster Session (Board #17), Sat, 1:15 PM-5:00 PM**

**A randomized clinical trial for the treatment of glioblastoma multiforme with the individualized dendritic cell-based cancer immunotherapy AV0113.** *Presenting Author: Thomas Felzmann, Activartis Biotech GmbH, Vienna, Austria*

**Background:** We recruited 78 patients aged 18-70 years suffering from newly diagnosed glioblastoma multiforme (GBM) into a randomized clinical trial designed for demonstrating the efficacy of the individualized dendritic cell-based cancer immunotherapy concept AV0113 (GBM-Vax, EudraCT 2009-015979-27). DC are charged with autologous tumor antigens and contacted with lipopolysaccharide (LPS) in the presence of Interferon (IFN) -$\gamma$ enabling IL-12 secretion for 1 day thus priming cytolytic anti-tumor immune responses. Exposure to LPS/IFN-$\gamma$ is limited to 6 hours in order to permit DC/T-lymphocyte interaction in the presence of IL-12. **Methods:** Patients underwent first line GBM therapy (surgery, radiotherapy, chemotherapy) according to the standard of care; patients randomized into the treatment group received AV0113 as add-on therapy. Primary and secondary objectives were PFS and OS. After progression, patients were treated with Bevacizumab, which was not part of the protocol. The study still collects follow up information. **Results:** AV0113 DC-CIT was well tolerated. Reactions at the injection site were mild and included redness and swelling; some patients developed fever. There are some imbalances of severe adverse events between control and treatment groups, which, however, didn't appear to be linked to CIT. No signs of autoimmunity were observed. A trend analysis of one-year survival revealed that 45% of control group patients died during the first year; in the AV0113 treatment group only 16% died during the first year of their disease. A similar trend is observed in overall survival. DC-CIT didn't improve progression free survival, but increased the number of surviving patients. Accompanying immunological assays demonstrated a correlation of longer survival with signs of polarization of the immune system towards cytotoxicity. **Conclusions:** Randomization for the GBM-Vax study was completed in May 2013; hence we expect a complete data set for the one-year survival in May 2014 and will present this outcome. If the current trend is confirmed, we expect a first demonstration of efficacy for IL-12 secreting DC in the treatment of GBM. Clinical trial information: 2009-015979-27.

**2053 General Poster Session (Board #18), Sat, 1:15 PM-5:00 PM**

**Phase II trial of triple tyrosine kinase receptor inhibitor nintedanib in recurrent high-grade gliomas: Final results.** *Presenting Author: Andrew David Norden, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Bevacizumab is FDA-approved for patients with recurrent GBM. However, the median duration of response is only 4 months. Potential mechanisms of resistance include upregulated FGF signaling and increased PDGF-mediated pericyte coverage. Nintedanibis an oral, small-molecule tyrosine kinase inhibitor of PDGFR $\alpha/\beta$, FGFR 1-3, and VEGFR 1-3 that may overcome resistance to prior anti-VEGF therapy. **Methods:** This was an open-label, phase II trial in adults with first or second recurrence of GBM, stratified by prior bevacizumab. The primary endpoint was PFS6 in the bevacizumab-naive arm (arm A) and PFS3 in the post-bevacizumab arm (arm B). A Simon two-stage design was employed. Up to 10 anaplastic glioma (AG) patients were accrued to each arm in exploratory cohorts. **Results:** Twenty-two patients enrolled in Arm A and 14 in Arm B. Accrual to both arms was stopped after the first stage due to futility. Arm A included 12 GBMs (55%), 13 patients with one prior regimen (59%), and median age 54 years (range 28-75). Arm B included 10 GBMs (71%), one patient with one prior regimen (7%), and median age 52 years (range 32-70). Median KPS overall was 90 (range 60-100). There were no responses. In Arm A (GBM only), PFS6 was 0%, median PFS 28 days (95% CI: 27-83), and median OS 6.9 months (3.7-8.1). In Arm B (GBM only), PFS3 was 0%, median PFS 28 days (22-28), and median OS 2.6 months (1.0-6.9). In Arm A (AG only), PFS6 was 0% and median PFS 28 days (27-68). In Arm B (AG only), PFS3 was 0% and median PFS 28 days (7-56). Rare grade $>3$ toxicities included transaminase elevation, hypophosphatemia, hypertension, intracranial hemorrhage, and abdominal pain. Two participants died during therapy, one from thromboembolism and one from colon perforation. **Conclusions:** Nintedanib is not active against recurrent high-grade glioma, regardless of prior bevacizumab therapy. Clinical trial information: NCT01380782.

**2054 General Poster Session (Board #19), Sat, 1:15 PM-5:00 PM**

**REBECA: A phase I study of bevacizumab (BEV) and whole-brain radiation therapy (WBRT) for treatment of solid tumors brain metastases (BM), EudraCT: 2009-015977-11.** *Presenting Author: Christelle Levy, Centre François Baclesse, Caen, France*

**Background:** BM, the most frequent malignancy in the central nervous system, remains of poor prognosis. Standard treatment is WBRT. Neoangiogenesis plays an important role in BM growth. Angiogenesis inhibitors, particularly agents targeting the VEGF/VEGFR pathway like BEV, could be optimal partners of radiotherapy (RT) for treating BM. Adding BEV to standard RT-based treatment of newly diagnosed glioblastoma improves progression free survival. REBECA aims at assessing the recommended phase II dose (RP2D) of BEV plus WBRT for BM and delivering preliminary efficacy data. **Methods:** A multicentric phase I trial assessed BEV combined to conventional WBRT for unresectable BM of solid tumors with a 3+3 dose-escalation design. BEV was administered every 2 weeks (wks) for a total of 3 injections at day 1, 15 and 29 (5, 10 or 15 mg/kg for dose levels (DL) 0, 1 and 2) with WBRT starting at day 15, for a total dose of 30 Gy in 15 fractions/3 wks. DL3 consisted in BEV 15 mg/kg with WBRT delivered from day 15 in 30 Gy/10 fractions/2 wks. Safety was evaluated using NCI-CTCAE v3. BM response was assessed 6 wks and 3 months after the end of treatment by MRI using RECIST 1.1 criteria. **Results:** Among 21 patients (pts) enrolled (including 14 breast cancers), 19 were treated: 3 in DL0, 4 in DL1, 3 in DL2 and 9 in DL3, including 3, 3, 3 and 7 pts assessable for dose limiting toxicity (DLT), respectively. No DLT occurred: DL3 could be defined as RP2D. Among the 19 pts, treatment-related toxicity (excluding alopecia) included a grade(gr) 2 asthenia at DL1 and 7 gr2 (2 HTA, 1 asthenia, 1 digestive disorders, 1 mouth dryness, 1 lymphopenia and 1 liver injuries) occurring in 4 out of 9 pts at DL3. Gr1 events were noted for 7 pts in all DLs: HTA, headache, asthenia, nausea/vomiting, pain and appetite loss. No BM progression was observed during treatment but 2 pts at DL1 and 1 pt at DL3 died of disease progression during the 3 months post-treatment period. *Per Protocol* efficacy analysis concerned 16 pts: 8 had a BM partial response (1/3 at DL0, 1/3 at DL1, 2/3 at DL2, 4/7 at DL3). **Conclusions:** In absence of DLT, BEV+WBRT appears safe for the treatment of BM. DL3 seems optimal for further efficacy evaluation in phase II trials. Clinical trial information: NCT01332929.

**2055 General Poster Session (Board #20), Sat, 1:15 PM-5:00 PM**

**GEINOFOTE: Safety and activity analysis of the use of fotemustine (FT) in different schedules in progressive high-grade glioma (HGG) in Spain.** *Presenting Author: Pedro Pérez-Segura, Medical Oncology Department, Hospital Universitario Clínico San Carlos, Madrid, Spain*

**Background:** Previous studies showed that FT may be useful as treatment in recurrent high-grade glioma (HGG). The present study evaluate the activity and toxicity of FT in recurrent malignant glioma patients in the clinical setting in Spain. **Methods:** Patients (age $>18$ years) with HGG that was progressive (first or second recurrence) after prior standard radiotherapy plus TMZ chemotherapy were eligible for the study. Patients were scheduled to receive FT in different schedules (Addeo vs others). Tumor response was assessed by MRI every 8-12 weeks. The primary end point was safety; secondary points included progression free survival (PFS), overall survival (OS). We analyze the differences between Addeo schedule (A) vs others (O) and 1º recurrence (1ºR) vs 2º recurrence (2ºR) in terms of safety and activity. **Results:** 114 patients were assessed (84 glioblastoma and 30 grade III glioma); all of them began FT previously Nov 31, 2012. There were 60 males, and the median age was 52.5 years (ranged from 19 to 73). The median KPS was 70 (30-100). Addeo schedule was used in 85 pts (74.6%). FT in first recurrence was used in 51 pts (44.7%) and 58 pts (50.9%) in second recurrence. The median PFS was (A 1ºR / O1ºR/ A 2ºR / O 2ºR) 3.37/2.41/3.04/2.68 months, the median OS was (A 1ºR / O1ºR/ A 2º R / O 2ºR) 5.62/5.59/5.09/3.97 months. The most common toxicities include neutropenia and thrombocytopenia. There were no statistical differences in Grade III or IV toxicities in relation with the type of schedule (A vs O) nor the 1º or 2º R (20%-32.6%). The patients in 1ºR received more frequent A schedule than in 2ºR (86.3% vs 62.1%, p=0.004). No differences between A vs O in terms of clinical benefit, PS improve or less dexametasone use. Time to response: patients in A schedule spent less time to get the better response than patients with O schedules, whenever we use FT (no significant differences). **Conclusions:** FT has modest activity for recurrent high grade glioma with acceptable toxicity, regardeless the type of schedule. Probably, A get better response in less time than O schedules.

**2056 General Poster Session (Board #21), Sat, 1:15 PM-5:00 PM**

**Management of primary intraocular lymphoma (PIOL): Results from the prospective German PIOL registry (PIOL-R).** *Presenting Author: Kristoph Jahnke, Department of Hematology and Oncology, Charité Campus Benjamin Franklin, Berlin, Germany*

**Background:** The optimal management of primary intraocular lymphoma (PIOL) is yet to be defined. We report on clinical characteristics, treatment and outcome of newly diagnosed, immunocompetent PIOL patients enrolled in the prospective German PIOL registry (PIOL-R). **Methods:** Patient data in this prospective, non-interventional multicenter study were compiled by standardized questionnaires sent to Ophthalmology and Hematology/Oncology centers in Germany. **Results:** Twenty-seven patients (17 female, median age 67 years, median Karnofsky performance status 90%) were included between August 2008 and December 2013. Median time from onset of symptoms to PIOL diagnosis was 5 (range, 1-36) months. Diffuse large B-cell histology was found in all patients. First-line treatment included high-dose methotrexate (MTX)- or ifosfamide-based systemic chemotherapy with or without rituximab in 21 (including high-dose chemotherapy [HDCT] with autologous stem cell transplantation [ASCT] in 4), intraocular (i.o.) chemotherapy with MTX (n=1) and/or rituximab (n=10) in 11, ocular radiation in 2, and vitrectomy only in one patient(s). Two patients received prophylactic intrathecal treatment with MTX but none had whole-brain radiotherapy (RT). The PIOL remission rate was 100% with complete remission in 19/23 evaluable patients and partial remission in 4 patients. Median progression-free survival of patients without prior brain involvement (n=23) was 21 (95% CI, 1.2-39.9) months. Overall survival has not yet been reached. Relapses were located in the brain (n=9), eye (n=3), eye/brain (n=3) and eye/meninges (n=1) and were treated with systemic chemotherapy in 12 (including HDCT with ASCT in 3), systemic and i.o. chemotherapy in one, whole brain/spine RT in 2 and best supportive care in one patient(s). **Conclusions:** Although the awareness of PIOL and diagnostic possibilities have improved, time from symptom presentation to diagnosis seems to remain at previously reported levels. There appears to be a shift from local ocular treatments and RT to systemic therapy as compared to anecdotal data with promising response and survival rates. However, relapse rates remain high with the brain frequently being involved.

**2057 General Poster Session (Board #22), Sat, 1:15 PM-5:00 PM**

**Therapeutic implications of perivascular invasion in the context of high-density brain microvascular networks: A study on recursive pattern formation in malignant glioma.** *Presenting Author: Gregory Joseph Baker, University of Michigan, Ann Arbor, MI*

**Background**: Malignant glioma cells use distinct brain structures for tumor growth and invasion. However, the cellular mechanisms and biological consequences of malignant glioma growth patterning remain poorly understood. **Methods**: We utilized multiple experimental imaging modalities (i.e. confocal-, multi-photon-, epifluorescence-, and electron- microscopy) to examine the routes of intracranial malignant glioma invasion using implantable and genetically-induced glioma models; we also examined brain tissue specimens from patients affected by primary human glioblastoma and brain metastasis. The clinical implications of our findings are discussed. **Results**: Mouse, rat, and human experimental malignant glioma cells commonly utilized the dense brain microvascular network as a scaffold for tumor invasion. Perivascularly invading brain tumors became vascularized as they engulfed brain microvessels at the invasive margin over the entire course of tumor progression. Macroscopic tumor formation occurred as a consequence of recursive inter-vessel displacement of normal brain tissue by mitotic glioma cells localized within the perivascular space. Based on these observations, we implemented a computational model that recapitulates this pattern of brain tumor growth. Notably, a parameter for neoangiogenesis was not required to obtain continued *in-silico* perivascular growth and recursive space filling. Treatment of perivascularly invading brain tumors with anti-VEGF (bevacizumab) or anti-VEGFR-2 antibodies (DC101) did not prolong animal survival, yet potentiated long distance glioma cell invasion, especially in a model of human glioma stem cells. **Conclusions**: Perivascular invasion, high brain microvascular network density, and recursive inter-vascular space filling is a common pattern of malignant brain tumor growth that supports tumor progression independently of VEGF-A signaling.

**2058 General Poster Session (Board #23), Sat, 1:15 PM-5:00 PM**

**Histogram analysis of apparent diffusion coefficient within enhancing and nonenhancing tumor volumes in recurrent glioblastoma patients treated with bevacizumab.** *Presenting Author: Rifaquat Rahman, Harvard Medical School, Boston, MA*

**Background:** While patients with recurrent glioblastoma receiving anti-angiogenic therapy demonstrate significant response rates, the benefit on patient survival is less clear. We assessed whether histogram analysis of diffusion weighted MRI can stratify for progression-free and overall survival. **Methods:** Baseline and 3-6 week post-treatment MRI exams of 91 patients with recurrent glioblastoma treated with bevacizumab were retrospectively evaluated. Histograms of apparent diffusion coefficient (ADC) within the volume of contrast enhancing and nonenhancing T2/FLAIR lesions were analyzed using curve-fit analysis. Overall survival (OS) and progression-free survival (PFS) were assessed using ADC parameters in a Cox proportional hazards model adjusted for clinical variables. **Results:** Baseline $ADC_L/ADC_M$ within nonenhancing T2/FLAIR volume ($>$ or $\leq 0.64$) can stratify OS (HR=2.24, p=0.002) and PFS (HR=1.90, p=0.005). $\%ADC_H$ within enhancing T1+C volume ($>$ or $\leq 25\%$) can also stratify OS (HR=0.59, p=0.034) and PFS (HR=0.56, p=0.01). Stratification of patient survival can be improved by merging these two ADC parameters into a single combined ADC factor (HR= 0.17, p<0.0001). The median OS ratio of patient groups stratified by this combined factor was 2.03, larger than median OS ratio when stratifying by either $\%ADC_H$ within T1+C volume alone (1.3) or $ADC_L/ADC_M$within T2/FLAIR alone (1.86). **Conclusions:** ADC histogram analysis within both enhancing and nonenhancing components of tumor can be used to stratify for PFS and OS in patients with recurrent glioblastoma.

**2060 General Poster Session (Board #25), Sat, 1:15 PM-5:00 PM**

**Expression profile of angiogenic factors in paired initial and recurrent glioblastoma.** *Presenting Author: Emeline Tabouret, Aix-Marseille University, AP-HM, Service de Neuro-Oncologie, CHU Timone, Marseille, France*

**Background:** Angiogenesis is one of the key features of Glioblastoma (GB). Our objective was to identify the changes in the expression of angiogenic factors in GB after radio-chemotherapy. **Methods:** Analysis of all patients with available frozen tumor material from initial and recurrent surgery for GB treated with chemo-radiotherapy (CTRT) in first line setting in our institution between 2003 and 2009. Molecular screening was realized using two types of $RT^2$Profiler PCR arrays (Qiagen). The RNA expression profile of selected genes was validated using quantitative RT PCR. Protein expression was analyzed by immunohistochemistry (IHC). Explants of newly GB were treated with temozolomide, radiotherapy and anti-CXCR4 (AMD3100). **Results**: Twenty nine patients were included with median age of 57.1 years (37.2-74.1). The $RT^2$Profiler PCR arrays results allowed a selection of seven genes: VEGFA, VEGFR2, VEGFR1, Adrenomedullin, SDF1, CXCR4, and HIF1$\alpha$. The steady state levels of CXCR4 RNA at recurrence was significantly increased (p=0.029) while HIF1$\alpha$ RNA was significantly decreased (p=0.009). A trend for a decrease of VEGFR2 RNA (p=0.081) and an increase of SDF1 RNA (p=0.107) was observed. Changes of SDF1 RNA tended to be correlated to changes of CXCR4 RNA (p=0.077) and inversely correlated to changes of HIF1 $\alpha$ RNA (p=0.064). By IHC, VEGFR2 staining was significantly decreased at recurrence (p=0.004) while SDF1 expression tended to increased (p=.096). Medians initial and at recurrence overall survival (OSI and OSR) of this selected population were 25.5 (95% confidence interval (CI) 17-34) and 11.4 (95%CI 9-13.9) months respectively. By multivariate analysis, VEGFR2 RNA initial and at recurrence levels were significantly correlated to OSI (p=0.019, Hazard ratio (HR) =3.650) and OSR (p=0.024, HR=2.536) while HIF1 $\alpha$ RNA level at baseline was correlated to OSI (p=0.012, HR=0.300). In newly GB explants, a higher anti-tumoral effect was observed with the combination of AMD3100 and CTRT versus CTRT alone. **Conclusions**: Acquired resistance of GB to chemo-radiation could be associated with a switch of angiogenic pattern from VEGFR2-HIF1$\alpha$ to SDF1-CXCR4 pathway, leading to new perspectives in angiogenic modulation and GB treatment.

**2061 General Poster Session (Board #26), Sat, 1:15 PM-5:00 PM**

**Targetable signaling pathway mutations and progression of *IDH*-mutant glioma.** *Presenting Author: Hiroaki Wakimoto, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA*

**Background:** Isocitrate dehydrogenase (*IDH*) gene mutations occur in low-grade and high-grade gliomas. We sought to identify the genetic basis of malignant phenotype heterogeneity in *IDH*-mutant gliomas. **Methods:** We prospectively implanted tumor specimens from 20 consecutive *IDH1*-mutant glioma resections into mouse brains and genotyped all resection specimens using a CLIA-certified molecular panel. Gliomas with cancer driver mutations were tested for sensitivity to targeted inhibitors *in vitro*. Associations between genomic alterations and outcomes were analyzed in patients. **Results:** By 10 months, 8 of 20 *IDH1*-mutant gliomas developed intracerebral xenografts. All xenografts maintained mutant *IDH1* and high levels of 2-hydroxyglutarate on serial transplantation. All xenograft-producing gliomas harbored "lineage-defining" mutations in *CIC* (oligodendroglioma) or *TP53* (astrocytoma), and 6 of 8 additionally had activating mutations in *PIK3CA* or amplification of *PDGFRA*, *MET,* or *N-MYC*. Only *IDH1* and *CIC*/*TP53* mutations were detected in non-xenograft-forming gliomas ($P = 0.0007$). Targeted inhibition of the additional alterations decreased proliferation *in vitro*. Moreover, we detected alterations in known cancer driver genes in 13.4% of *IDH*-mutant glioma patients, including *PIK3CA*, *KRAS*, *AKT* or *PTEN* mutation or *PDGFRA*, *MET* or *N-MYC* amplification. *IDH*/*CIC* mutant tumors were associated with *PIK3CA*/*KRAS* mutations while *IDH*/*TP53* tumors correlated with *PDGFRA*/*MET* amplification. Presence of driver alterations at progression was associated with shorter subsequent progression-free survival (median 9.0 vs. 36.1 months, $P=0.0011$). **Conclusions:** A subset of *IDH*-mutant gliomas with mutations in driver oncogenes has a more malignant phenotype in patients. Identification of these alterations may provide an opportunity for use of targeted therapies in these patients.

**2062 General Poster Session (Board #27), Sat, 1:15 PM-5:00 PM**

**QOL and neurocognitive functions in patients with GBM.** *Presenting Author: Christine Marosi, Medical University Vienna, Vienna, Austria*

**Background:** The importance of QOL and neurocognitive functions in patients with GBM is meanwhile beyond controversy. We followed newly diagnosed patients with GBM during first and second line therapy by evaluating their QOL and cognitive functions **Methods:** Consecutive newly diagnosed patients with GBM were included in this study. To assess QOL we used the EORTC QLQ C30 and BN20 questionnaire and the computer based NeuroCog FX for neurocognitive assessments. The first assessment was done at the beginning of radiotherapy and was followed by further 5 evaluations every three months **Results:** 42 patients underwent radiation therapy with concomitant and adjuvant temozolomide. Non enzyme enhancing antiepileptic drugs (NEIAED) was prescribed for the majority of the patients (71%). Median progression free survival was 9.6 months (2.5-30.9 months). Second line therapies applied were bevacizumab in 11 patients (26%), dose-dense temozolomide in 10 patients (24%) and imatinib in 8 patients. (19%). Neither QOL nor cognitive scales differed considering prescription of antiepileptic drugs and type of second line therapy, whereas limited data was available after progression of disease (19/42 patients) **Conclusions:** QOL and cognition of patients with GBM under NEIAEDs did not differ from patients without NEIAED. Similarly, no difference was found between patients receiving different drugs in second line therapy, however, just a minority of the patients is able to do QOL and cognitive assessments after progression of disease. Clinical trial information: EK 976/2009.

**2063 General Poster Session (Board #28), Sat, 1:15 PM-5:00 PM**

**Delayed contrast MRI: A new paradigm in neuro-oncology.** *Presenting Author: Yael Mardor, Sheba Medical Center, Ramat Gan, Israel*

**Background:** Conventional MRI is unable to differentiate tumor progression from treatment-induced effects (pseudoprogression/radiation-necrosis) in brain tumor patients, thus significantly impacting patients' management with no current solution. **Methods:** We have applied a novel MRI-based methodology for high resolution depiction of tumor/non-tumor tissues. This unique model-independent technique is based on robust MRI sequences acquired with a delay, enabling complete separation between tumor (contrast clearance at the delayed time point) and treatment effects (contrast accumulation) with no overlap. 498 treatment response assessment maps were calculated for 149 patients with primary/metastatic brain tumors and 9 with AVM recruited/followed on study. **Results:** The maps were validated by comparing pre-surgical maps of 51 patients with primary/metastatic brain tumors who underwent surgery with histology, resulting in 100% sensitivity and 94% specificity to active tumor. This validation confirms that contrast clearance in the maps represent morphologically active tumor while contrast accumulation represents non-tumor tissues. Following initial validation, the maps were used for making 231 clinical decisions. In 67 cases the decision was to continue follow-up (no treatment change) and in 164 cases to change treatment (including surgery, chemoradiation, radiation treatments, switch to Avastin, etc). Our data demonstrates the application for management of patients with various types of tumors after various treatments, for depiction of residual tumor post surgery, detection of tumor within hemorrhages and differentiating malignant transformation from treatment effects. **Conclusions:** Our high resolution, easy to interpret, model-independent maps provide complete/clear differentiation between tumor/non-tumor tissues in patients with brain tumors. The increasing rate in which the maps are being used for clinical decisions making in Israel reflects their added value as an efficient/friendly tool for decision making in neuro-oncology. Excellent agreement between pre-surgical maps and histology suggests that the maps may be further applied for planning high precision procedures such as biopsies, resections, SRS and iMRT.

**2064 General Poster Session (Board #29), Sat, 1:15 PM-5:00 PM**

**Surgery for central nervous system tumors in the Brazilian National Health Care System: A review of 57,361 cases in DATASUS.** *Presenting Author: Julio Leonardo Barbosa Pereira, Instituto de Ensino e Pesquisa da Santa Casa de Belo Horizonte, Belo Horizonte, Brazil*

**Background:** In low- and middle-income countries, resource limitations make the management of central nervous system (CNS) tumors challenging, particularly in Brazil, a country with major socioeconomic and health access disparities. We aimed to evaluate cancer-related neurosurgical procedures in the public health care system. **Methods:** Based on Brazilian's public health system database (DATASUS), we collected data for neurosurgical procedures related to CNS tumors performed between January 2008 and November 2013. Information about number of procedures, costs, length of stay and number of inpatient deaths were analyzed for each State and then correlated to State specific population, gross domestic product (GDP) per capita and number of procedures. **Results:** 57,361 procedures were performed, the majority (45.9%) in the Southeast region. Total cost was $108,363,829.00; average cost per admission was $1,889.00. Average cost in each State, for a fixed number of procedures and population, tended to decrease as GDP per capita increased (OR -0.14; 95% CI -0.4 to -0.1; $p=0.001$). The mean length of hospital stay was 14.4 days, longer for patients treated at the North of the country (19.9 days). On multivariate analysis, number of procedures, GDP per capita, and population had an independent association with days of hospitalization. A total of 4,079 patients died, translating into an inpatient mortality rate of 7.11%, higher than expected based on US and European data. Northern States had the highest rates (12.76% for the region and 17.6% for the State with the highest mortality). Mortality rates decreased as number of procedures ($p<0.001$), GDP per capita ($p<0.001$) or State population increased ($p<0.001$). On multivariate analysis, only number of procedures (OR 0.93; 95% CI 0.91 to 0.96; $p<0.001$) and State population (OR 1.25; 95% CI 1.13 to 1.38; $p<0.001$) had an independent association with mortality. **Conclusions:** This is the first study to evaluate disparities in CNS tumor surgery in a middle income country, confirming that regional disparities exist and that clinical and economic outcomes correlate with income level, number of procedures and state population.

**2065 General Poster Session (Board #30), Sat, 1:15 PM-5:00 PM**

**Hypofractionated (HRT) versus standard (SRT) radiotherapy with or without temozolomide (T) for elderly patients with glioblastoma (GBM).** *Presenting Author: Shyam Kumar Tanguturi, Harvard Radiation Oncology Program, Boston, MA*

**Background**: No randomized trials among elderly GBM patients using HRT have compared efficacy to the Stupp regimen of SRT+T, and many elderly patients in the United States receive SRT+T. **Methods**: We evaluated 88 consecutive patients ≥ 65 years old with GBM diagnosed from 1994-2010 who received HRT or SRT with or without concurrent T. Overall survival (OS) was calculated by the Kaplan-Meier method. Prognostic factors were evaluated using the Cox proportional hazards model and Fisher exact test. HRT consisted of 40 Gy/15 fractions, and SRT consisted of 59.4-60 Gy/30-33 fractions. **Results**: Patients received SRT+T (n = 26), SRT (n = 35), HRT+T (n = 21), or HRT (n = 6). Median age was 70 among SRT±T patients and 80 among HRT±T patients ($P < 0.001$), KPS was lower among HRT±T patients ($P < 0.001$), and SRT-alone patients were more likely to be treated prior to the year 2000 ($P < 0.001$); there were no significant differences between groups with regard to gender, tumor size or multifocality, extent of resection, or MGMT methylation status. With a median follow up of 9.7 mo, median OS was 10.1 mo (SRT+T), 9.5 mo (SRT), 10.8 mo (HRT+T), and 3.0 mo (HRT). On multivariate analysis, compared to SRT+T, mortality was significantly lower for HRT+T (AHR = 0.39; 95% CI, 0.16-0.91; $P = 0.030$) and higher for HRT (AHR = 3.94; 95% CI, 1.16-13.42; $P = 0.028$). Increasing age (AHR = 1.08; 95% CI, 1.01-1.15; $P = 0.018$), lower KPS (AHR = 1.03; 95% CI, 1.01-1.04, $P = 0.002$), and multifocal tumors (AHR = 3.18; 95% CI, 1.57-6.46; $P = 0.001$) were also associated with higher mortality. **Conclusions**: Among elderly GBM patients, HRT+T was associated with improved survival compared to SRT+T, despite older age and lower KPS at baseline. These data suggest that with the addition of T, the number of radiotherapy treatments may be reduced by half with no decrement in survival, and should be explored in a randomized setting.

**2066 General Poster Session (Board #31), Sat, 1:15 PM-5:00 PM**

**A phase 1 study of repeat radiation, minocycline, and bevacizumab in patients with recurrent glioma (RAMBO).** *Presenting Author: Adam Louis Cohen, Huntsman Cancer Institute, Salt Lake City, UT*

**Background:** There are no proven therapies for glioblastoma after progression on bevacizumab. Mesenchymal shift mediated by microglia-mediated NF-kappaB activation is one mechanism of treatment resistance in recurrent glioblastoma. Minocycline inhibits NF-kappaB activation and can restore radiation sensitivity to glioblastoma in vitro and in vivo. **Methods:** RAMBO is a phase 1 study of reirradiation, bevacizumab, and minocycline in people with glioblastoma that has progressed on bevacizumab who are at least one year away from prior radiation. The minocycline is dose escalated in a 3+3 design with planned cohorts of 100mg PO BID (cohort 1), 200mg (cohort 2), and 400mg PO BID (cohort 3). **Results:** Cohorts 1 and 2 have been completed. Completion of cohort 3 is expected by the meeting. No dose limiting toxicities have been encountered. Two people dropped out because of clinical progression and decision to go to hospice, and one person dropped out after 1 week due to unwillingness to take antiemetics for grade 1 nausea. No grade 3 toxicities unrelated to tumor progression have been seen other than one case of grade 3 asymptomatic hypertension attributed to bevacizumab and one case of grade 3 hypokalemia. Grade 2 toxicities have included 3 cases of fatigue, one case of anemia, one case of hiccups, three cases of hypertension, one case of intracranial hemorrhage, one case of nausea, one case of thrush, and one case of vertigo. Of these, only the nausea, fatigue, and thrush were thought possibly related to the minocycline. **Conclusions:** Minocycline can be safely combined with radiation and bevaciuzmab in glioblastoma patients who have progressed on bevacizumab. Clinical trial information: NCT01580969.

**2067 General Poster Session (Board #32), Sat, 1:15 PM-5:00 PM**

**Prognostic value of pretreatment MRI in breast cancer related leptomeningeal metastases.** *Presenting Author: Emilie Le Rhun, Centre Oscar Lambret, Lille, France*

**Background:** The National Comprehensive Cancer Network (NCCN) guidelines considers radiographic bulky disease as assesed by MRI as a negative prognostic factor in leptomeningeal metastases (LM). Our aim was to determine the prognostic value of pre-treatment MRI in patients with breast cancer (BC) related LM. **Methods:** We retrospectively evaluated pretreatment MRI in a cohort of 60 women with BC and LM to determine the correlation between CNS MRI abnormalities and survival. All images were reviewed by a neuroradiologist and a neuro-oncologist. Statistical analyses were performed using SAS software V9.3. **Results:** At LM diagnosis, patient median age was 56 (range, 35-81) and ECOG performance status was 0-2 in 64.5%. Breast cancers were invasive ductal carcinoma in 70.5%. Estrogen receptor and progesterone receptor were present in 71.5% and 56.5% respectively. 25% of tumors were HER2 positive and 16.5% were triple negative. Malignant cells were observed in the CSF in 64%. Brain MRI showed abnormalities consistent with LM in 73% including ; hydrocephalus (10% of all patients), focal (29%) or a diffuse (35.5%) linear leptomeningeal contrast enhancement (CE), subependymal CE (27%), sulci (35.5%), folia (46%) and cranial nerve (30.5%) CE and intracranial nodules (12.5%). Spine MRI revealed the following : linear focal (8.5%) or diffuse (54%) CE (71%) and subarachnoid nodules (16.5%). The cauda equina showed enhancement in 71% of patients. 91.5% of patients received intra-CSF chemotherapy, 59.5% systemic therapy and 18% radiotherapy. All but one patient died. Survival was less than 2 months in 33.5% and greater than 6 months in 36%. Median progression free survival (PFS) was 2.5 months (range, 0.03-3.3). Median overall survival was 4 months (0.03 – 34.88). Patients with linear focal leptomeningeal CE had a significantly better PFS (p=0.02) however no other MRI characteristic was associated with survival. **Conclusions:** In this retrospective cohort of patients with BC and LM, linear focal leptomeningeal CE by pre-treatment MRI was the only significant radiographic abnormality that correlated with survival. These data will be confirmed in a larger cohort of patients.

**2068 General Poster Session (Board #33), Sat, 1:15 PM-5:00 PM**

**Venous thromboembolism in patients with glioblastoma multiforme.** *Presenting Author: Natasha Edwin, Cleveland Clinic Foundation, Cleveland, OH*

**Background:** Patients with glioblastoma (GBM) are at increased risk of venous thromboembolism (VTE) as well as intracranial bleeding and clinicians are reluctant to use anticoagulants. The natural history of VTE in GBM in the post-bevacizumab era is not well understood. We conducted a cohort study to evaluate the risk of recurrent VTE and bleeding **Methods:** We studied consecutive Cleveland Clinic patients with GBM presenting with objectively diagnosed deep vein thrombosis (DVT) or pulmonary embolism (PE) from 2008 to 2013 with at least 6-month follow-up. We collected information on patient demographics, VTE, treatment, recurrence and bleeding. **Results:** The study population comprised 450 patients of whom 129 (28.7%) developed 229 VTE events. Of these, 24 (10.4%) were PE and 205 (89.5%) were DVT. Sixty (46.5%) VTE occurred in the first 30 days post-operatively, 45 (34.9%) on chemotherapy and 70 (54.3%) in the outpatient setting. Inpatient thromboprophylaxis rates were low in eligible patients (N=10/59, 16.9%). Treatment of VTE included enoxaparin monotherapy (N=32, 24.8%), warfarin (N=11, 8.5%) or vena caval filters either alone (N=39, 30.2%) or in combination with anticoagulation (N=18, 13.9%)Recurrent VTE occurred in 24% (N=31)at a median of 39 days (range, 2-375 days). Forty percent occurred in the immediate postoperative period (N=13, 41.9%). There were 20(15.5%) episodes of major bleeding after index VTE; a majority were intracranial (N=15, 75%).Two(10%) bleeds occurred in the absence of anticoagulation, 10 (50%) on enoxaparin and 4(5%) on warfarin. **Conclusions:** GBM patients with VTE are at high risk for both recurrent VTE (24%) and major bleeding (15.5%), seemingly confirming clinicians' concerns regarding anticoagulation. However, bleeding is common both with and without anticoagulation. Both primary and recurrent VTE are common in the post-operative period and improved adherence to thromboprophylaxis in this setting could reduce the risk. A prediction tool to individualize risk of VTE and bleeding could optimize use of anticoagulation in prophylaxis and treatment.

**2069 General Poster Session (Board #34), Sat, 1:15 PM-5:00 PM**

**Outcomes in patients with unresected glioblastoma including assessment of treatment with bevacizumab as a component of initial therapy.** *Presenting Author: Stuart Burri, Levine Cancer Institute-Radiation Oncology, Charlotte, NC*

**Background:** Radiation therapy (RT) and concurrent temozolomide (CRT) is the accepted standard for newly diagnosed glioblastoma (GBM). Despite promising results in recurrent settings, addition of bevacizumab (BEV) to CRT did not improve survival in prospective trials where the majority of patients underwent surgery with gross total resection. The biologic mechanism of BEV, however, suggests increased efficacy in tumors with intact blood supply, such as unresected GBM (UGB). Given the dismal prognosis of UGB, we have incorporated use of BEV into the management of select patients with UGB. We performed a retrospective analysis of our UGB patient population to assess outcomes and evaluate effectiveness of BEV in addition to CRT. **Methods:** Retrospective review for all UGB patients (stereotactic biopsy only) treated 2005-2012 was performed. 67 patients were identified. Treatment was categorized by treatment intent : hospice referral (group 1)-24%, palliative RT (group 2)-7%, definitive CRT (group 3)-55%, and CRT+BEV (group 4)-12%. Median age was 65; median ECOG PS 2. **Results:** Median overall survival (OS) was 4.8 months. Survival was similar for PS 1 and 2 and inferior for PS 3-4. Patient's <65 OS was superior at 8.3 months vs. 3.7 months (p=.005) versus >65. OS for patients <75 was 6.0 versus 2.3 months (p=.002). Median OS for groups 1-4 were 1.0, 1.7, 7.9 and 15.9 months, respectively. In Cox multivariate analysis adjusted for age and PS CRT+BEV patients survival was superior to group 1 (p<.001) and group 2 (p=.002) with a trend compared to CRT (p=.108). 7 patients survived > 24 mos. 3 (43%) were in the CRT+BEV group (representing only 12% of all treated patients). 4.5% of the patients suffered hemorrhage at biopsy and expired in < 1 month. **Conclusions:** Patients treated with CRT+BEV had median OS > three times the group median and twice that of patients treated with CRT. The median survival of 15.9 months in UGB treated with CRT+BEV is numerically similar to patients treated with resection followed by CRT in other series. Adjusting for age and PS there remained a statistical trend to superior OS for CRT+BEV versus standard CRT. Further study regarding the benefit of BEV in patients with UGB is warranted.

**2070 General Poster Session (Board #35), Sat, 1:15 PM-5:00 PM**

**Intratumoral heterogeneity of 1p/19q codeletion in brain tumors.** *Presenting Author: Maria Martinez-Garcia, Medical Oncology, Hospital del Mar, Barcelona, Spain*

**Background:** Evaluation of 1p and 19q is a relevant diagnostic, prognostic and predictive test for oligodendroglial tumors. The aims of this study were to determine the reliability of core specimens to assess 1p/19q codeletion in brain tumors, as well as to provide additional data on its potential role in glioblastoma (GB). **Methods:** We evaluated 1p/19q codeletion by FISH using 1p/1q and 19p/19q probes (Vysis) in a tissue microarray (TMA) from brain tumor specimens, mostly GB. Four 1mm-diameter cores were punched from selected areas of each donor block. We used a cutoff value of 50%. In order to compare the percentage of deletion between the four cores the intraclass correlation coefficient (ICC) was calculated. In 23 cases Pearson correlation coefficient was used to compare results from TMA with those from tumor sections. Also, for each sample we extracted DNA for *MGMT* methylation (MSP-PCR) and *IDH1*mutation (Real time allele-specific PCR) analysis. Clinical outcome for GB patients was correlated with these biomarkers. **Results:** We selected 45 grade IV gliomas (42 GB and 3 gliosarcoma). Mean age was 59 years and 29 were men. Fifteen tumors were *MGMT* methylated (33%) and 7(16%) *IDH1* mutated. There were 38 patients (84%) with 1p deletion (at least one of the cores) and 17 (38%) with 1p/19q codeletion. In tumor sections 2/23 (8.6%) had 1p/19q codeletion. There was a low rate of correlation between cores of the same patient. The ICC for 1p and 19q were 0.324 and 0.743, respectively. We observed a high correlation between the mean percentage of deletion in cores and sections. The correlation between the mean of the cores and the sections for 1p was 0.819 and for 19q was 0.810. With a median follow-up of 11 months the OS was 10.5 months. 1p/19q codeletion had no impact on survival and neither did isolated loss of 1p or 19q or *MGMT* methylation. *IDH1*mutation was significantly correlated with survival (P= 0.046). **Conclusions:** Our data show substantial intratumoral heterogeneity of 1p/19q codeletion in grade IV glioma and establishes the need to test for this biomarker in whole sections or in several cores if only TMA is available. The outcome supports the lack of correlation between 1p/19q codeletion and OS in GB.

**2071 General Poster Session (Board #36), Sat, 1:15 PM-5:00 PM**

**Phase IB trial of carboxyamidotriazole orotate (CTO) and temozolomide for recurrent malignant glioma (MG): A novel mechanism for modulation of multiple oncogenic pathways.** *Presenting Author: Antonio Marcilio Padula Omuro, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** A possible mechanism of resistance to targeted therapeutics is the existence of redundant signaling pathways. CTO is an oral inhibitor of non-voltage-dependent calcium signaling resulting in simultaneous modulation of several receptor-mediated, calcium-dependent signal transduction pathways, including EGFR, MEK, RAS, HDAC, HSP90, WNT/$\beta$-catenin and VEGF. A phase I single-agent study in solid tumors found a safe toxicity profile and predictable pharmacokinetics at doses of 75-427 mg/m$^2$/day, with responses seen in refractory tumors with different mutations. CTO crosses the blood-brain barrier, and pre-clinical studies have shown single-agent activity in glioblastoma xenografts and robust synergism with temozolomide (TMZ), prompting this phase IB study. **Methods:** Patients with recurrent glioblastoma or MG were eligible regardless of number of recurrences and previous bevacizumab exposure. The primary objective was to establish the maximum tolerated dose (MTD) of daily oral CTO combined with TMZ 150 mg/m$^2$x5 every 28 days, using a standard 3+3 design. **Results:** The combination was well tolerated, with no dose-limiting toxicities observed at the 4 dose levels examined (N=15), ranging from 219mg to 481mg/m$^2$/day. The most frequent adverse events were fatigue, nausea, vomiting, and dizziness, all of which grades 1 or 2; no QTc prolongation was seen. PK data demonstrated therapeutically relevant metabolite (CAI) levels starting at 219mg/m$^2$doses, with no significant interactions with TMZ. Preliminary evidence of activity was observed: three radiographic responses among 11 evaluable patients; 7 patients continuing treatment beyond 2 cycles; stable disease as durable as 9+ cycles. Tissue correlates and analysis of DCE-perfusion MRI are ongoing. **Conclusions:** CTO at doses as high as 481mg/m$^2$/day is safe and well tolerated in combination with TMZ, with no MTD defined after examination of all pre-established dose-escalation levels; further escalation to increase CNS exposure may be warranted. The early signals of activity in this heavily pre-treated population are encouraging and deserve further investigation. Clinical trial information: NCT01107522.

**2072 General Poster Session (Board #37), Sat, 1:15 PM-5:00 PM**

**Phase II study of arsenic trioxide and temozolomide in combination with radiation therapy in patients with malignant gliomas.** *Presenting Author: Priya Kumthekar, Northwestern University Health System, Chicago, IL*

**Background:** Current standard treatment for GBM is radiation (RT) and temozolomide (TMZ). We published phase I data of the addition of arsenic trioxide (ATO) to RT and TMZ. We now present the phase II data. **Methods:** Patients with newly diagnosed malignant gliomas were eligible for treatment in this single arm phase II. Patients were treated with RT (60GY), TMZ (75 mg/m2 daily x 42 days) and ATO 0.20 mg/kg daily in week 1 then twice a week x 5 weeks. **Results:** Twenty-five patients (14 M and 11 W) were enrolled with a median age of 56 (28-73). Histology was GBM 18, AA 6 and AO 1. All patients completed RT/TMZ/ATO. Median number of post RT cycles of TMZ was 3 (0-12); 9 patients completed 6 or more cycles. Median PFS was 6 m for GBM and 15 m for AG and median OS was 15 m for GBM and NR for AA. Response was SD in 20, PR in 1 and PD in 4. **Conclusions:** Adding ATO to RT and TMZ is feasible and tolerable but does not appear to improve outcome compared to RTOG 0525 data where OS is 16.6 months in newly diagnosed GBM. Tissue MGMT status is being analyzed. Clinical trial information: NCT00275067.

**2073 General Poster Session (Board #38), Sat, 1:15 PM-5:00 PM**

**Application of a validated predictive model for venous thrombo-embolism in cancer to patients with glioblastoma.** *Presenting Author: Ajay P Abad, Wilmot Cancer Center, University of Rochester Medical Center, Rochester, NY*

**Background:** Venous thromboembolism (VTE) is a major cause of morbidity and mortality in patients with Glioblastoma (GBM). Despite a 7-28% incidence of VTE in GBM, there is no data to initiate thromboprophylaxis. A risk score developed by Khorana et al. for non-CNS malignancies incorporates histology, BMI, and pre-chemotherapy blood counts, reliably predicting those patients at highest risk of VTE. We sought to determine if this risk score could identify those GBM patients at highest risk and therefore, potential candidates for thromboprophylaxis. **Methods:** We performed an IRB-approved retrospective study of all GBM patients at the Wilmot Cancer Center from January 2005 to May 2011. Baseline blood counts and BMI were obtained and charts were reviewed to determine occurrence of VTE. We assigned 1 point each for PLT≥350,000/$\mu$l, Hgb<10 g/dl, WBC >11,000/$\mu$l, and BMI≥35 kg/m$^2$; all patients received 2 points for having a high-risk histology. We assessed whether patients with a risk score ≥3 had a higher occurrence of VTE compared to patients with a risk score of 2. **Results:** 167 GBM patients (median age=64) were identified and 20% developed VTE. VTE was characterized as DVT only in 15 patients, PE only in 13 patients, and concomitant DVT/PE in 6 patients. 46% (n=77) had a risk score of 2 (intermediate risk), and 64% (n=90) had a risk score ≥3 (high risk). 15.6% of patients with a score of 2 developed VTE compared to 18.9% with risk score ≥3 (p=0.575). **Conclusions:** VTE is common in GBM and our rate of 20% is consistent with previous reports. All GBM patients were intermediate or high risk, and the percentage of patients developing VTE (18.9%, score ≥3, 15.6%, score=2) far exceeds that reported in non-CNS cancers (6.7%, score ≥3, 2.0%, score=2). Although there was no statistical difference in this relatively small cohort of patients, our findings suggest that this risk model can discriminate higher risk patients. Future risk models specific to GBM may benefit from incorporating post-operative ambulation status, extent of resection and biomarkers such as tissue factor.

**2074 General Poster Session (Board #39), Sat, 1:15 PM-5:00 PM**

**Plasma levels and tumor tissue RNA of MMP2 and MMP9 exhibit similar distribution in newly diagnosed and recurrent glioblastoma (GB).** *Presenting Author: Emeline Tabouret, Aix-Marseille University, AP-HM, Service de Neuro-Oncologie, CHU Timone, Marseille, France*

**Background:** We have previously showed that a high MMP2, and to a lesser extend a low MMP9 plasma levels were associated to a high response rate, a prolonged PFS and OS in recurrent GB treated with bevacizumab (BEV), but not with cytotoxic agents, (Tabouret and col. Neuro-Oncol 2013). In order to further explore the optimal timing of bevacizumab administration, we analyzed potential differences of MMP2/MMP9 plasma levels and tumor RNA in patients with newly diagnosed and recurrent GB. **Methods:** Plasma was collected before radiotherapy in newly diagnosed GB patients (pts) (Pop ND) and in a distinct population of pts at the time of recurrence (Pop RD). MMP2 and MMP9 plasma levels were assessed using ELISA. In a third population with paired initial and recurrent GB tumors (Pop NDT and RDT respectively), MMP2 and MMP9 RNA were analyzed using quantitative RT PCR. Correlations were analyzed using the Mann Whitney U test, the Spearman corelation and the T-test. **Results:** MMP plasma levels were tested in 44 ND and 76 RD pts. Mean levels of ND and RD MMP2 levels were 196.4 pg/ml (± 9.6) and 218.2 pg/ml (± 9.6). Mean levels of ND and RD MMP9 levels were 365.4 pg/ml (± 50.7) and 302.0 pg/ml (± 34.9). No significant difference was observed between ND and RD plasma levels of MMP9 and MMP2. In ND pts, no correlation was found between MMP2 and MMP9 plasma levels, neither between these plasma markers and KPS or age. In NR pts, MMP2 and MMP9 plasma levels were inversely correlated (p<0.001). Paired MMP9 and MMP2 RNA were available in NDT and RDT for 29 pts. No difference was observed between NDT and RDT expressions of MMP9 and MMP2. At initial diagnosis, MMP9 and MMP2 were 95.7-fold and 15.9-fold over-expressed compared with normal brain. At recurrence, MMP9 and MMP2 were 80.6-fold and 25.9-fold over-expressed. MMP2 and MMP9 RNA were correlated in NDT (p=0.001) but not in RDT. **Conclusions:** In this retrospective study, the prebiomarkers of BEV activity, MMP2 and MMP9, did not show significant change between GB initial presentation and recurrence both for plasma levels and tumor RNA. These results may suggest that BEV could be similarly active for pts with newly diagnosed and recurrent GB. Adequate prospective studies are warranted.

**2075 General Poster Session (Board #40), Sat, 1:15 PM-5:00 PM**

**Impact of adverse effects of bevacizumab on survival outcomes of patients with recurrent glioblastoma.** *Presenting Author: Mohamed Ali Hamza, OhioHealth, Columbus, OH*

**Background:** Bevacizumab (bev) is widely used for treatment of patients with recurrent glioblastoma (GB). Adverse effects (AEs) to bev or bev-containing regimens can cause discontinuation of treatment. The effects of these adverse effects on survival outcomes are not well defined. **Methods:** In this retrospective chart review, we identified patients with recurrent GB, who were treated with BEV alone or BEV-containing regimens between 2006 and 2011, and who discontinued bev treatment either because of AEs (bleeding, stroke, hypertension, renal disease or low blood counts) or because of physician's decision. We excluded those who had disease progression before discontinuation. Data was analyzed to determine overall survival (OS) and progression free survival (PFS). **Results:** A total of 65 patients were identified, of whom 39 patients who discontinued bev because of AEs and 26 patients who discontinued bev because of physician's decision. There were no significant differences in age, performance status, extent of resection, number of lesions, time from diagnosis to first recurrence, time from diagnosis to start of bev, number of recurrences before bev start, and duration of bev treatment between the two groups. Patients who discontinued bev because of AEs progressed earlier after bev discontinuation (3.9 months vs 5.7 months, $P$= 0.02), had significantly lower PFS (10.4 months vs 14.2 months, $p$ = 0.01) and had significantly lower OS from bev start (13.9 months vs 32.5 months, $P$ = 0.009) and lower OS from diagnosis (20 months vs 49.3 months, $p$=0.007) when compared to patients who discontinued bev because of physician's decision. **Conclusions:** In patients with recurrent GB who were treated with bev, discontinuation of bev because of AEs is associated with earlier progression and shorter OS when compared with patients who discontinued bev because of physician's decision. These results indicate that AEs to bev or bev-containing regimens are associated with unfavorable glioma-related outcomes in patients with recurrent GB.

**2076 General Poster Session (Board #41), Sat, 1:15 PM-5:00 PM**

**Molecular profiling of low-grade gliomas (LGG) in Colombia (ONCOL-Group).** *Presenting Author: Andres F. Cardona, Clinical and Traslational Oncology Group, Fundacion Santa Fe de Bogota, Bogotá, Colombia*

**Background:** LGG are classified according to the WHO as being astrocytoma (DA), oligodendroglioma (OD) or mixed glioma (OA). TP53 mutation and 1p19q codeletion have been the main molecular abnormalities recorded to date. Although IDH1/2 mutations have been described in up to 85% of LGG, IDH negative gliomas do occur. It has recently been found that ATRX plays a significant role in glioma oncogenesis. **Methods:** We searched for P53 and Olig2 protein expression, MGMT methylation status (pMGMT), 1p19q codeletion and IDH/ATRX status in 63 Colombian LGG patients (pts). Overall survival (OS) rate was estimated and compared between groups and according to genotype. **Results:** Mean age was 40.1-yo (±12.3), 50% of the pts were male, mean lesion diameter was 41.7 mm (±17.2 mm) and histological distribution was 61.9%, 25.4% and 12.7% for AD, OD and OA, respectively. Surgical resection was total in 47.6%, subtotal in 31.7% and biopsy was performed in 20.6% of the cases. Alterations in IDH1/2 were found in 57.1%, pMGMT+ in 65.1%, overexpression of p53 and Olig2 in 30.2% and 44.4%, and 1p19q codeletion in 34.9%. The presence of alterations in ATRX was analysed in 25 patients, being positive in 16% (all IDH1+/1p19q-). Median follow-up was 15.8 months (95%CI 7.6-42.0), OS was 39.2 months (95%CI 2.5-274) and the variables positively modifying OS were pMGMT+ (p=0.004), 1p19q codeletion (p=0.015), the extension of surgical intervention (p=0.011) and the number of lobes involved (p=0.021). Multivariate analysis showed that pMGMT and 1p19q codeletion modified the OS in our population (p=0.039 and 0.047, respectively). **Conclusions:** This is the first study which has evaluated the molecular profile in LGG pts from Latin-America. Our findings confirmed the prognostic relevance of pMGMT and 1p19q codeletion, without finding a positive relation for IDH1/2 mutations. This finding could have been explained by sample size and selection bias. Mutations in ATRX are limited to the population of pts having AD/OA and IDH1+/1p19q-.

**2077 General Poster Session (Board #42), Sat, 1:15 PM-5:00 PM**

**Cost utility analysis of a randomized radiation therapy trial among patients with one to three brain metastases.** *Presenting Author: Anna Likhacheva, Banner MD Anderson Cancer Center, Gilbert, AZ*

**Background:** Two common options for the treatment of 1-3 brain metastases (BM) are whole brain radiotherapy with stereotactic radiosurgery boost (WBRT+SRS) and stereotactic radiosurgery alone (SRS). These two approaches entail differences in efficacy, neurocognitive toxicity and cost. Currently, there is an absence of evidence contrasting these two strategies both in terms of effectiveness and cost in a randomized setting. **Methods:** A randomized single institution trial tested the difference between outcomes and utilities among patients with 1-3 BM receiving WBRT+SRS or SRS alone. Patients receiving SRS alone could undergo salvage SRS or WBRT. Between 2001 and 2007, 58 patients were randomized to one of two arms. Another 42 patients refused the assigned treatment at randomization but were still followed prospectively. Institutional costs were utilized and adjusted using the Consumer Price Index. Overall survival (OS) was estimated by the Kaplan-Meier method. Utility score was derived using a time trade-off method. Cost per life-years saved and cost per quality-adjusted life-year (QALY) saved were calculated. **Results:** OS and utility scores in the SRS alone group were significantly higher than SRS+WBRT group among randomized patients ($p=0.005$ and $p=0.05$) while neither metric was statistically different in the non-randomized cohort ($p=0.72$ and $p=0.5$). The incremental cost effectiveness ratios (ICER) of SRS alone over WBRT+SRS were $47201, $74,560, and $56,455 per QALY for randomized patients, non-randomized patients and all patients, respectively. Sensitivity analysis demonstrated that the likelihood of having 1 versus 2-3 BM had the highest impact on ICER. **Conclusions:** The degree of cost effectiveness for SRS alone, as estimated by patient level costs in a prospective study, varied with whether the patients were randomized or chose their own treatment. Nonetheless, SRS alone for 1-3 brain metastases is a reasonable option from the payor perspective in all populations.

**2078 General Poster Session (Board #43), Sat, 1:15 PM-5:00 PM**

**A phase II study of whole brain radiotherapy with simultaneous integrated boost using volumetric modulated arc therapy for 1 to 10 brain metastases.** *Presenting Author: Alan Nichol, BC Cancer Agency, Vancouver, BC, Canada*

**Background:** Local control of brain metastases reduces risk of death from intracranial progression and improves survival in selected patients. Volumetric modulated arc therapy can deliver a fraction of whole brain radiotherapy (WBRT) and a simultaneous integrated boost (SIB) to multiple brain metastases in about 5 minutes. This is the first registered clinical trial (NCT01046123) to report WBRT and SIB for up to 10 brain metastases. **Methods:** Sixty subjects with 1-10 brain metastases were accrued to a single-institution phase II study of a 5-fraction course of 20 Gy WBRT and 50 Gy SIB. Eligible subjects had Karnofsky Performance Status (KPS) 70 - 100, maximum diameter of the largest metastasis $\leq$ 3 cm, and estimated $\geq$ 6-month median life expectancy. The phase II primary endpoint was a comparison of 3-month local control with that of the WBRT (37.5 Gy/15) and stereotactic radiosurgery (SRS: 15-24 Gy/1) arm of the RTOG 95-08 study (90%). Overall survival for subgroups with 1-3 and 4-10 metastases were compared. **Results:** The median number of brain metastases was 3 (range: 1-10). Known prognostic factors for overall survival in the 1-3 subgroup ($n = 33$) and the 4-10 subgroup ($n = 27$) were not significantly different. The cancers were: 53% lung, 32% breast and 15% other. The minimum follow-up was 5 months and the median follow-up was 9 months. The 3-month radiographic responses were: 10% complete, 48% partial, 33% stable (90% local control) and 10% progressive disease. Grade 3-4 radionecrosis occurred in 7% (4/60) of subjects at a median of 9 months. The median survival was 10 months in the 1-3 subgroup and 12 months in the 4-10 subgroup ($p = 0.8$). Multivariable analysis of overall survival showed that KPS 70-80 ($HR = 3.2$, $p < 0.004$), extracranial disease ($HR = 2.9$, $p = 0.04$) and no use of targeted systemic therapy ($HR = 7.5$, $p = 0.0003$) were associated with worse survival, but age ($HR = 0.98$, $p = 0.1$) and number of metastases 1-3 vs. 4-10 ($HR = 1.1$, $P = 0.8$) were not. **Conclusions:** WBRT and SIB had similar 3-month local control to the WBRT and SRS arm of RTOG 95-08. Equivalent survival of the 1-3 and 4-10 subgroups justifies including selected patients with 4-10 brain metastases in phase III trials for brain metastases. Clinical trial information: NCT01046123.

**2079 General Poster Session (Board #44), Sat, 1:15 PM-5:00 PM**

**Lenalidomide in the treatment of relapsed primary central nervous system lymphoma (PCNSL).** *Presenting Author: Caroline Houillier, APHP-CHU Pitié-Salpêtrière, Paris, France*

**Background:** Lenalidomide is an immunomodulator agent that exhibits efficacy in multiple myeloma and haematological malignancies including refractory/relapsed diffuse large B-cell (DLBC) systemic lymphoma (Witzig et al, Ann Oncol 2011). **Methods:** Retrospective review of PCNSL patients treated with lenalidomide at the Pitié-Salpêtrière hospital. Inclusion criteria were: (1) immunocompetent status (2) pathologically proven diagnosis of DLBC-PCNSL, (3) recurrent or refractory disease after at least two prior chemotherapy treatments, including intravenous high-dose methotrexate and cytarabine based regimens, (4) lenalidomide administered orally, at a dose of 25 mg/day on days 1-21 of a 28-days cycle. MRI scans were performed monthly. Response was evaluated according to the IPCG criteria. **Results:** Between June 2011 and March 2013, 6 patients (4 women and 2 men) met the inclusion criteria. Lenalidomide was given as 3rd line in 4 patients, as 4th line in 1 and 5th line in 1. Median age was 73.5 years (range 64-78) and median Karnofsky Performance Status was 60 (range 40-70). Two patients achieved complete response (CR). Patient 1 received a total of 9 monthly cycles of lenalidomide without any steroids and is still in remission after a follow-up of 18 months from the start of the treatment. Patient 2 achieved a CR and was off-steroids at the time of CR, but relapsed during the third cycle and died after 14 weeks. Patient 3 achieved a partial response after one cycle but died suddenly during the second cycle. Patients 4, 5, and 6 progressed and died 2, 5, and 6 months respectively after the start of lenalidomide. One of them who suffered from an oculo-cerebral relapse demonstrated a partial ocular response while progressing in the brain. Apart from the sudden death of unknown cause, the treatment was well tolerated. None of the patients experienced any grade III or IV toxicity. **Conclusions:** These results suggest that lenalidomide exhibits activity in heavily pre-treated PCNSL and is well tolerated in elderly patients. Lenalidomide efficacy on PCNSL needs to be evaluated prospectively, alone or in association with other cytotoxic agents. A phase II trial combining rituximab and lenalidomide for recurrent PCNSL is ongoing in France (NCT01956695).

**2080 General Poster Session (Board #45), Sat, 1:15 PM-5:00 PM**

**Preoperative chemotherapy as a new strategy of treatment for low-grade gliomas in eloquent areas: A phase II study.** *Presenting Author: Roberta Ruda, Department of Neuro-Oncology, University and City of Health and Science Hospital of Turin, Turin, Italy*

**Background:** Total/near total resection has been associated with increased survival and reduced risk of malignant transformation in low grade gliomas (LGGs). This study is aimed to evaluate whether preoperative chemotherapy with temozolomide can reduce tumor infiltration and improve the surgical resectability of LGGs in eloquent areas. **Methods:** Patients with LGG after biopsy or partial resection at a previous surgery, who progressed with increasing seizures and/or radiologically, received 1 week on/1 week off temozolomide to a maximum of 12 cycles. Response on MRI-FLAIR images was evaluated every 3 months based on RANO and volumetric criteria. Changes on diffusion tensor imaging (DTI) were assessed by histogram analysis and Functional Diffusion Maps and compared with RANO and volumetric criteria, and response of seizures. **Results:** 24 patients with an histological diagnosis of LGG according to WHO 2007 were enrolled from 2008 to 2013. Reasons for chemotherapy were either a large residual tumor in 15/24 (seizures in 13/15) or tumor progression in 9/24 (seizures in 3/9). Nineteen of 24 patients are evaluable for response so far. Best response according to RANO was: MR in 3/19 (16%), SD in 14/19 (74%) and PD in 2/19 (10%). Among patients with response or stable disease according to RANO, tumor volume reduction on FLAIR images ranged between 4.3% and 42.7% (median: 26.6%). In all patients significant changes in diffusion patterns, suggestive of a reduced tumor infiltration, were observed after 3 cycles ($p<0.05$) and became more significant ($p<0.01$) after 6 cycles. Twelve out of 15 patients had a significant reduction of seizure frequency concurrent with significant changes on DTI despite a volumetric stability. Seventeen out of 19 patients underwent reoperation: overall, a near-total resection ($\geq$ 95%) was achieved in 9/19 (47%) patients of the whole series. In 4 patients total resection was confirmed by the absence of IDH1 mutated cells in tumor margins. **Conclusions:** Preoperative chemotherapy in patients with LGG in "eloquent" areas can allow a total near-total resection at reoperation in a significant subset of patients. DTI could improve the evaluation of feasibility and timing of reoperation.

**2081 General Poster Session (Board #46), Sat, 1:15 PM-5:00 PM**

**Preliminary evaluation of the tolerability and feasibility of combining 5-amino-levulinic acid (5-ALA) with carmustine wafers (Gliadel) in the surgical management of primary glioblastoma.** *Presenting Author: Colin Watts, University of Cambridge, Cambridge, United Kingdom*

**Background:** Fluorescence-guided resection of glioblastoma improves surgical cytoreduction, which may improve therapeutic benefit from intra-operative carmustine wafers. The objective of this study was to establish the safety and tolerability of combining fluorescence-guided surgical resection (5-ALA) with intra-operative chemotherapy (carmustine wafers) in patients with primary glioblastoma (GBM) prior to standard treatment with radiotherapy and temozolomide. **Methods:** A single arm design with the following inclusion criteria: Age 18+ years; patient reviewed at a specialist neuro-oncology MDT; imaging evaluated by a neuro-radiologist and judged to be a GBM; radical resection judged to be realistic by the neurosurgeons (i.e. NICE criteria for the use of Carmustine wafers can be met); and WHO performance status 0 or 1 on clinical review **Results:** Seventy-two patients were recruited from 8 UK sites between July 2011 and May 2013; 64 patients received carmustine wafer implants and 59 patients were found to be eligible after surgery. Thirteen patients were ineligible due to wafers not inserted ($n$=8); GBM not diagnosed post-operatively ($n$=4); simultaneous diagnosis of cutaneous sebaceous carcinoma ($n$=1). There were 8 surgical complications reported in 6 patients: wound infections in 5 patients (8%) and cerebrospinal fluid leakage in 3 patients (5%). One patient was unable to begin chemoRT (1/33, 3%), and 4 patients (4/33, 12%) were not able to begin chemoRT within 6 weeks of surgery, due to surgical complications. After a median follow-up of 10.8 months, 25 patients (42%) are alive without progression, 16 patients (27%) are alive having progressed and 18 patients (31%) have died. Thirty-three patients (56%) have reported 68 adverse events of grade 3 or higher, 5 of these were reported as being 'possibly' related to the combination of 5-ALA and carmustine wafers: sepsis ($n$=2), wound infection ($n$=2), seizure ($n$=1). **Conclusions:** The combination of 5-ALA and carmustine wafers is safe and tolerable in the surgical management of primary glioblastoma. A phase III randomised controlled trial is being designed to confirm efficacy Clinical trial information: 77105850.

**2082 General Poster Session (Board #47), Sat, 1:15 PM-5:00 PM**

**Single-institution retrospective review of newly diagnosed glioblastoma (GBM) patients (pts) treated on bevacizumab (BEV) in clinical practice.** *Presenting Author: Henry S. Friedman, Duke University Medical Center, Durham, NC*

**Background:** Following the FDA approval of BEV for recurrent GBM pts, two multicenter phase III trials, RTOG0825 and AVAglio, evaluated the addition of BEV to radiation and temozolomide in newly diagnosed GBM. These trials failed to show statistically significant increased survival [median overall survival (OS) of 15.7 and 16.8 months for the BEV groups, respectively]. We performed a retrospective chart review of newly diagnosed GBM pts treated with BEV at Duke, with the goal to identify subgroups of pts who might benefit from BEV in the community. **Methods:** Newly diagnosed adult GBM pts treated at Duke were identified through our "Primary and Recurrent Glioblastoma Registry". We conducted a retrospective chart review of pts who initiated BEV off clinical trial between January 1, 2009 and May 14, 2012. Pts who participated in a clinical trial prior to receiving BEV were excluded from analysis. Pts alive on May 15, 2012 consented to the prospective collection of their data. Demographic, clinical, and outcome data were analyzed. **Results:** Thus far, a total of 181 pts have been identified. Median age at start of BEV was 57 years (range 20-80) and 66% were male. Gross total resection was obtained in 46%, biopsy in 20%, and subtotal resection in 34% of pts. At a median follow-up of 31.2 months, median OS from the time of GBM diagnosis was 26.2 months (95% Confidence Interval [CI], 23.3-32 months) and median progression-free survival (PFS) was 17.8 months (95%CI, 14.9-19.8 months). Grade 3 or higher proteinuria occurred in 6% of pts; grade 3 or higher thromboembolic events occurred in 9% of pts. Two grade 2 intracranial hemorrhages were observed. **Conclusions:** This retrospective review suggests a median OS of 26.2 months and median PFS of 17.8 months in newly diagnosed GBM pts treated on BEV in clinical practice. One possible explanation for the long-term survival could be our practice of continuing BEV at progression. Further prospective and retrospective analyses to identify subgroups of pts who can benefit from the addition of BEV to the standard of care will be performed.

**2083 General Poster Session (Board #48), Sat, 1:15 PM-5:00 PM**

**"Salvage" neoadjuvant bevacizumab in newly diagnosed glioblastoma multiforme (GBM).** *Presenting Author: Ciprian Barlog, APHP Service de Neuro-Oncologie, Paris, France*

**Background**: Some patients (pts) with GBM are in such a poor condition at the onset of radiotherapy (RT), particularly because of severe steroid-resistant intracranial hypertension (ICH), that RT is cancelled. Our objective was to evaluate if upfront bevacizumab (BEV) could be of help in this rare setting, allowing some patients to resume standard radio-chemotherapy treatment. **Methods**: We retrospectively analyzed all pts with newly diagnosed GBM who could not start RT because of severe ICH or altered neurological status incompatible with the requirements for administering RT and who received BEV as neo-adjuvant therapy. Clinical, radiological characteristics and response to BEV were recorded. It was also noted if radio-chemotherapy could be secondarily delivered. **Results**: Twelve pts received neo-adjuvant BEV because of larger tumor volume (N=8) or altered neurological status (N=4). All but one were diagnosed by biopsy. Median age was 60 years (range 19-72). All pts were under high dose steroids. Seven pts (58%) could receive standard RT after BEV administration. After BEV and before RT, neurological status was improved in 6 pts, and 8 had stable or partial response on MRI. Completion of RT was correlated to age ($p<0.001$), but not to initial tumor volume ($p=0.886$) nor KPS ($p=0.381$). Median progression free survival (PFS) and overall survival (OS) were 3.7 (95% confidence interval (CI):1.4-6.0) and 10.1 (95%CI: 0-20.4) months, respectively. Median PFS for patients with or without RT were 8.2 (95%CI: 0.1-16.4) and 2.5 (95%CI: 2.2-2.9) months ($p=0.150$), respectively. **Conclusions**: "Salvage" neo-adjuvant BEV may be of help in some GBM patients whose very poor clinical condition, often with impeding herniation, does not allow the safe onset of RT. Prospective evaluation is warranted.

**2084 General Poster Session (Board #49), Sat, 1:15 PM-5:00 PM**

**Immune checkpoint blockade for glioblastoma: Preclinical activity of single agent and combinatorial therapy.** *Presenting Author: David A. Reardon, Dana-Farber Cancer Center Institute, Boston, MA*

**Background:** Outcome for glioblastoma (GBM) remains dismal and innovative treatment strategies are desperately needed. Growing data support the contribution of local and systemic immune checkpoint molecules mediating immunosuppression by GBM tumors. **Methods:** Luciferized GL261 cells (GL261-Luc) were stereotactically implanted intracranially in albino C57BL/6 mice. Cohorts of mice with growing tumors (increasing bioluminescence) were treated with murine monoclonal antibodies (MAb) against PD-1, PD-L1, PD-L2, and CTLA-4 (single agent and combinations) every 3 days X 8 beginning 6 days following tumor implantation and were followed for overall survival. Subsets of mice underwent MRI as well as analysis of tumor infiltrating immune cells, and systemic immune cells and immunocytokines. Tumor re-challenge experiments were performed among long-term surviving mice. **Results:** Immune checkpoint blockade was well tolerated with no apparent morbidity or mortality among treated animals. Improved survival was noted among mice treated with immune checkpoint blockade compared to appropriate controls. The most robust survival benefit was noted among mice treated with combinatorial therapy including 12/18 (75%) mice treated with anti-PD-1 + anti-CTLA-4 MAbs alive at 140 days with no evidence of residual tumor. MRI imaging among long-term surviving animals demonstrated clear evidence of initial tumor growth followed by regression and eradication of tumors. Long-term surviving mice appeared fully intact neurologically and exhibited no evidence of tumor growth following re-challenge of GL261-Luc cells injected subcutaneously. Characterization of tumor infiltrating immune cells as well as systemic immune cells and immunocytokines is ongoing. **Conclusions:** Immune checkpoint blockade provides significant survival benefit and appears safe in this immunocompetent, orthotopic syngeneic GBM model. Re-challenge experiments demonstrate evidence of long-term immunologic memory and further elucidation of underlying mechanisms of immune-mediated anti-tumor activity is ongoing. These data strongly support the evaluation of immune checkpoint inhibitors among patients with GBM.

**2085 General Poster Session (Board #50), Sat, 1:15 PM-5:00 PM**

**Angiogenic and procoagulant factors in plasma of brain tumor patients treated with bevacizumab.** *Presenting Author: Andrea Pace, Neurology, Regina Elena National Cancer Institute, Rome, Italy*

**Background:** Glioblastoma (GBM) is one of the most vascularized human tumors and GBM cells produce proangiogenic factors, including vascular endothelial growth factor (VEGF). Bevacizumab (BV), a monoclonal antibody against VEGF, has shown antitumor activity, but so far no biomarkers have been identified to predict outcome. The purpose of the present study was to investigate the possible predictive value of circulating VEGF, von Willebrand factor (vWF) and procoagulant factors in patients with recurrent GBM. **Methods:** We conducted a prospective analysis of recurrent malignant gliomas (MG) patients treated with BV alone or in combination with chemotherapy performing serial evaluations of plasma VEGF levels, vWF antigen and procoagulant factors such as thrombin-antithrombin complex (TAT), prothrombin fragment F1+2 (F1+2), Factor VIII and D-Dimer. Baseline, and post-treatment samples were collected at each administration of BV. **Results:** Forty-nine recurrent MGs (glioblastoma=26, astrocytoma=17, oligodendroglioma=6) who received BV at 10 mg/kg intravenously every 3 weeks, of whom 26 in association with chemotherapy were included in the study. Median age was 45 years (22-73), median Karnofsky performance status was 80 (60-100). Out of the 48 evaluable, 17 partial responses (35%), 7 stable disease (15%) and 24 disease progressions (50%) were observed. At baseline all patients presented with laboratory signs of coagulation activation (i.e. high TAT and FVIII levels). Circulating plasma levels of VEGF and vWF antigen significantly increased in all patients post-treatment of BV ($p=0.0001$ and 0.009 respectively). No responder patients showed significantly higher vWF antigen levels than responders ($p=0.01$) after second administration of BV. **Conclusions:** These preliminary data suggest that low vWF antigen levels might help predict response in recurrent MG patients treated with BV. This marker should help clinicians to decide the right therapy, advise them of the generation of mechanisms of drug resistance during antiangiogenic treatment.

**2086 General Poster Session (Board #51), Sat, 1:15 PM-5:00 PM**

**Effect of inhibition of $\alpha$-secretase activity on cleavage of p75 neurotrophin receptor (p75NTR) and proliferation of brain tumor initiating cells (BTICs) and malignant gliomas (MGs).** *Presenting Author: Rajappa Kenchappa, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

**Background:** MGs are highly invasive, proliferative, and are resistant to treatment. The identification of Glioma Stem Cells (GSCs a.k.a. BTICs) suggests MGs may arise from these cells. By using an unbiased strategy of serial *in vivo* selection, we identified p75NTR as a novel mediator of invasion of MGs/BTICs, and p75NTR proteolysis by $\gamma$-Secretase was required for glioma invasion (Johnston et al., 2007; Wang et al., 2008). However, p75NTR's role in glioma proliferation is unknown. We hypothesized that p75NTR also mediates BTICs proliferation via proteolysis by $\gamma$-Secretase. **Methods:** We used frozen human MG tissues and BTICs isolated from fresh human MGs, examined the expression of neurotrophin receptors and their ligands, and studied their role in proliferation. Gene expression data from TCGA and a validation set from the Moffitt Cancer Center MG datasets were also used. **Results:** We show that BTICs express neurotrophin receptors (p75NTR, TrkA, TrkB and TrkC), their ligands (NGF, BDNF and NT3), and predominantly secrete NGF. Down regulation of p75NTR significantly decreased BTICs proliferation. Conversely, exogenouous NGF, stimulated BTIC proliferation through $\gamma$-secretase mediated p75NTR cleavage and release of its intracellular domain (ICD). In contrast, overexpression of the p75NTR-ICD induced proliferation. Interestingly, inhibition of Trk signaling blocked NGF stimulated p75NTR cleavage and BTIC proliferation; suggesting the Trk receptors role in p75NTR signaling and BTIC proliferation. Further, knockdown of p75NTR or pharmacologic inhibition of cleavage attenuated Akt activation in BTICs, suggesting role of Akt in p75NTR mediated proliferation. We also found that p75NTR, Trk receptors, $\alpha$-secretase and the $\gamma$-secretase enzymes were elevated in GBM patients. Importantly, the ICD of p75NTR was commonly found in MG patient specimens suggesting that the receptor is activated and cleaved in patient tumors. **Conclusions:** These results show that p75NTR proteolysis is required for BTIC proliferation and is a novel clinical target.

**2087 General Poster Session (Board #52), Sat, 1:15 PM-5:00 PM**

**Association of increased progression-free survival in primary glioblastomas with lymphopenia at baseline and activation of NK and NKT cells after dendritic cell immunotherapy.** *Presenting Author: Marica Eoli, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy*

**Background:** DENDR1 is a phase I-II phase study aimed at evaluating dendritic cell (DC) immunotherapy in patients with first diagnosis of glioblastoma multiforme (GBM). Here we provide results of the interim analysis on 22 patients **Methods:** Patients with post-surgery volume $\leq$10 cc underwent leukapheresis before radiotherapy and chemotherapy with temozolomide (TMZ) (Stupp et al, 2005). DC prepared under GMP procedures were loaded with whole tumor lysate (Nava et al, 2012). Three intradermal injections of mature DC were done before adjuvant chemotherapy. The subsequent 4 injections were performed 17 $\pm$3 days after adjuvant TMZ. MRI, clinical and immunological follow-up were performed every 2 months **Results:** Median age at surgery was 54.5 years (28-69). After a median follow up of 14 months (6-27), the median progression-free survival (PFS) was 9 mo, with PFS6 90% (C. I. 0.78-1.029%) and PFS12 42% (C. I: 0.20-0.64) at Kaplan Meier analysis. Median overall survival (OS) was 22 mo with OS 12 70%. (C. I. 0.50-0.9). RT-TMZ induced significant lymphopenia (<1000 lymphocytes/microl) in 17/22 patients (77.2%). Patients with >1000 lymphocytes/microl (5/22) before first vaccination had shorter PFS than others ($p<0.005$). Peripheral Blood Lymphocytes (PBLs) were analyzed by flow cytometry to identify CD8+ T cells, NK and NKT cells before and after DC vaccines. The ratio of vaccination/baseline cell frequencies (V/B ratio) was calculated for each patient and the median of all values used as the cut off value to separate patients. Increased V/B ratio for NK cells and NKT cells, but not for CD8 T lymphocytes, was significantly associated with prolonged PFS (median PFS 14 vs 8.0 mo, $p=0.01$; 15.0 vs 8.0 mo). 2/4 patients with MGMT methylation were in the group of high V/B ratio. Interferon-gamma in peripheral blood was significantly higher in patients with PFS12 ($p<0.02$). **Conclusions:** The results show significant positive association between PFS and increased peripheral levels of NK and NKT cells, encouraging the expansion of this study to a larger number of primary GBM. Clinical trial information: 2008-005035-15.

**2088 General Poster Session (Board #53), Sat, 1:15 PM-5:00 PM**

**Gene expression analysis of B-cell receptors (BCR) pathway for identification of PDE4B gene as potential therapeutic target to overcome glucocorticoid resistance in primary CNS lymphoma.** *Presenting Author: Ariz Akhter, University of Calgary, Calgary, AB, Canada*

**Background:** Gene expression profile (GEP) and supervised learning has identified effective targeted therapies and B-cell receptors (BCR) pathway inhibitors have improved outcomes in refractory Diffuse Large B-cell lymphoma (DLBCL) patients (pts). Primary lymphoma of the central nervous system (PCNSL) is a specific DLBCL entity arising in and confined to the CNS. BCR pathway is frequently dysregulated in PCNSL due to mutations affecting CD79B, *CARD11*, and *MYD88* genes. Studies focusing on GEP in PCNSL; thus providing clinical tool for selection of novel targeted therapies is lacking. **Methods:** Here, we report GEP data on BCR related genes and associated downstream pathways (154 gene-probeset) in a cohort (n=21) of PCNSL pts, utilizing mRNA from diagnostic tissue, assessed by Nano string technology. **Results:** Hierarchical clustering (based on BCR genes) revealed two distinct clusters (A, n=15 and B, n=6) with differential expression of *CD79a, CD79b, Bcl10* and *CARD-11* ($p<0.002$). Cell of origin signatures were not distinct between two clusters ($p=0.825$). However, MAP kinase pathway (*MEK1/ERK2*) ($p<0.018$); *TAB2/TAB3* ($p<0.05$); *CCDN1* ($p<0.05$); *TLRs* ($p<0.02$) genes were differentially expressed. *PDE4B* gene, that regulates responses to BCR signaling and apoptosis, exhibited higher (1.5 x) expression in cluster A vs. cluster B (0.004). *PDE4B* expression correlated well with mTOR expression ($p=0.018$). **Conclusions:** BCR activity defines two distinct sub-groups within PCNSL with distinct signatures including expression of *PDE4B*. PCNSL pts may benefit from *PDE4B* inhibitors, through improving glucocorticoid sensitivity. It also demonstrates that insights into disease pathogenesis can be exploited to rationally overcome drug resistance.

**2089 General Poster Session (Board #54), Sat, 1:15 PM-5:00 PM**

**Comparison of hypofractionated radiation with temozolomide to the current standard of care in the treatment of glioblastoma: Results from a single institution.** *Presenting Author: Melissa Azoulay, McGill University Health Centre, Montreal, QC, Canada*

**Background:** The multimodality treatment of patients with glioblastoma (GBM) includes adjuvant radiation with concomitant chemotherapy. At this time the optimal radiation fractionation is yet to be determined. In this retrospective study, we compared different fractionation regimens and identified independent prognostic variables associated with outcome. **Methods:** 457 underwent surgery for GBM between January 2005 and December 2012. Data related to clinical information, extent of surgery and adjuvant treatment was collected using electronic records and patient charts. Patients excluded were those who did not receive or complete adjuvant radiation and patients with infra-tentorial lesions. Univariate and multivariate analysis was performed using Cox model in order to identify variables associated with the primary endpoint, overall survival (OS). **Results:** 276 patients with a median follow-up of 13.4 months were included in this analysis. There were 147 patients in the conventional fractionation (CF) group of 60 Gy/30 fractions, 86 patients in the hypofractionation group of 60 G/20 fractions (HF60), and 43 patients in the 40 Gy/15 fractions group (HF40). Ninety-five percent of patients in both the CF and HF60 group received concomitant temozolomide, while 49% in HF40 group of patients received it. The median survival (MS) was 15.7 months for the CF group with a 2 year OS of 30.6%. MS was 13.8 months and 7 months in the HF60 and HF40 groups with a 2-year OS of 26.2% and 5.3%, respectively. Cox analysis showed no significant difference in terms of OS between the CF and HF60 group (HR1.22, $P$=0.20) but worse outcome in the HF40 group (HR 2.09, $P$=0.004). Multivariate analysis showed age, performance status, extent of surgery, repeat surgery, concomitant chemotherapy and methylation status to be significant factors associated with survival. **Conclusions:** HF60 shows OS comparable to CF while allowing for a shorter treatment time and potential radiobiological benefit without added toxicity. Our data also confirms that HF40 should be reserved for the palliative setting. There is a need for a prospective trial comparing the HF60 regimen to the current standard of care.

**2090 General Poster Session (Board #55), Sat, 1:15 PM-5:00 PM**

**Revised graded prognostic assessment (GPA) index for small cell lung cancer (SCLC) patients (pts) with brain metastases (BM).** *Presenting Author: Lingling Du, Cleveland Clinic Foundation, Cleveland, OH*

**Background:** Pts with SCLC commonly develop BM and the GPA is frequently used as a prognostic index for overall survival (OS). GPA includes 4 groups (GPA scores 0-1.0 (worst), 1.5-2.0, 2.5-3.0, and 3.5-4.0 (best)). The purpose of this study is to develop a revised GPA in this population using a contemporary pt cohort. **Methods:** With IRB approval, the Cleveland Clinic Brain Tumor and Neuro-Oncology Center's database was used to identify SCLC BM pts treated between 2000 and 2013. OS from the diagnosis (dx) of SCLC BM was the primary endpoint. Cox proportional hazards models with stepwise variable selection were used to identify independent prognostic factors. **Results:** 197 pts (52% male) with BM from SCLC were included for analysis. Median age at dx of BM was 64 yrs (range 36-85). 41% had BM at the initial dx of SCLC. Median number (No.) of BM was 2 (Range 1-25). 6% had leptomeningeal disease. Median OS after the dx of BM was 9.5 months (m) (95%C.I. 7.8-10.1 m). Conventional GPA for lung cancer is derived from KPS, No. of BM, presence of extracranial mets, and age. Overall GPA was prognostic of OS ($p<.0001$) but the categorizations of the factors comprising it were not optimal. A revised set of factors was identified (Table): the 4 original factors, but with different characterizations and weights, and control of the primary tumor. The revised GPA index categorizes pts into 3 groups - unfavorable (total score $<8$; 27% of pts), intermediate (8-13; 43% of pts), and favorable ($>13$; 30% of pts); with OS of 3.0m (vs 6.4m for pts with GPA $<1.0$; 36% of pts), 9.6m, and 15.8m (vs 13.3 for pts with GPA$>2.5$; 29% of pts) respectively ($p<.0001$). **Conclusions:** A revised prognostic index consisting of modified versions of the factors comprising the GPA and primary controlled/uncontrolled in pts with BM from SCLC is proposed.

| Factor | No. of points | Hazard ratio | p |
|---|---|---|---|
| **No. of extracranial mets (based on liver, bone, and soft tissue mets).** | | | |
| **0** | 6 | 1.62 (1.26-2.06) | .0001 |
| **1** | 2 | | |
| **≥2** | 0 | | |
| **No. of BM** | | | |
| **0, 1, or 2** | 4 | 1.88 (1.30-2.70) | .0007 |
| **≥3** | 0 | | |
| **KPS** | | | |
| **≥80** | 4 | 1.71 (1.20-2.43) | .003 |
| **<80** | 0 | | |
| **Age** | | | |
| **<65** | 3 | 1.65 (1.16-2.35) | .005 |
| **≥65** | 0 | | |
| **Primary controlled** | | | |
| **Yes** | 4 | 1.85 (1.20-2.85) | .006 |
| **No** | 0 | | |

**2091 General Poster Session (Board #56), Sat, 1:15 PM-5:00 PM**

**The potential role of $^{18}$F-FDOPA PET imaging in low-grade gliomas.** *Presenting Author: Carmine Maria Carapella, Neurosurgery, Regina Elena National Cancer Institute, Rome, Italy*

**Background**: Brain tumors have been widely evaluated with 3,4-dihydroxy-6-$^{18}$F-fluoro-L-phenylalanine ($^{18}$F-FDOPA) PET examination, that demonstrated higher sensitivity and specificity for gliomas than $^{18}$F-FDG PET imaging. The aim of the present study is to evaluate the potential role of $^{18}$F-FDOPA PET in low grade glioma (LGG). **Methods**: We enrolled 56 patients (35 males and 21 females) affected by LGG; 23% were newly diagnosed, 45% were studied during chemotherapy, and 32% were observed out of treatment during a periodic follow-up. The mean age at diagnosis was 44.5 years. All patients underwent $^{18}$F-FDOPA PET and MRI examinations. Both FLAIR and contrast-enhanced T1 sequences were considered for the assessment of therapeutic response according to RANO criteria. PET images were considered as positive when the lesion definitely presented $^{18}$F-FDOPA accumulation taking into account background and controlateral site. The slices with a maximal $^{18}$F-FDOPA uptake in the ROI were chosen for quantitative measurement of metabolic activity of the tracer [standardized uptake value (SUV)]. In order to evaluate the concordance between diagnostic test 1 (MRI) and diagnostic test 2 ($^{18}$F-FDOPA) we calculated the unweighted kappa statistic and its relative 95% Confidence Interval (CI). This value was interpreted in a qualitative manner on the basis of Landis and Koch criteria. **Results**: The Kappa statistic for the whole sample was equal to 0.301 (95% CIs from 0.21 to 0.40) showing a fair concordance between the two tests in terms of diagnostic ability. We found a good correlation between residual volume and SUV max ($r=0.435$, $p=0.002$ by Spearman Rank Correlation Coefficient), indicating that greater the residual volume, higher is the SUV max. Also multivariate analysis showed that a SUV max greater than 1.65 was the only independent predictor of tumor progression (HR=4.59, 95% CIs from 0.99 to 21.31, $p=0.054$). This implies that a patient with a SUV max higher than 1.65 had an almost 5-fold increased risk of progressive disease, regardless of its clinical and MRI characteristics. **Conclusions**: Our results confirm that $^{18}$F-FDOPA PET imaging could assume a relevant role mainly in the prognostic assessment of patients affected with primary and recurrent LGG.

**2092 General Poster Session (Board #57), Sat, 1:15 PM-5:00 PM**

**A phase I study of niraparib in combination with temozolomide (TMZ) in patients with advanced cancer.** *Presenting Author: Razelle Kurzrock, University of California, San Diego, La Jolla, CA*

**Background:** Niraparib (Np) is an oral, highly potent and selective PARP1/2 inhibitor. The hypothesis for this study is 1) PARP inhibition of DNA repair damage is potentiated with TMZ. 2) PARP inhibition restores sensitivity to TMZ mismatch repair-deficient tumors. **Methods:** This was a multi-center (3), open-label, non-randomized two-part study in patients with advanced cancers. Patients were treated with Np (once daily continuously) + TMZ (once daily for first five days) in 28-day treatment cycles. In Part A, the objective was to determine the preliminary MTD of the two drugs in combination. Part B was to explore the efficacy and tolerability of this combination in two cohorts (recurrent GBM and melanoma). The study was closed after defining MTD in Part A. **Results:** There were 19 patients treated in Part A with Np at 3 dose levels 30 mg (6 subjects), 40 mg (10 subjects), and 70 mg (3 subjects) and 150 mg/m2 TMZ once daily. The MTD and RP2D was determined to be 40 mg Np and 150 mg/m2 TMZ. The DLT of Grade 4 Thrombocytopenia occurred in 2/10 patients at the 40 mg dose level for Np. The DLT of Grade 4 neutropenia occurred in 1/3 patients at the 70 mg dose level for Np. At this dose level all 3 patients enrolled experienced Grade 4 thrombocytopenia with only one patient meeting protocol-specified DLT criteria. The most frequently reported AEs were thrombocytopenia (78.9%), anemia (68.4%), and leukopenia (57.9%). The most common ≥ grade 3 AEs were thrombocytopenia (52.6%), neutropenia (31.6%), and neoplasm progression (15.8%). Based on the in vitro metabolism data, the likelihood of a drug interaction between Np and TMZ is highly unlikely. Out of 16 evaluable subjects, 1 subject reported a PR (Glioblastoma), 2 subjects experienced SD (Malignant melonama and Serous ovarian carcinoma) and 13 subjects had PD. **Conclusions:** Niraparib, dosed at 40 mg continuously in combination with 150mg/m2 TMZ was tolerable and demonstrated antitumor activity. 40 mg Np and150 mg/m2 TMZ was considered an MTD and RP2D. A future study will evaluate full dose, 300 mg daily Np in combination with escalating TMZ dose levels. Clinical trial information: NCT01294735.

**2093 General Poster Session (Board #58), Sat, 1:15 PM-5:00 PM**

**The frequency and impact of ROS1 rearrangement on clinical outcomes in GBM.** *Presenting Author: Miriam Dorta, Fundación Jiménez Díaz University Hospital, Madrid, Spain*

**Background:** The tirosine kinase (TK) receptor ROS1 is described in several preclinical analysis of glioblastoma (GBM) cells and its role in gliomagenesis has been reported as well. Since TK inhibitors has changed clinical response of ROS1 rearranged lung cancer, new therapeutic approach has emerged for GBM. However its rearrangement in GBM human tissue still has not been explored and it should be defined to check if those are relevant to assess ROS1 inhibitors in these neoplasms. We performed ROS1 FISH in human GBM tissue and correlates molecular alterations with overall survival (OS) and progression free survival (PFS) in a cohort of uniformly treated GBMs. **Methods:** Clinical history of 54 patients treated from GBM at Doce de Octubre Spanish Hospital, between 2008 and 2010, were reviewed. Only 33 patients had accessible data, tumor specimen, received treatment out of any other clinical trial and had an adequate follow-up. To better analyze the series of 33 cases, a tissue array paraffin platform was performed, and we disposed probes for ROS1 split. 30 samples from 33 from tissue array keeped enough quality to ROS1 microscope analysis. Results were sorted and pooled in non-mutated and mutated, including deletions and rearrangements in mutated group. **Results:** Mutations were found in 51,5% of samples. Deletion was the most common mutation (48,5%). Only 1 sample showed rearrangement (3%). 39,4% was not mutated, and 3 patients were not evaluable for ROS1 (9.1%). The median overall survival (OS) and progression-free survival (PFS) of the whole series (33 samples) was 19 months (CI 95 %: 13.66-24.34) and 8 months (95 % CI: 6.47 to 9.53), respectively. For ROS1 subgroup, median OS resulted in 19 versus 11 months for non-mutated and mutated cases, respectively, with statistical signification ($p = 0.005$). ROS1 median PFS was 9 versus 6 months for non-mutated and mutated respectively, also with statistical significance ($p = 0.044$). **Conclusions:** In our series of human GBM tissues treated uniformly, a high frequency of genetic splits is estimated, with just 3% of rearrangements. These findings have prognostic relevance by the relation resulted between ROS1 status and patients survival, being significantly worse for those with ROS1 rearrangements or deletions.

**2094 General Poster Session (Board #59), Sat, 1:15 PM-5:00 PM**

**Feasibility of lymphocyte harvesting and reinfusion in patients with newly diagnosed high-grade gliomas.** *Presenting Author: Jian Li Campian, Washington University in St. Louis, St. Louis, MO*

**Background:** Standard radiation (RT), temozolomide (TMZ), and dexamethasone cause severe treatment-related lymphopenia (TRL) (total lymphocyte counts (TLC) $<500$ cells/mm$^3$) two months after initiating therapy in patients with newly diagnosed high grade gliomas (HGG). Published studies suggest that severe TRL is related to radiation of circulating lymphocytes and is associated with shorter survival due to tumor progression. This study was designed to evaluate the feasibility of harvesting lymphocytes before radiation and reinfusing them after radiation is completed. **Methods:** Ten patients with newly diagnosed HGGs and baseline TLC $>1000$ cells/mm$^3$ were enrolled. Lymphocytes were harvested with a single 120 minute apheresis procedure via peripheral veins, cryopreserved, and reinfused immediately after RT was complete. Weekly blood counts were followed for 20 weeks. A post-reinfusion TLC rise of $>300$ cells/mm$^3$was desired. **Results:** 10 patients were harvested and 8 received lymphocyte reinfusion. Median age was 55.5 years (range 40-67); median dexamethasone dose was 3 mg/day (range 0-4mg/day), and 70% was glioblastoma multiforme. Their baseline median TLC was 1980 cells/mm$^3$ (range: 1060-2290) and a median of $8.9x10^7$ lymphocytes/Kg (range $3.4\text{-}11.1x10^7$) were harvested. After 6 weeks of therapy, the TLC fell 63% (median 605 cells/mm$^3$, $p<0.0001$). A median of $7.0x10^7$ lymphocytes/Kg (range: $2.7\text{–}9.5x10^7$) were reinfused. Four weeks after reinfusion the average increase in TLC was 274 cells/mm$^3$ (STD: $\pm$ 298, $p=0.045$). Overall, 7 of 8 patients (88%; 90%CI: 53-99%) had an absolute increase in TLC $>300$ cell/mm$^3$in the 14 weeks following reinfusion and this persisted in 4 of 7 (57%) patients. No adverse events occurred related to harvest or reinfusion. **Conclusions:** Lymphocyte harvest and reinfusion is feasible in HGG patients on dexamethasone and no toxicities were noted. An increase in TLC $>300$ cells/mm$^3$ was seen in 88% of reinfused patients during the 14-week observation period post reinfusion. Future studies are being designed to document the role of lymphocyte reinfusion in the increase in TLC. Clinical trial information: NCT01653834.

**2095 General Poster Session (Board #60), Sat, 1:15 PM-5:00 PM**

**Cognitive function and depressive symptoms in patients with newly diagnosed primary brain tumors: A potential interactive relationship.** *Presenting Author: John E. Schmidt, University of Pittsburgh Cancer Institute, Pittsburgh, PA*

**Background:** Primary Brain Tumor (PBT) and its treatment result in reduced cognitive function which significantly interferes with work, personal, and social activities. Depression is also a clinically significant problem in patients with PBT at diagnosis, during and post-treatment. Recent research in non-cancer patients with mild-cognitive impairment has found strong associations between reduced cognitive function and depression; however this association has been little researched in PBT patients. The goal of the present study was to explore the potential interactive relationship between cognitive function (psychometrically assessed) and depression in patients undergoing primary adjuvant treatment for newly diagnosed PBT. **Methods:** Participants included 49 patients (51% male, mean age 48.0) with glioblastoma (n=18), oligodendroglioma (n=17), and astrocytoma (n=14). All completed a pre-treatment psychological and cognitive assessment. The assessment was repeated twelve months later. Assessments included depression (CES-D), physical symptoms and interference (MDASI-BT), and cognitive function (STROOP, Digit Symbol Coding). **Results:** At both assessments, mean scores on Digit Symbol Coding were in the low-average to borderline range compared to WAIS-IV norms. Mean STROOP T-scores fell in the average to low-average range. No significant differences were found in physical symptom severity or interference between assessments (p's>.05). Performance on the STROOP and Digit Symbol Coding declined significantly (rANOVA, p's<.05). Depression scores did not change (p's>.05). When pretreatment depression scores were included as a covariate, changes in cognitive function were no longer significant. The majority of the participants were working or in school at baseline (n=34, 70%), but were on disability or unemployed at second assessment (n=33, 67%). **Conclusions:** The results suggest that depressive symptoms may contribute to declines in cognitive function over time in PBT patients. It is tempting to speculate that interventions focused on improving cognitive function in these patients might be enhanced by early intervention to reduce depressive symptoms.

**2096 General Poster Session (Board #61), Sat, 1:15 PM-5:00 PM**

**Etirinotecan pegol (EP, NKTR-102) in the treatment of high-grade glioma (HGG): A phase 2 trial.** *Presenting Author: Seema Nagpal, Stanford Cancer Institute, Stanford, CA*

**Background:** Patients with recurrence of HGG after bevacizumab (BEV) have an extremely poor prognosis and generally do not respond to further treatment. EP is the first long-acting topoisomerase-I inhibitor designed to concentrate in and provide continuous tumor exposure throughout the entire chemotherapy cycle. Becasue irinotecan has demonstrated activity against HGG, we conducted a Phase 2, single arm, open label trial to evaluate EP in HGG patients who progressed after BEV. **Methods:** Patients age $>18$ with histologically proven anaplastic astrocytoma (AA) or glioblastoma (GB) who previously received standard chemo-radiation and recurred after BEV were eligible. A predicted life expectancy $> 6$ weeks, KPS $\geq 50$ and adequate organ and bone marrow functions were required for entry. Primary endpoint was PFS at 6-week, secondary endpoints were survival from first EP infusion, overall survival from date of pathologic diagnosis of HGG, and safety profile of EP. Response was assessed by RANO criteria. EP as a single agent is administered IV every 3 weeks at 145mg/m2. Patients did not receive BEV while on EP. **Results:** Between August 2012-May 2013, 20 patients were enrolled. Median age was 50 years, median KPS was 70%. 90% of patients had GB with a median time of 1 year from a diagnosis of HGG to study entry with a median of 3 prior lines of therapy. Patients received a median of 3 cycles (1-19) of EP. All patients were evaluable for PFS and toxicity. 2 patients (both with GB) had partial MRI responses. 10 patients had stable disease. 2 patients are still on treatment after receiving 19 and 9 treatment cycles. 6-week PFS was 55%. Median and 6-month PFS were 1.9 mos and 10%, respectively. Median overall survival from first EP infusion was 4.1 months. Only one patient (5%) had a Grade 3 toxicity (diarrhea with dehydration) attributable to EP. Hematologic toxicity was mild. **Conclusions:** Despite discontinuing BEV prior to starting EP, 2 patients had confirmed partial responses (10%) according to RANO criteria and an additional six patients had stable disease at their 1$^{st}$ and 2$^{nd}$ imaging assessment. These encouraging clinical data combined with a favorable safety profile warrant further clinical investigation of this agent in GB. Clinical trial information: NCT01663012.

**2097 General Poster Session (Board #62), Sat, 1:15 PM-5:00 PM**

**Neurocognitive functions in adults treated with radiation for primary brain tumors: A longitudinal study.** *Presenting Author: Kim Edelstein, Princess Margaret Cancer Centre, Toronto, ON, Canada*

**Background:** Cranial radiation is associated with progressive declines in processing speed, attention, memory and executive functions, presumably due to deleterious effects on white matter growth in children and accelerated cognitive aging in older adults. However, little is known about the longitudinal effects of radiation in the adult brain tumor population. **Methods:** In this retrospective cohort study, we conducted neurocognitive assessments in 21 adults diagnosed with a primary brain tumor (12 male; mean age 44 years, range 21-66) within a year of radiation (baseline mean ± SD: 0.17 ± 0.36 years, range -0.15 to 1.1 years), and 3.05 ± 1.83 years later (range 0.51 to 6.77 years). Patients who required additional surgery, or developed tumor progression prior to neurocognitive follow up were excluded from analyses. Neurocognitive test scores were converted to scaled scores according to published criteria, and transformed to z-scores (mean 0, SD 15). Tests measuring the same construct were averaged to provide 4 cognitive domains: Speed, Attention, Memory, and Executive Functions. **Results:** At baseline, Memory, Attention, and Executive Function were below population norms, and Speed was within normal limits (one-sample t-tests, respective means ±SD: -0.66±0.84;-0.40±0.74; -0.70±1.12; -0.30±0.94; all $p<0.05$). At follow-up, only Attention was below average (-0.40±0.81). Moreover, there was no difference in performance at baseline compared to follow-up across domains, nor was there an interaction between time and domain (time x domain repeated measures ANOVA, all $p>0.1$). There was also no difference in the number of tests that were impaired (defined as one standard deviation below the population mean) at baseline compared to follow up. **Conclusions:** Adult brain tumor patients showed deficits in cognitive functions that did not appear to decline over time after radiation in the absence of tumor progression. Longitudinal assessments of neurocognitive functions following radiation treatment in a larger sample is warranted to identify factors contributing to neurocognitive decline across the lifespan in this population.

**2098 General Poster Session (Board #63), Sat, 1:15 PM-5:00 PM**

**The utility of MR enhancement as a noninvasive predictor for high-grade histology in patients with progressive low-grade gliomas: Is histology needed to guide therapy?** *Presenting Author: Amol Narang, The Johns Hopkins Department of Radiation Oncology, Baltimore, MD*

**Background:** In patients with low-grade gliomas, pathologic grade at time of progression has important therapeutic and prognostic implications. Whether surrogate radiographic variables such as new MR contrast enhancement can be used with high accuracy to predict malignant degeneration is uncertain. **Methods:** Patients with a pathologic diagnosis of low-grade glioma (WHO grade I or II) who underwent biopsy or resection at time of progression from 1995-2010 were retrospectively reviewed. Radiologic studies were examined to determine the presence of new MR contrast enhancement, which was analyzed as a predictor of high-grade transformation. **Results:** One hundred and eight patients underwent biopsy or resection for progressive low-grade gliomas, with 19 patients undergoing multiple repeat resections, allowing a total of 127 evaluable records. Median age at initial diagnosis was 36.2 years, while 10% of patients were under the age of 18. Initial pathology consisted of astrocytoma (43%), oligodendroglioma (39%), oligoastrocytoma (11%), and pilocytic astrocytoma (11%). Of the 127 instances of progression, malignant degeneration was present in 74 specimens (58%). Sensitivity (sens) and specificity (spec) of MR contrast enhancement for high-grade transformation were 89% and 57% respectively, while positive (PPV) and negative predictive values (NPV) were 74% and 79%. Values were similar when patients under 18 or with pilocytic astrocytoma were excluded (sens 89%, spec 57%, PPV 71%, NPV 81%), or when patients who only underwent biopsy at time of progression were excluded (sens 91%, spec 64%, PPV 79%, NPV 83%). **Conclusions:** Radiographic enhancement and pathologic grade were discordant in greater than 20% of cases, largely due to the lack of specificity of new MR enhancement for predicting malignant degeneration. As such, additional radiographic or clinical predictors are needed to better non-invasively identify tumors that have undergone malignant degeneration. Meanwhile, pathologic confirmation of grade at time of progression should be considered when safe.

**2099 General Poster Session (Board #64), Sat, 1:15 PM-5:00 PM**

**Primary and secondary malignant meningiomas: A clinical and histological comparison.** *Presenting Author: Tareq A. Juratli, Carl Gustav Carus University Hospital Dresden - Department of Neurosurgery, Dresden, Germany*

**Background:** Malignant meningiomas WHO Grade III (MM °III) represent the most rare but aggressive subtype of all meningioma. They may progress from low- grade meningiomas °I or °II (secondary MM) or develop as de novo primary MM. In this study, we compared clinical and histological factors influencing outcome and survival of primary and secondary MM. **Methods:** The dataset of over 1200 patients with intracranial meningiomas was used toidentify patients with histological proven MM. Of those patients clinical, histological, radiological, tumor- and treatment-related data were evaluated and analyzed. **Results:** We identified 22 MM patients (median follow-up of 8 years); 12 patients with a secondary MM and 10 patients with a primary MM. Histologically, primary and secondary MM were largely indistinguishable. Even the immunohistochemistry including proliferation index (MIB-1), vascular density as well as PDGFR-/ EGFR- and VEGFR-expression failed to show significant differences between either groups or a significant influence on the overall survival. A typical feature of secondary MM were that they are preferentially located at the skull base, whereas primary MM aroused at the convexity ($p=0.049$). Patients with secondary MM underwent in average 4 surgeries, in opposite to patients with primary MM who had in average a single operation ($p=0.002$). 8 patients with secondary MM and all patients with primary MM received radiotherapy; whereas only 3 patients in each group underwent adjuvant chemotherapy. Repeated operations demonstrated a marked survival benefit in both groups in respect to the extent of resection ($p=0.025$). The median overall survival rate for secondary MM following the confirmation of malignant histology was 2.2 years; whereas this wasn't reached yet in the patients group with primary MM at follow-up after 10 years ($p<0.05$). **Conclusions:** Secondary MM seem to be of more aggressive nature than primary ones with a higher risk toward recurrence and with a significantly reduced survival time. Surgery is an effective treatment for secondary and primary MM WHO °III at initial presentation and recurrence. In addition, repeated surgery was the only identified significant prognostic factor for improved PFS and OS in both groups.

**2100 General Poster Session (Board #65), Sat, 1:15 PM-5:00 PM**

**Comprehensive analysis of demographics and survival of pediatric medulloblastoma.** *Presenting Author: Therese A. Dolecek, University of Illinois at Chicago, Chicago, IL*

**Background:** We evaluated the American College of Surgeon's National Cancer Data Base (NCDB) to describe current hospital-based epidemiologic frequency and survival patterns of pediatric medulloblastoma. **Methods:** We analyzed NCDB 1998-2010 data on medulloblastoma defined as ICD-0-3 histology codes 9470, 9471, 9474 diagnosed in primary site brain codes C71.0-C71.9 for children ages 0-19 years. Demographic variables analyzed were age, gender, race and Hispanic origin. Comparisons were also made among histologic subtypes and primary site. Frequencies and Kaplan-Meier relative survival estimates were generated using SEER*Stat software version 8.1.2. **Results:** A total of 3,067 cases of medulloblastoma were identified. Among pediatric age groups, frequency was highest for 5-9 years and lowest in infants. Males were observed to have higher incidence than females. Whites had highest counts among race groups and non-Hispanics were observed to have more frequent diagnoses than Hispanics. The most common histologic subtype was classic medulloblastoma (9470), accounting for 88.2% cases. More than 75% of cases occurred in infratentorial sites C71.6 (cerebellum) or C71.7 (brain stem). Better relative survival was observed as age at diagnosis increased. Females were observed to have better survival than males. No significant differences in survival were observed among race or origin groups. Statistically significantly better 5-year relative survival was observed for cases diagnosed with histologic subtypes 9470 (75.5%) and 9471 (desmoplastic, 79.6%) than 9474 (anaplastic/large cell, 50.6%). Site at diagnosis did not appear to influence survival time for medulloblastoma. **Conclusions:** We report an extensive demographic and survival analysis of pediatric medulloblastoma. Observed differences likely reflect biology across age, gender, race and origin groups.

**TPS2101 General Poster Session (Board #66A), Sat, 1:15 PM-5:00 PM**

**Randomized phase IIb study of nivolumab (anti-PD-1; BMS-936558, ONO-4538) alone or in combination with ipilimumab versus bevacizumab in patients (pts) with recurrent glioblastoma (GBM).** *Presenting Author: John Howard Sampson, The Preston Robert Tisch Brain Tumor Center at Duke University Medical Center, Durham, NC*

**Background**: GBM, the most common primary brain tumor in adults, has an aggressive clinical course and a median survival of 12–15 months post first-line therapy with maximal surgical resection, radiation, and temozolomide. Bevacizumab is approved in the US for pts with progressive disease following therapy; no data has shown durable improvement of disease-related symptoms or overall survival (OS). With limited efficacy of current therapy, more effective treatments to extend survival and preserve quality of life are needed. Ipilimumab, a cytotoxic T-lymphocyte antigen-4 receptor blocking antibody, has shown clinical activity in advanced melanoma pts with brain metastases; preclinical studies demonstrate a benefit from combining a programmed death-1 (PD-1) pathway inhibitor with radiation in a mouse glioma model. We present a phase IIb, randomized, open-label study to evaluate the efficacy and safety of nivolumab, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody, alone or with ipilimumab, vs bevacizumab in pts with recurrent GBM. **Methods**: Pts with Karnofsky performance status ≥70, grade IV malignant glioma treated with radiotherapy and temozolomide, and documented first GBM recurrence within 28 days of randomization are eligible. Pts with >1 recurrence of GBM, extracranial disease, autoimmune conditions, or previous VEGF inhibitor or anti-angiogenic treatment are ineligible. Safety cohort 1; nivolumab 3 mg/kg [n=10; Q2W x 4] and nivolumab 1 mg/kg + ipilimumab 3 mg/kg [n=10; Q3W x 4 followed by nivolumab 3 mg/kg Q2W]) will establish safety and tolerability in GBM pts. Upon successful completion of cohort 1, efficacy cohort 2 will enroll up to 240 pts with recurrent GBM, randomized 1:1:1 to receive nivolumab, nivolumab + ipilimumab (dosed as cohort 1), or bevacizumab (10 mg/kg Q2W). The primary objectives are to evaluate safety in cohort 1 and OS in cohort 2, vs bevacizumab, with secondary objectives of PFS and ORR. Responses will be assessed (Response Assessment Neuro-Oncology criteria) at the end of wks 6 and 12, and Q8W until progression or treatment discontinuation. Clinical trial information: NCT02017717.

**TPS2102 General Poster Session (Board #66B), Sat, 1:15 PM-5:00 PM**

**Phase II study of atorvastatin in combination with radiotherapy and temozolomide in patients with glioblastoma.** *Presenting Author: Abdullah Khalaf Altwairgi, Comprehensive Cancer Center, King Fahad Medical City, Riyadh, Saudi Arabia*

**Background:** Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults. Despite recent advances in the understanding of the molecular mechanism of tumorigenesis, the outcome remains poor. Atorvastatin is an inhibitor of HMG-CoA reductase, a rate-limiting enzyme in the mevalonate pathway. Preclinical studies have demonstrated pro-apoptotic, anti-proliferative, anti-invasive, and radiosensitizing properties of statins. To date, no prospective studies have addressed the anti-tumor effects of statins in GBM. This trial was designed to determine the efficacy and safety of atorvastatin in combination with radiotherapy and temozolomide (TMZ) in patients with newly diagnosed GBM. **Methods:** In this open-label, prospective, single-arm, phase II study, eligible patients will receive oral atorvastatin (40 mg/d for 3 weeks and 80 mg/d thereafter) until disease progression or significant toxicity, in combination with standard therapy comprising radiotherapy (60 Gy/30 fractions) and TMZ (75 mg/m$^2$/d) in the 6-wk concurrent phase, then with TMZ (150-200 mg/m$^2$/d on days 1-5 for 6 cycles). The key eligibility criteria includes: adults (≥18 years) with newly diagnosed GBM, who have undergone surgical resection or biopsy, ECOG performance status ≤ 2, adequate organ function, no prior chemotherapy or radiotherapy, stable dose of steroids for ≥14 days prior to registration, and written informed consent. The primary endpoint is progression free survival (PFS) at 6 months (RANO criteria). Secondary endpoints include overall survival (OS), and safety. A minimum of 80% power required at least 32 eligible patients to be enrolled starting January 2014 with a planned interim analysis after the first 15 evaluable patients. Statistical analysis plan includes Kaplan Meir techniques and Cox proportional hazard modeling. Clinical trial information: NCT02029573.

**TPS2103 General Poster Session (Board #67A), Sat, 1:15 PM-5:00 PM**

**A phase I trial of sorafenib with whole brain radiotherapy (WBRT) in breast cancer patients with brain metastases and a correlative study of FLT-PET brain imaging to evaluate treatment response after WBRT sorafenib.** *Presenting Author: Aki Morikawa, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** WBRT is a standard therapy for metastatic breast cancer (MBC) patients with brain metastases (BM). Despite WBRT, disease progression in the brain is common, and survival is poor. One approach to improve outcome is the use of radiosensitizers. Sorafenib, a multi-kinase TKI with anti-VEGF activity, has demonstrated anti-tumor efficacy in MBC and radiosensitizing activity in preclinical studies. Concurrent use of anti-VEGF drug with radiotherapy (RT) has a potential to confound response assessments due to pseudo-progression and pseudo-response using brain magnetic resonance imaging (MRI). FDG PET is not ideal for brain imaging due to high background glucose uptake. Thus, a newer imaging modality is warranted for accurate response assessment. [18F] 3'deoxy-3'-fluorothymidine (FLT) is a new PET tracer which has shown to correlate with cellular proliferation and may be useful in improving response assessment. **Methods:** We are conducting a phase I trial of sorafenib with WBRT in MBC patients with BM using a 3+3 design. Sorafenib is given orally daily and continuously with the start of WBRT for a total of 21 days. Dose limiting toxicities are assessed weekly for 4 weeks. There are 3 doses levels: 200mg, 400mg, and 600mg daily. The primary endpoints are to determine a maximum tolerated dose (MTD) and to evaluate safety and toxicity. The secondary endpoint is central nervous system progression-free survival. An additional 6 patients will be enrolled as a safety-expansion cohort at the MTD. Key eligibility criteria include MBC with new or progressive ≥ 1cm BM, age≥18 , ECOG PS 0-2, planned WBRT, non-escalating dose of corticosteroid for ≥5 days, and no other concurrent anti-tumor therapy other than trastuzumab.In addition, as an imaging correlative study, we are evaluating FLT-PET to assess radiographic changes after WBRT sorafenib with planned sample size of 20 patients (10 patients in the sorafenib + WBRT cohort and 10 patients in the WBRT only cohort). A total of 3 FLT scans are done: baseline, 7-10 days and 10-12 weeks after the WBRT. Accrual is currently ongoing. Clinical trial information: NCT01724606 and NCT01621906.

**TPS2104 General Poster Session (Board #67B), Sat, 1:15 PM-5:00 PM**

**Salvage therapy with bendamustine for temozolomide-refractory recurrent anaplastic gliomas: A prospective phase II trial.** *Presenting Author: Marc C. Chamberlain, Fred Hutchinson Cancer Research Center, Seattle Cancer Care Alliance, Seattle, WA*

**Background:** There is no standard therapy for recurrent anaplastic glioma (AG). Salvage therapies include alkylator-based chemotherapy (temozolomide [TMZ] or lomustine [CCNU]), re-resection with or without carmustine implants, re-irradiation and bevacizumab. Bendamustine is a novel bifunctional alkylator with CNS penetration but never previously evaluated in AG. Objective: Assess response and toxicity of bendamustine in recurrent AG following prior surgery, radiotherapy and TMZ in a prospective Phase II trial. **Methods:** 26 adults (11 males; 15 females: median age 38 years {range 30-65}) with TMZ refractory recurrent AG (8 anaplastic astrocytoma, 10 anaplastic oligodendroglioma, and 8 anaplastic oligoastrocytoma) were treated with bendamustine. 14 patients were treated at first recurrence and 12 patients were treated at second recurrence. Prior salvage therapy included re-resection in 14 (carmustine implant in 1), TMZ re-challenge in 13 and bevacizumab in 3. A cycle of bendamustine was defined as 2 consecutive days of treatment (100mg/m2/day) administered once every 4 weeks (maximum number of cycles 6). Success of treatment was defined as progression free survival at 6 months of 40% or better. **Results**: Grade 3 toxicities included lymphopenia (14 patients), myalgia, diarrhea, leukopenia, allergic reaction and thrombocytopenia in 1 patient each. No grade 4 or 5 toxicities were seen. The median number of cycles of therapy was 2 (range 1-7). Best radiographic response was progressive disease in 13 (50%) and stable disease in 13 (50%). Response did not differ by histology. Median progression free survival (PFS) was 3.5 months (range 1-14 months), 6-month PFS was 30.8% and 12 month PFS was 15%. **Conclusions**: In this small prospective series of patients with recurrent AG refractory to TMZ, bendamustine appears to have modest single agent activity though not meeting pre-specified criteria (40% 6-month PFS) with manageable toxicity. Confirmation in a larger series of similar patients is required. The study was supported in part through research funds provided by TEVA Pharmaceuticals and the National Comprehensive Cancer Network. Clinical trial information: NCT00823797.

**TPS2105^ General Poster Session (Board #68A), Sat, 1:15 PM-5:00 PM**

**An Internet-based registry for the documentation of neoplastic meningitis.** *Presenting Author: Herwig Matthias Strik, University of Marburg, Marburg, Germany*

**Background:** Cerebrospinal fluid (CSF) and meningeal neoplastic involvement is rare, but severe and often limits patient survival. Only few randomized studies investigated different treatment strategies and achieved no conclusive results. New prospective studies with homogeneous entities are difficult to establish and some initiatives failed recently. An open, multicentric registry may be an adequate alternative for a prospective documentation of a large number of cases of neoplastic meningitis from different primary neoplasms. **Methods:** To enable an easy multicentric access, an internet-based database was chosen. Secutrial is a professional database which enables pseudonymized registration of clinical courses and meets all requirements for the protection of personal data. Predefined routines allow for a immediate calculation of parameters like survival or toxicity also with newly documented data. The configuration of the database allows for a separate documentation of treatment responses of primary neoplasm, systemic and solid central nervous system metastases as well as of neoplastic meningitis. Also, complications of the disease and toxicity of treatment can be documented. By such, the database is able to discriminate between different causes of clinical deterioration and death.

**TPS2106 General Poster Session (Board #68B), Sat, 1:15 PM-5:00 PM**

**Phase I study of the intratumoral administration of an oncolytic polio/rhinovirus recombinant (PVSRIPO) in recurrent glioblastoma (GBM).** *Presenting Author: Annick Desjardins, Duke University Medical Center, Durham, NC*

**Background:** PVSRIPO is the live attenuated, oral (SABIN) serotype 1 poliovirus vaccine containing a heterologous internal ribosomal entry site stemming from human rhinovirus type 2. PVSRIPO recognizes nectin-like molecule-5, an oncofetal cell adhesion molecule and tumor antigen widely expressed ectopically in malignancy. We report a phase I study evaluating the intratumoral convection-enhanced delivery (CED) of PVSRIPO. **Methods:** Eligibility criteria for adult patients (pts) with recurrent supratentorial GBM included: 1-5 cm in diameter; ≥1cm away from the ventricles; ≥4 weeks after chemotherapy, bevacizumab (BEV) or study drug; adequate organ function; KPS >70%; and positive anti-poliovirus titer. Dose was rapidly escalated using a two-step continual reassessment method with anticipated accrual of 1 pt each on dose levels 1-4, and up to 21 pts at dose level 5. **Results:** Thus far, 10 pts have been treated (1 each at levels 1 and 3, 2 at level 2, 2 at level 4, 4 at level 5). One dose limiting toxicity (pt #8) was observed at level 5, a grade 4 intracranial hemorrhage at the time of catheter removal, which required de-escalation to level 4. Adverse events possibly related to study include: hemiparesis (grade 3, n=1; grade 2, n=1; grade 1, n=1); lymphopenia (grade 3, n=1); seizure (grade 2, n=1; grade 1, n=2); lethargy (grade 1, n=4); headache (grade 1, n=2); one each of grade 2 diarrhea, paresthesia, dysphasia and hyperbilirubinemia; and one each of grade 1 fever, cough, nasal congestion, memory impairment, thrombocytopenia, anemia, nausea and vomiting. Eight pts remain alive, with pts #1 and #2 now 20 and 19 months post PVSRIPO, respectively. Two BEV failure pts died six months post-infusion after initiating hospice care due to persistence of baseline neurologic limitations. After observing prolonged steroid use in 5 of 7 pts treated on dose levels 3 to 5 and considering the clinical effects of the complex host inflammatory response to viral tumor infection, it was agreed upon that dose level 2 is probably the optimal dose level. The study has been amended to treat a total of 6 pts at dose level 2. **Conclusion:** Infusion of PVSRIPO via CED is safe thus far and observed efficacy outcomes are intriguing. Clinical trial information: 01491893.

**TPS2107 General Poster Session (Board #69A), Sat, 1:15 PM-5:00 PM**

**A phase I/II study of the combination of indoximod and temozolomide for adult patients with temozolomide-refractory primary malignant brain tumors.** *Presenting Author: Yousef Zakharia, Georgia Regents University Cancer Center, Augusta, GA*

**Background:** Indoleamine 2, 3-dioxygenase (IDO) is a key immune-modulatory endogenous enzyme that inhibits CD8+ T cells and enhances the suppressor activity of Tregs. IDO is expressed in a large proportion of solid tumors, including 50% to 90% of glioblastomas (GBMs). High IDO expression is correlated with poor prognosis in GBM. IDO inhibitors such as indoximod (1-Methyl-D-tryptophan / D-1MT) can improve anti-tumor T cell responses which slows tumor growth *in vivo*. We have demonstrated a synergistic effect of indoximod when combined with temozolomide (TMZ) and radiation in a syngeneic orthotopic brain tumor model. The purpose of this ongoing phase I study is to determine maximal tolerated dose (MTD) of indoximod in combination with TMZ in GBM. This will be followed by an expansion phase II cohort, testing the activity of the indoximod-TMZ combination in several relevant situations, including the addition of bevacizumab or stereotactic radiosurgery in clinically-indicated cases. **Methods:** After progression to standard front line-therapy, patients with GBM are currently being enrolled in a phase I dose escalation study of indoximod (600, 1000 or 1200 mg twice daily given orally) with a standard fixed dose of TMZ. Then, in the phase II portion, patients will be separated into 3 cohorts: Cohort 2a: indoximod with TMZ, cohort 2b: indoximod with TMZ and bevacizumab (for patients who are currently on bevacizumab), cohort 2c: indoximod with TMZ and stereotactic radiosurgery. **Statistical analysis:** The study uses a 3+3 dose escalation design, until reaching the MTD or the maximal absorbed dose. Sample size in phase II is based on the primary endpoint of 6 months progression free survival (PFS). **Correlative studies:** This study will assess primary tumor samples for methylguanine-DNA methyltransferase, IDO expression, intra-tumoral T cells (CD4:CD8 ratio); patient serum for biomarkers of IDO activity (kynurenine and tryptophan) and indoximod pharmacokinetics. Clinical trial information: NCT02052648.

**TPS2108 General Poster Session (Board #69B), Sat, 1:15 PM-5:00 PM**

**Successful treatment of multiple intracranial meningiomas with mifepristone (RU486).** *Presenting Author: Patrizia Farina, Medical Oncology 1, Venetian Institute of Oncology-IRCCS, Padua, Italy*

**Background:** Meningiomas, the most frequent primary brain tumors in adults, are twice more frequent in females compared to males. Several evidence suggest a role for female sex hormones, and particularly progesterone, whose receptor (PR) is highly expressed in the majority of grade I meningiomas. Mifepristone (RU 486) is a synthetic steroid with high affinity for both the progesterone and glucocorticoid receptors. In vitro and in vivo studies suggest an antitumor effects of mifepristone on meningiomas. A phase III randomized trial failed to demonstrated its efficacy in meningioma patients. However a subgroup of patients may still benefit from RU486, particularly multiple meningiomas (diffuse meningiomatosis) which are less frequent, but have a higher female predominance and a higher PR expression. **Methods:** Three female patients with multiple meningiomas inaccessible to either surgical or radiosurgical treatment were treated with mifepristone at 200 mg per day. Results. The treatment was well tolerated (one patient reported hypothyroidism, one patient reported benign ovarian cystadenoma). MRI brain follow-up revealed a partial response (>50% reduction) in two patients and a complete stabilization in the other. All the three patients are now stable after 5 to 9 years of treatment. Conclusion. These encouraging results strongly support a prospective clinical trial in this pre-selected population of multiple meningioma female patients.

**TPS2109 General Poster Session (Board #70A), Sat, 1:15 PM-5:00 PM**

**Phase I/II study of dianhydrogalactitol in patients with recurrent malignant glioblastoma multiforme (GBM).** *Presenting Author: Kent C. Shih, Tennessee Oncology, Nashville, TN*

**Background:** Median survival for patients with recurrent GBM is < 6 months. Front-line systemic therapy is temozolomide but resistance due to $O^6$-methylguanine-DNA-methyltransferase (MGMT) activity is implicated in poor outcomes. Dianhydrogalactitol (VAL-083) is a structurally unique bi-functional DNA alkylating agent that accumulates in brain tumor tissue. Previous clinical studies suggest that VAL-083 has anti-tumor activity against a range of cancers including GBM. In *in vitro* studies VAL-083 demonstrated activity in pediatric and adult GBM cell lines, as well as GBM cancer stem cells. Notably, VAL-083 overcomes resistance to MGMT *in vitro*. In light of extensive safety data from clinical trials and promising efficacy in CNS tumors, DelMar initiated a new clinical studyto establish the maximum tolerated dose (MTD) and identify a dose and dosing regimen for future efficacy trials in GBM. Dose limiting toxicity is expected to be myelosuppression, the management of which has improved in recent years. Early in the development of VAL-083, a cumulative IV dose of 125 mg/m$^2$ delivered in a 35 day cycle in combination with radiation was shown superior to radiation alone in brain cancer (Eagan, et al. 1979). In the present study, the cumulative dose in a 33 day cycle ranges from 9 mg/m$^2$ (cohort 1) to 240 mg/m$^2$ (cohort 7). Five dose cohorts, with the highest 33 day cycle cumulative dose of 120 mg/m$^2$, have completed the trial with no drug-related serious adverse events: MTD was not yet reached. Enrollment for cohort 6 (33 day cumulative dose: 180 mg/m$^2$) has been initiated. The final cohort of this study, cohort 7 (33 day cumulative dose: 240 mg/m$^2$), will be initiated subject to no DLT in cohort 6; the results will determine the design of the safety and efficacy registration trial. **Methods:** Open-label, single-arm Phase I/II dose-escalation study in patients with histologically-confirmed initial diagnosis of malignant GBM. The study utilizes a 3+3 dose-escalation design. Patients receive VAL-083 IV on days 1, 2, and 3 of a 21 day cycle. GBM patients previously been treated with surgery and/or radiation, if appropriate, must have failed both bevacizumab and temozolomide, unless contraindicated. Clinical trial information: NCT01478178.

**TPS2110 General Poster Session (Board #70B), Sat, 1:15 PM-5:00 PM**

**GEINO-11: A prospective multicenter, open label, phase II pilot clinical trial to evaluate safety and efficacy of PF-299804 (dacomitinib), a pan-HER irreversible inhibitor, in patients with recurrent glioblastoma with EGFR amplification or presence of EGFRvIII mutation.** *Presenting Author: Juan Manuel Sepúlveda, 12 de Octubre Universitary Hospital, Madrid, Spain*

**Background:** Recurrent GBM has a very poor prognosis and there is an unmet need for new treatment options. EGFR is an attractive therapeutic target for GBM, due to high rates of amplifcation and the growing evidence linking the activation of the EGFR and tumor proliferation, survival, angiogenesis and invasion. Amplification of *EGFR* is reported in approximately 50% of GBM and approximately 50% of these cases are associated with deletion of the extracellular ligand binding domain, the constitutively active mutant protein EGFRvIII. Dacomitinib (DA) is a second-generation, oral, irreversible, pan-HER tyrosine kinase inhibitor active in erlotinib and gefitinib-resistant nonclinical models of lung cancer. **Methods:** This multicenter, 2-stage, open-label, phase II trial aims to assess the efficacy and safety of DA in pts with recurrent GBM with EGFR gene amplification with or without EGFRvIII mutation. DA will be administered orally at a dose of 45 mg/day, until disease progression, unacceptable adverse side effects or study end. Pts at first recurrence will be enrolled onto 1 of 2 cohorts that will be recruited and analysed independently. *Cohort A* will include patients who have EGFR gene amplification and EGFRvIII mutations. *Cohort B* will include patients who have EGFR gene amplification but no EGFRvIII mutations. The primary endpoint is progression-free survival at six months (PFS6m) according to RANO criteria and each cohort will follow a Simon´s 2-stage optimal design (P0 = 15% PFS6m; P1=35% PFS6m; a, b error = 0.1, 0.1). For each cohort, 17 patients will be accrued in the stage 1. Additional 15 patients per cohort will be enrolled in stage 2 if the predetermined PFS6m of at least 3 patients is met in that cohort in stage 1. Secondary endpoints include safety, response rate, OS, duration of response and changes in steroid use. In December 2011 the study protocol received institutional review board approval and in April 2012 the trial commenced enrolment in 12 Spanish institutions members of GEINO.

**TPS2111 General Poster Session (Board #71A), Sat, 1:15 PM-5:00 PM**

**First combined intravenous and intracerebral application of an oncolytic virus, parvovirus h-1, in a phase I/IIa clinical trial in patients with recurrent glioblastoma multiforme (ParvOryx01).** *Presenting Author: Karsten Geletneky, University of Heidelberg, Heidelberg, Germany*

**Background:** The management of glioblastoma multiforme (GBM) is an unsolved problem and medium survival has remained at dismal 15 months. Among alternative treatments is the use of oncolytic viruses which preferentially kill tumor cells. Preclinical work using rat glioma models showed that the oncolytic rodent parvovirus H-1PV was able to cure gliomas after single intratumoral or multiple intravenous injections (K. Geletneky et al. *Neuro-Oncology* 2010), forming the basis for a clinical trial with H-1PV. **Methods:** ParvOryx01 (NCT01301430) is a dose-escalation phase I/IIa clinical trial treating patients with recurrent GBM with H-1PV. The trial has two arms of 9 patients each, subdivided in 3 dose groups of 1E6, 5E7 and 1E9 pfu H-1PV. In arm A patients first receive an intratumoral injection of H-1PV followed by tumor resection and virus injection in the tumor-surrounding infiltration zone 10 days after the first treatment. In arm B patients receive for the first time in a clinical trial a combined intravenous/intracerebral virus injection. At days 1 to 5 half of the designated dose is injected intravenously followed by tumor resection and virus injection in the peritumoral brain as in arm A. Main inclusion criteria are a single and completely resectable recurrent GBM, 18+ years of age, confirmed diagnosis of GBM (WHO IV), failed previous radio- and/or chemotherapy, Karnofsky Performance Score ≥60, commitment to omit exposure to infants < 18 months of age. Patients have to be isolated during treatment (K. Geletneky et al. *BMC Cancer* 2012). Arm A has been completed without DLT. As intratumoral injection in arm A led to asymptomatic systemic exposure to H-1PV, arm B can be conducted at the two higher dose levels only. Due to the lack of DLT the trial was amended with 3 additional patients in arm A receiving a high dose of 5E9 pfu. At the moment patients are recruited for Arm B and high-dose arm A. The trial design allows for the in depth analysis of infected tumor tissue and H-1PV penetration into the tumor after systemic injection. Clinical trial information: NCT01301430.

**TPS2112 General Poster Session (Board #71B), Sat, 1:15 PM-5:00 PM**

**Multidose oxygen therapeutic for radiation sensitization treatment of glioblastoma multiforme.** *Presenting Author: David Brown Wilson, NuvOx Pharma, Tucson, AZ*

**Background:** NuvOx is running a Phase 1b/2 evaluation of dodecafluoropentane emulsion (2% DDFPe) as a radiation sensitizer administered intravenously prior to radiation treatment (RT) in Glioblastoma (GBM) patients. Pre-clinically, DDFPe has been shown to increase tumor pO2 concentration of hypoxic solid tumors with an increase in survival. An NDA for DDFPe was previously to the FDA and considered safe and effective as an imaging agent in over 2200 patients. Subsequently DDFP was found to have 200 times the oxygen carrying capacity relative to hemoglobin, which led to the hypothesis that relatively low doses of DDFPe would be safe and effective at reversing hypoxic conditions and improve the effectiveness of the standard fractionated RT in post-resected GBM patients. **Methods:** This study is intended to determine the safe and effective therapeutic dose for fractionated radiation treatment of GBM. The dosing schedule begins at 0.05cc/kg and escalates to 0.35 cc/kg. The study is in two parts; the first part being dose optimization and the second will be expansion at the optimal dose to include enough patients to establish progression free survival statistics at 6 months post-treatment. Tumor hypoxia will be measured using Tissue Oxygen Level Dependent MRI at proscribed points during the course of therapy along with other molecular, hematologic and biochemical markers indicative of hypoxia. The FDA has granted the right of reference to the NDA submission as an imaging agent and provided guidance for the development strategy for DDFPe as an oxygen therapeutic. Elevated tumor pO2 provides a background for more efficient RT in solid tumors. Data will be presented regarding the status of enrollment, residual tumor size and relative oxygenation during treatment, changes in tumor size, as well as hematologic, and other indicators of safety and efficacy as a consequence of DDFPe administration. Ethics Committee approval was granted as of the preparation of this abstract and dosing will begin very soon. The intent of this presentation is to delve further into the study design as well as present data regarding the pharmacokinetic parameters and biomarker determination reflecting tumor oxygenation data collected thus far.

**2500** **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**A phase I/IIa study evaluating the safety, efficacy, pharmacokinetics, and pharmacodynamics of lucitanib in advanced solid tumors.** *Presenting Author: Jean-Charles Soria, Gustave Roussy, Villejuif, France*

**Background:** Lucitanib is a potent, oral inhibitor of the tyrosine kinase activity of FGFR1/2, VEGFR1-3 and PDGFRA/B. These well-described signaling pathways are essential for tumor growth, survival, migration, and angiogenesis. Further, several tumor types, including carcinoma of the breast, demonstrate amplification of FGF-related genes. Currently, there are no approved drugs for patients (pts) with molecularly defined FGF-aberrant (*FGFR1* or *FGF3/4/19* amplified) tumors. **Methods:** The first in human 3-part study is evaluating oral lucitanib monotherapy. Part 1 employed a 3+3 ascending cohort design in pts with advanced solid tumors to establish a recommended dose for further study. Parts 2 and 3 evaluated safety and efficacy of lucitanib in pts with FGF aberrant or angiogenesis sensitive tumors using continuous (part 2) or intermittent schedules (part 3) of administration. **Results:** 109 (part 1 n=17; part 2 n=59; part 3 n=33) pts were treated. Median age was 55 yrs [range 34-80]; 59 female; 105 stage IV; 29 breast cancer, 16 colon, 13 thyroid and 51 other tumor. Doses from 5 mg to 30 mg were evaluated with dose limiting toxicities (DLTs) dominated by VEGF-inhibition related toxicity at the 30 mg dose level. The most common adverse events (all grades, all cohorts, continuous and intermittent dosing schedules) were hypertension (86%), asthenia (73%) and proteinuria (69%). Exposure increased with dose and a $t_{1/2}$ of 25-40 hours, deemed suitable for once daily administration. Clinical activity was observed at all doses tested with durable RECIST PRs in a variety of tumor types. In evaluable FGF-aberrant breast cancer pts, 50% (6 of 12) achieved RECIST PR with a median PFS of 9.4 months for all treated patients. Additionally, 1 of 3 pts with advanced squamous NSCLC experienced SD for 8 months with lucitanib therapy. **Conclusions:** Lucitanib demonstrated promising clinical activity and a tolerable side-effect profile in pts with advanced solid tumors, including those with FGF pathway aberrations. A phase 2 program in FGF aberrant breast and squamous NSCLC is underway in US and Europe. Clinical trial information: NCT01283945.

**2501** **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**Phase 1 study of JNJ-42756493, a pan-fibroblast growth factor receptor (FGFR) inhibitor, in patients with advanced solid tumors.** *Presenting Author: Rastislav Bahleda, Drug Development Department (DITEP), Gustave Roussy Institute, Villejuif, France*

**Background:** JNJ-42756493 is an orally bioavailable FGFR 1, 2, 3 and 4 inhibitor with nanomolar antitumor activity in cell lines and in vivo models with FGFR pathway aberration. **Methods:** This first in human study consists of 3 parts: dose escalation part 1to determine the recommended phase 2 dose (RP2D), dose confirmation part 2 with focus on pharmacodynamic effects, and dose expansion part 3 to evaluate the antitumor activity in selected solid tumors with FGFR gene amplification, mutation or translocation at the RP2D. Biomarkers include tumor tissue genomic profiling, skin/tumor biopsies and soluble serum markers. Toxicity is graded with CTCAE-4 and antitumor activity is assessed using RECIST 1.1. **Results:** As of 27 January 2014, 37 patients have been treated at 6 dose levels (0.5, 2, 4, 6, 9 and 12 mg daily continuously) in part 1. Most common (≥ 20% of patients) adverse events (AEs) were hyperphosphatemia (60%), asthenia (46%), dry mouth (30%), constipation (27%), abdominal pain (22%), stomatitis (22%), and vomiting (22%); all were ≤ Grade 2 in toxicity. Ten (27%) patients had ≥ Grade 3 AEs, and one dose limiting toxicity of Grade 3 AST/ALT elevation was noted at 12 mg dose. Daily 9 mg continuous dosing was declared the RP2D. Seven (19%) patients had serious AEs, including 1 death, but none were drug-related. Six (16%) patients had dose reductions due to drug-related hyperphosphatemia at 9 and 12 mg. Pharmacokinetics were linear, dose proportional and predictable with a half-life of 50 to 60 hours. Exposure dependent increases in phosphate blood levels were observed at doses up to 9 mg, thereafter reaching a plateau. Also a trend was seen for increase in FGF23 and decrease in PTH. Out of 8 patients enrolled to date with FGFR pathway aberration, we observed 1 partial response in a bladder cancer patient with FGFR3-TACC3 translocation and 1 near complete response in an urothelial cancer of renal pelvis harboring FGFR2 truncation at the RP2D. Four patients (2 lung cancer, 1 chondrosarcoma and 1 breast cancer patients with FGFR1 amplification) had stable disease. **Conclusions:** JNJ-42756493 has favorable pharmaceutical properties, with manageable side effects at the RP2D and evidence of antitumor activity. Clinical trial information: NCT01703481.

**2502** **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**Phase 1 open label, dose escalation study of RXDX101, an oral pan-trk, ROS1, and ALK inhibitor, in patients with advanced solid tumors with relevant molecular alterations.** *Presenting Author: Filippo G. De Braud, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

**Background:** RXDX-101 is an oral small molecule inhibitor of TrkA, TrkB and TrkC, as well as ROS1 and ALK, with high potency and selectivity. RXDX-101 has demonstrated potent pharmacological activity in preclinical studies and has the potential to be first-in-class against the Trk family of kinases. This study aims to determine the MTD, PD, PK, and anti-tumor activity in patients with advanced cancer with applicable molecular alterations. **Methods:** Phase 1 dose escalation in patients with advanced solid tumors. Patients were treated with RXDX-101, dosed orally once each day in a 4 day on, 3 day off schedule for 3 weeks, followed by a 7 day rest period, in continuous 28-day cycles. A minimum of 3 patients were enrolled at each dose level. Endpoints include safety, PK, and tumor response by RECIST. **Results:** 17 patients have been treated at 5 dose levels (100, 200, 400, 800, and 1200 mg/m2). RXDX-101 has been well tolerated to date; the MTD has not been reached in this trial. The most common AEs (all grade 1-2), considered possibly treatment-related, included paresthesias, nausea, dysgeusia, and diarrhea. No treatment related grade 3/4 AEs or SAEs were observed; one patient had grade 3 dyspnea considered to be disease-related. No DLTs seen to date. A patient with neuroblastoma (ALK+) has a PR and is in cycle 13. Two patients have prolonged stabilization of their disease and remain on treatment; a patient with NSCLC (ALK+) in cycle 11, and a patient with pancreatic cancer (ROS1+) in cycle 8. PK analysis shows maximum concentrations of RXDX-101 were generally achieved within 2 to 4 hours following dosing. Despite a degree of variability, RXDX-101 exposure (Cmax and AUC) increased with dose, with minimal accumulation following multiple doses. Average terminal half-life was ~21 hours across the dose range of 100 to 400 mg/m2/day, but increased to 32 hours in patients treated with 800 mg/m2/day; steady state was reached within 4-days. **Conclusions:** RXDX-101 has been well tolerated in patients with advanced solid tumors. Continued clinical development is supported by the tolerability and early evidence of antitumor activity in patients with relevant molecular alterations.

**2503** **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**Phase I trial of AZD1775 (MK1775), a wee1 kinase inhibitor, in patients with refractory solid tumors.** *Presenting Author: Khanh Tu Do, Center for Cancer Research, National Cancer Institute, Bethesda, MD*

**Background:** Wee1 tyrosine kinase phosphorylates and inactivates Cdk1, causing G2 cell cycle arrest in response to DNA damage. AZD1775 is a novel inhibitor of Wee1 kinase with single-agent anti-tumor activity in preclinical models. Objectives of this study were to establish the safety, toxicity, maximum tolerated dose (MTD) of single agent AZD1775; determine the pharmacokinetics (PK) of AZD1775; evaluate for target modulation in paired tumor biopsies. **Methods:** Eligible adult patients (pts) had refractory cancers that had progressed on standard therapy; ECOG PS 0-2; adequate organ function. Dose level (DL) 1 was 225 mg BID x 5 doses, q 21d cycles. Dose escalation: 225 mg (DL 2) or 300 mg (DL 3) BID x 5 doses for 2 wks, q21d cycles; 3 + 3 design. Blood sampling for PK and circulating tumor cells (CTCs) occurred on C1D1 and C1D3. Tumor biopsies at MTD were performed at baseline and C1D3 (2-5 hrs post-drug) and were evaluated for pTyr15-Cdk to assess target modulation. **Results:** 18 pts treated; median age 54; median # of prior therapies 4; cancer dx (#pts): sarcoma (8); NSCLC (2); head and neck (3); fallopian tube (1); cervical (1); granulosa cell tumor (1); breast (1); appendiceal cancer (1). One pt with BRCA mutated head and neck cancer had a confirmed PR. Common toxicities were myelosuppression and diarrhea. Two DLTs occurred at DL 3: 1 pt had Gr 4 myelosuppression, developed pneumonia, and died; a second pt had SVT. At the MTD of DL 2, average Cmax was 1650 nM on D3; total exposure on D3 was 2-3 fold higher than on D1. Reduction in phosphorylated Tyr15-Cdk levels was shown in 3 of 5 paired tumor biopsies; quantitation of γH2AX, a DNA damage marker, is ongoing in CTCs and tumor biopsies. **Conclusions:** This is the first single-agent trial of AZD1775 in pts with refractory solid tumors. MTD was established at 225mg BID x 5 doses/week, 2 of 3 wks, with evidence of antitumor activity in a pt with BRCA mutated head and neck cancer. Accrual is ongoing for BRCA+ pts. The accumulation of drug on the BID regimen is consistent with a $t_{1/2}$ of ~ 24 hrs, which supports a QD schedule for future trials. Target modulation was demonstrated in paired tumor biopsies. CTCs were isolated from 2 pts with non-epithelial cancers. Analysis of tumor biopsies and CTCs for γH2AX is ongoing. Clinical trial information: NCT01748825.

**2504** **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**A phase I study of DNIB0600A, an antibody-drug conjugate (ADC) targeting NaPi2b, in patients (pts) with non-small cell lung cancer (NSCLC) or platinum-resistant ovarian cancer (OC).** *Presenting Author: Howard A. Burris, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN*

**Background:** NaPi2b (*SLC34A2*) is a multi-transmembrane, sodium-dependent phosphate transporter expressed in ~70% non-squamous NSCLC and ~90% OC. DNIB0600A is an ADC consisting of a humanized IgG1 anti-NaPi2b monoclonal antibody conjugated to an anti-mitotic agent MMAE that shows anti-proliferative activity in xenograft models . **Methods:** This study evaluated safety and activity of DNIB0600A (0.2-2.8 mg/kg) given by intravenous infusion every 3 weeks (q3w) to pts with NSCLC or platinum-resistant OC. A traditional 3+3 design was used for dose escalation followed by expansion at the recommended Phase 2 dose (RP2D) of 2.4 mg/kg in patients with NSCLC and OC. Tumor NaPi2b expression was evaluated by immunohistochemistry (IHC) in archival tissue. **Results:** As of 10 Dec 2013, 73 pts have enrolled (43 NSCLC; 30 OC), median age 62 (range 39-85), PS 0-1, median number of prior regimens 3 (1-10) in NSCLC, and 5 (1-12) in OC. Pts received a median of 4 (range 1-28) cycles of DNIB0600A. One pt experienced a DLT (Grade 3 dyspnea) at 1.8 mg/kg; no additional DLTs occurred through the maximally administered dose of 2.8 mg/kg. The most common related AEs (all grades) were fatigue (55%), nausea (40%), peripheral neuropathy (36%), decreased appetite (34%), vomiting (26%), and alopecia (19%). Related Grade 3/4 adverse events included neutropenia (8%), anemia, peripheral neuropathy, and pneumonia (each 3%), dehydration, dyspnea, fatigue, hyperglycemia, hyperkalemia, hypertensions, transaminitis, and URI (each 1%)— only dyspnea led to study treatment discontinuation. At the RP2D of 2.4 mg/kg q3w, 7/17 (41%) of IHC 2/3+ pts with OC had confirmed PRs (DoR range 1.4+ to 9.4+ months). In NSCLC, 2/21 (10%) of IHC 2/3+ pts had confirmed PRs (DoR 4.3 and 4.8 months), and 5/21 (24%) had unconfirmed PRs for best response. No pt with an IHC Score of 0 showed clinical response by RECIST criteria. + : censored. **Conclusions:** DNIB0600A administered q3w has an encouraging safety profile and evidence of anti-tumor activity in both OC and NSCLC. These data support Phase 2 development in OC with further clinical evaluation of DNIB0600A in NSCLC. Clinical trial information: NCT01375842.

**2505** **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**A first-in-human phase 1 study of anticancer stem cell agent OMP-54F28 (FZD8-Fc), decoy receptor for WNT ligands, in patients with advanced solid tumors.** *Presenting Author: Antonio Jimeno, University of Colorado Denver, Aurora, CO*

**Background:** The WNT/FZD signaling pathway is implicated in tumor cell de-differentiation and cancer stem cell (CSC) function in numerous cancer types. As a first-in-class recombinant fusion protein, OMP-54F28 binds WNT ligands and blocks WNT signaling through its domain of an extracellular part of human Frizzled 8 receptor (fused to a human IgG1 Fc fragment). In patient-derived xenograft models, OMP-54F28 inhibits growth and CSC frequency, promotes differentiation of tumor cells, and synergizes with chemotherapy in a broad spectrum of malignancies. **Methods:** A 3+3 design was used; OMP-54F28 was given intravenously every 3 weeks. Objectives were determination of maximum tolerated dose (MTD), safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy. **Results:** 25 patients were treated in 7 dose-escalation cohorts (0.5, 1, 2.5, 5, 10, 15 and 20 mg/kg). No further dose escalation was pursued as animal data and PK modeling indicated 10 mg/kg as the target efficacious dose. Most common related Grade 1 and 2 adverse events (AEs; ≥20% of patients) were dysgeusia, decreased appetite, fatigue, muscle spasms, nausea, and vomiting. No related Grade ≥3 AEs were reported. OMP-54F28 had a half-life of ~4 days at ≥10 mg/kg. Consistent with WNT pathway inhibition in bone, 5 patients had doubling from baseline of bone turnover marker β-C-terminal telopeptide (β-CTX), an event that was reversible (β-CTX return to baseline) upon treatment with a single dose of zoledronic acid. PD modulation of WNT pathway genes was shown in hair follicles at ≥2.5 mg/kg. Two desmoid tumor patients have experienced stable disease (SD) for >6 months. 4 of 4 patients at 20 mg/kg with ≥1 on-study tumor assessment continue on study with SD. **Conclusions:** OMP-54F28 is well tolerated up to 20 mg/kg, double the target efficacious dose. PD modulation in bone and hair follicles was observed. Several patients experienced prolonged SD. Dose escalation is completed, and 3 Phase 1b studies are ongoing (pancreas cancer with nab-paclitaxel and gemcitabine, ovarian cancer with carboplatin and paclitaxel, and hepatocellular cancer with sorafenib). Detailed efficacy, safety, PK and PD results will be presented. Clinical trial information: NCT01608867.

**2506** **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**A first-in-human (FIH) phase I study of SAR125844, a novel selective MET kinase inhibitor, in patients (pts) with advanced solid tumors: Dose escalation results.** *Presenting Author: Eric Angevin, Institut Gustave Roussy, Villejuif, France*

**Background:** SAR125844 (SAR) is a potent and highly selective MET kinase inhibitor ($IC_{50}$= 4.2 nM; Ki = 2.8 nM) demonstrated to be effective in MET-driven tumors with a good safety and pharmacokinetics (PK) profiles in preclinical models. This FIH phase I study was designed to determine the maximum tolerated dose (MTD), assess tolerance, PK and pharmacodynamics of SAR. **Methods:** Escalating doses of SAR, using a standard 3+3 escalation scheme, were administered intravenously (IV) every week in solid tumor pts with either high membrane total-MET protein expression or *cMET*-gene amplification. **Results:** 33 heavily pre-treated pts were enrolled: 17M/16F, median age 56 [range 27-75], ECOG-PS 0/1: 10/23 with a variety of solid tumors including 9 colorectal and 9 lung adenocarcinomas. A total of 434 infusions (median 10 [range 1-57]) of SAR was administered across 9 Dose Levels (DLs) ranging from 50 to 740 mg/m$^2$. DLTs were observed in 2 pts during the first 4 weeks consisting in grade (Gr) 3 transaminase increase (TI): 1 pt at 740mg/m$^2$ and 1 pt at 570mg/m$^2$. Recovery was obtained with dose omission and dose reduction. A Gr2 creatinine increase in 1 pt at 740mg/m$^2$ was also taken into account for dose selection. No dose-dependent adverse events (AE) were observed. No Gr≥3 related clinical toxicity was observed. Main drug-related Gr1-2 toxicities included: nausea/vomiting (33.3%), fatigue (18.2%), diarrhoea (15.2%), headache (12.1%), infusion site phlebitis (12.1%), pyrexia (9.1%). Blood exposure PK parameters (AUC and Cmax) increased in proportion with the dose, with a mean clearance of 32.2 L/h associated with a large volume of distribution (528L). Preliminary anti-tumor activity was observed at 570mg/m$^2$ with one partial response among a c*MET-gene* amplification lung adenocarcinoma pt. Seven pts with tumors not harbouring c*MET*-gene amplification experienced a long lasting stabilization over 3 months. **Conclusions:** SAR is well tolerated with early evidence of activity. SAR 570 mg/m$^2$is currently being confirmed in 2 extension cohorts. Clinical trial information: NCT01391533.

**2507** **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**Phase 1, open-label, dose-escalation, and expansion study of ABT-700, an anti-C-met antibody, in patients (pts) with advanced solid tumors.** *Presenting Author: John H. Strickler, Duke University Medical Center, Durham, NC*

**Background:** *MET* amplification (MA) is an oncogenic driver in multiple malignancies. MA is relatively rare in primary tumors (~1-5%), but may increase after treatment with inhibitors of the EGFR pathway or cytotoxic chemotherapy. We are developing ABT-700 (hz224G11), an antagonistic antibody directed against c-Met, as monotherapy in MA tumors. **Methods:** In a 3+3 dose escalation design, ABT-700 was administered at doses of 5, 10, 15 and 25 mg/kg once every 21 days. ABT-700 was then studied at the recommended single-agent dose of 15 mg/kg (chosen based on safety, pharmacokinetic (PK), and biomarker analyses) in 26 pts with advanced solid tumors (10 colorectal, 5 non-small cell lung, 4 ovarian, 3 gastric, 2 esophageal, 1 renal, 1 uterine). MA was assessed by fluorescence in situ hybridization (FISH). **Results:** As of Dec 17, 2013, 41 pts received between 1-12 doses of ABT-700. The PK demonstrated target-mediated disposition with a mean $T_{1/2}$ of 13.9 days at 15 mg/kg. (n=10, cycle 1 of expansion cohort). There were no acute infusion reactions. Common toxicities at the 15 mg/kg dose occurring in ≥15% of pts included constipation (24%), fatigue (24%), decreased appetite (21%), peripheral edema (21%), hypoalbuminemia (17%), hypokalemia (17%) and vomiting (17%). There was no dose limiting toxicity and no maximum tolerated dose identified. By RECIST, 3/5 (60%) of pts with MA tumors had a partial response (1 each ovarian, gastric and esophageal). Among these 3 pts, the duration of response was 19, 23, and 24 weeks, respectively. Two other pts with MA did not respond: 1 pt with papillary renal cancer treated at 5 mg/kg (considered to be sub-therapeutic based on preclinical studies) and 1 pt with gastric cancer treated at 15 mg/kg. Among pts with non-amplified tumors (n=36), no objective responses were observed, however 5 pts had stable disease at the 12 week assessment. **Conclusions:** ABT-700 is well tolerated at the recommended single-agent dose of 15mg/kg. ABT-700 monotherapy has demonstrated promising anti-tumor activity in pts with MA solid tumors. The study has been expanded to identify and enroll pts with MA tumors to better define predictive biomarkers of clinical benefit. Clinical trial information: NCT01472016.

**2508 Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**First-in-human study of AMG 337, a highly selective oral inhibitor of MET, in adult patients (pts) with advanced solid tumors.** *Presenting Author: David S. Hong, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Dysregulation of the MET pathway can promote tumor growth and metastasis, making MET an attractive target for cancer therapy. AMG 337 is an investigational, oral inhibitor of MET kinase activity. This study evaluated the safety, tolerability, pharmacokinetics, and efficacy of AMG 337. **Methods:** Key eligibility: age ≥ 18 years, advanced solid tumors, measurable disease, ECOG ≤ 2, adequate organ function. AMG 337 was administered orally QD or BID on D1 and D3–28. After 1 week without AMG 337 in the absence of dose-limiting toxicity (DLT) or progression, pts resumed AMG 337 until progression. The starting dose of AMG 337 was 25 mg with planned dose escalation of 50-500 mg QD and 100-200 mg BID (3-9 pts/cohort) until the maximum tolerated dose (MTD, highest dose at which < 33% of pts/cohort had a DLT) was reached or the highest dose was tested. Pts with MET overexpression/amplification/mutation could enroll to the highest dose deemed safe at any time. **Results:** As of OCT 2013, 66 pts (QD escalation: 3 at 25 mg, 4 at 50 mg, 14 at 100 mg, 9 at 150 mg, 15 at 200 mg, 8 at 300 mg, 6 at 400 mg; BID escalation: 5 at 100mg, 1 at 150mg; expansion: 1 at 300 mg) received ≥ 1 dose of AMG 337. Median age, 59 (19-79) years; men, 56%; ECOG ≤1, 96%. See Table for treatment-related AEs in >10% pts. 8 pts had DLTs: grade (G) 3 headache (150 mg QD, n=1; 200 mg QD, n=2; 300 mg QD, n=1; 400 mg QD, n=2); G3 hypertension (200 mg QD, n=1); G3 increased amylase (400 mg QD, n=1). QD MTD is 300 mg; BID MTD not yet reached. AMG 337 exposures increased with dose, with minimal accumulation after 28 days; half-life, 4.6-7.4 h. Tumor-response data (central read) were available for 45 pts: 1 complete response (CR), 4 partial response (PR), 28 stable disease (SD), 12 progressive disease (PD). Of these, 8 pts had known MET amplification, 7 with gastroesophageal cancer (1 CR [duration of response, 100 weeks], 4 PR, 1 SD, 1 PD) and one with renal cell carcinoma (PD). **Conclusions:** Responses were observed in a subset of pts with MET-amplified tumors. A dose-expansion phase will enroll up to 50 pts at the MTD (300 mg QD). Clinical trial information: NCT01253707.

| | Grade 1/2 n (%) | Grade ≥ 3 n (%) |
|---|---|---|
| **All AEs** | 34 (51.5%) | 17 (26%) |
| **Headache** | 30 (45%) | 6 (9%) |
| **Nausea** | 21 (32%) | 0 |
| **Vomiting** | 14 (21%) | 0 |
| **Fatigue** | 9 (14%) | 3 (4.5%) |
| **Peripheral edema** | 8 (12%) | 0 |

**2509 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

**Safety/efficacy of MK-8669 (ridaforolimus) plus MK-2206 (AKT inhibitor) in patients with advanced breast cancer with low RAS signature and PTEN deficient prostate cancer.** *Presenting Author: Shilpa Gupta, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

**Background:** The PI3K/AKT/mTOR signaling pathway is aberrantly activated in a variety of cancers. The combination of ridaforolimus (mTOR inhibitor) and MK-2206 may lead to blockade of the PI3K pathway. Methods**:** We conducted a phase 1 study with ridaforolimus + MK-2206 in advanced solid tumors (n=35). Part A defined the maximum-tolerated dose (MTD); part B evaluated preliminary clinical efficacy in enriched breast cancer (BCa) and prostate cancer (PCa) patients. BCa patients had low RAS gene signature; ER+ BCa patients required a high Ki67 index. PCa patients had evidence of PTEN deficiency. Results**:** Eleven patients were in part A and 24 patients were in part B (16 BCa/8 PCa patients). In addition, 1 BCa patient from part A was found to be biomarker-eligible when tested after a clinical response. Total of 124 BCa patients were prescreened: 98 tissues were evaluable; 51were biomarker-eligible. Sixty-eight PCa patients were prescreened: 40 tissues were evaluable; 24 had loss of PTEN. The MTD was 10 mg qd ridaforolimus 5 days/wk + 90 mg weekly MK-2206; 1/17 patients had a dose limiting toxicity of G3 rash. For BCa patients, investigator-assessed objective responses were seen in 2/16 (2 partial responses [PR], 12.5%), centrally read objective responses were seen in 2/14 (2 complete responses [CR], 14.3%), and objective responses using volumetric 3-D assessment were seen in 4/14 (2 PR + 2 CR, 28.6%). In addition, stable disease (SD) ≥6 months was seen in 1 patient by the investigator assessment and 1 patient by central read. For PCa patients, 1/8 patient had SD for > 6 months. No responses were seen in other non-biomarker-tested tumors in part A (although one subject with colorectal cancer had SD for 7 months). At the MTD, the following drug-related AEs were seen: rash (44.4%); stomatitis (38.9%); diarrhea and decreased appetite (27.8%); asthenia, nausea and fatigue (22.2%). Conclusions**:** The combination of ridaforolimus and MK-2206 shows promising activity in BCa patients with low RAS. This combination was overall well tolerated with rash, stomatitis, diarrhea and asthenia being among the most common drug-related AEs. Clinical trial information: NCT01295632.

**2510 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

**Phase I study of oral BKM120 and oral olaparib for high-grade serous ovarian cancer (HGSC) or triple-negative breast cancer (TNBC).** *Presenting Author: Ursula Matulonis, Department of Medical Oncology, Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA*

**Background:** In vivo synergy of the PI3-kinase inhibitor BKM120 and the PARP inhibitor olaparib is seen using a mouse model of BRCA1-related breast cancer (BrCa) and sporadic TNBC (Juvekar et al and Ibrahim et al, *Cancer Discovery* 2012). The PI3kinase pathway is activated in both TNBC and HGSC (www.cancergenome.nih.gov). Olaparib is active in HGSC and germlineBRCA mutation (gBRCAm) ovarian cancer (OvCa) and gBRCAm BrCa. These data were the rationale for this phase I, multi-center study (NCT01623349) combining BKM120 and olaparib in patients (pts) with recurrent HGSC or TNBC. **Methods:** This study has a 3 + 3 design, escalating dose levels (DL) if 0/3 or 1/6 pts have a dose limiting toxicity (DLT) during the first cycle (1st 28 days). Objectives are to determine the MTD and RP2D of daily oral olaparib (tablet formulation) and BKM120, assess toxicities, preliminary activity of this combination, and PK profiles of both drugs. Planned translational endpts include PI3kinase pathway effects, BRCA1 immunostaining/methylation, IL-8/circulating DNA levels, and somatic mutations in BRCA1/2 using FFPE tissue. Eligibility included: recurrent TNBC or HGSC *or* any histology of OvCa or BrCa with presence of a gBRCAmut, PS 0-1, and measurable/evaluable cancer. Prior PARP inhibitor use was allowed. **Results:** 34 pts to date have received study drugs; 9 pts w/TNBC and 25 pts wHGSC. 26 have known gBRCAm. Dosing started at DL1 (BKM120 60 mg and olaparib 100 mg BID); 2 DLTs were observed (1 gr 3 LFTs and 1 gr 3 hyperglycemia). A lower dose (-1) was pursued followed by re-escalation as below. DL 6 was not feasible because of of grade 3 LFTs and grade 3 depression early in cycle 2. Evidence of clinical benefit by RECIST 1.1 was observed on all DL's, and AEs seen were compatible with AE profile of BKM120 and olaparib. Expansion cohorts are accruing. **Conclusions:** Combined BKM120 and olaparib is feasible with evidence of clinical benefit seen at all DL's. Further studies combining PARP and PI3kinase inhibitors are warranted. Clinical trial information: NCT01623349.

| Dose level | Olaparib dose BID (mg) | BKM120 dose qD (mg) | # of patients |
|---|---|---|---|
| **1** | 100 | 60 | 3 |
| **-1** | 50 | 40 | 6 |
| **2** | 100 | 40 | 7 |
| **3** | 150 | 50 | 3 |
| **4A** | 200 | 40 | 3 |
| **4B** | 150 | 50 | 3 |
| **5A** | 300 | 40 | 3 |
| **5B** | 200 | 50 | 3 |
| **6 (DLT dose)** | 300 | 60 | 3 |

**2511 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

**Phase 1 study of the BRAF inhibitor dabrafenib (D) with or without the MEK inhibitor trametinib (T) in combination with ipilimumab (Ipi) for V600E/K mutation–positive unresectable or metastatic melanoma (MM).** *Presenting Author: Igor Puzanov, Vanderbilt-Ingram Cancer Center, Vanderbilt University, School of Medicine, Nashville, TN*

**Background:** D, T, and Ipi are each indicated for treatment of patients (pts) with MM (D+T in *BRAF* V600 mutation–positive MM). D and T can be safely combined and prolong progression-free survival compared with monotherapy. Combining D+T with the CTLA-4 antibody Ipi has the potential to improve treatment outcomes, but the safety profile is unknown. A recent report suggested caution in combining the BRAF inhibitor vemurafenib (V) with Ipi; V+Ipi resulted in G3 elevations of ALT in 6/10 pts leading to study discontinuation (NEJM2013 368; 14). The present study will characterize the safety of D±T+Ipi, select recommended phase 2 doses (RP2Ds), and report efficacy. **Methods:** Pts with stage IIIc/IV *BRAF* V600E /K mutation–positive MM and ≤1 prior treatments are eligible. Dose escalation occurs in cohorts of 3-6 pts followed by expansion (≤30 pts) at the RP2D. At data cutoff (Nov 8, 2013), 10 pts were enrolled: 4 received D+Ipi (doublet), 2 received D only (withdrawn before Ipi treatment), and 4 received D+T+Ipi (triplet). **Results:** Median age of the10 pts was 59.5 y (range, 32-75 y). Doublet: D 150 mg bid + Ipi 3 mg/kg q3w × 4 doses was well tolerated and selected as RP2D. No G3/4 ALT elevations or dose-limiting toxicities (DLTs) were observed. The most frequent adverse events (AEs; ≥2) were chills, fatigue, hand-foot syndrome, pyrexia, and maculopapular rash. Of 4 pts, 2 are ongoing and 2 stopped treatment (disease progression). Pts are currently being enrolled at this dose level in the expansion. Triplet: At current doses (D 100 mg bid/T 1 mg qd+Ipi 3 mg/kg q3w × 4), no G3/4 ALT elevations and 1 DLT (G3 colitis; associated with Ipi) occurred. The most frequent AEs (≥2) were pyrexia, chills, arthralgia, insomnia, and maculopapular rash. One pt had G4 renal insufficiency that reversed rapidly. Of 4 pts treated, 1 stopped treatment (DLT), and 3 are ongoing. Updated safety data and preliminary efficacy data will be presented for both cohorts. **Conclusions:** To date the combinations of D+Ipi and D+T+Ipi appear to be tolerable and have not been associated with significant hepatotoxicity in MM, suggesting differences between BRAF inhibitors when combined with Ipi. Clinical trial information: NCT01767454.

**2512 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

**Combinatorial effect of dabrafenib, trametinib, and adoptive cell transfer (ACT) in an immune-competent murine model of $BRAF^{V600E}$ mutant melanoma.** *Presenting Author: Siwen Hu-Lieskovan, UCLA Johnsson Comprehensive Cancer Center, Los Angeles, CA*

**Background:** The first clinical trial testing the combination of BRAF targeted therapy with vemurafenib and immunotherapy with ipilimumab was terminated early due to significant liver toxicities, possibly due to paradoxical activation of cells with wild type BRAF. MEK inhibitors can potentiate the MAPK inhibition in tumor, while alleviating the unwanted paradoxical MAPK activation. We hypothesized that addition of a MEK inhibitor would enhance the immunosensitization effects of BRAF inhibition, with decreased toxicity. **Methods:** A mouse model of syngeneic $BRAF^{V600E}$ driven melanoma (SM1) was developed. C57BL/6 mice treated with myeloid-depleting total body irradiation and bone marrow transplantation, were implanted SM1 tumors subcutaneously, followed by iv injection of $3x10^6$gp100 peptide-activated pmel-1 splenocytes when tumors reach 4-5mm. For bioluminescent imaging (BLI), splenocytes were transduced with luciferase-transfected retrovirus. Activated splenocytes from wild type C57 BL/6 mice were controls. BRAF inhibitor dabrafenib (D), MEK inhibitor trametinib (T), vehicle (V), or D+T, were given daily by oral gavage from the day of ACT. **Results:** Combination of D+T with pmel-1 ACT showed complete tumor regression, not observed in any other groups, including D+T with control ACT (mean volume of 0 mm2 pmel+D+T, vs 30 C57+D+T, 118 pmel +D on day 20, $P<0.0001$ by one way ANOVA). BLI showed increased T cell infiltration to tumors with the triple combination, compared to ACT with D, or V. Intracellular IFNr staining of the tumor infiltrating T cells did not show significant difference among groups, indicating trametinib is not detrimental to the effector functions. No significant toxicity observed with the triple combination by weight. **Conclusions:** The MEK inhibitor trametinib, when combined with the BRAF inhibitor dabrafenib and ACT immunotherapy, enhances the antitumor effect, with increased infiltration and preserved function of effectors. Our findings support the testing of this combination in patients with $BRAF^{V600E}$ mutant metastatic melanoma.

**2513 Poster Highlights Session (Board #27), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Activity of TGR-1202, a novel once-daily PI3K$\delta$ inhibitor, in patients with relapsed or refractory hematologic malignancies.** *Presenting Author: Howard A. Burris, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN*

**Background:** TGR-1202 is a novel, next generation PI3K$\delta$ inhibitor. Preliminary data from an ongoing Ph I study of TGR-1202 demonstrated clinical activity in patients (pts) with advanced hematologic malignancies. Herein we present updated results from this Phase I, first in human study of TGR-1202. **Methods:** TGR-1202 is administered orally daily following a 3+3 dose escalation design. Previously treated pts with an ECOG PS $< 2$ and confirmed diagnosis of B-cell non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), or other lymphoproliferative disorders are eligible. Endpoints include safety, PK/PD, and efficacy. **Results:** 27 pts have been enrolled to date across 7 dose levels: 50, 100, 200, 400, 800, 1200, and 1800 mg QD. 74% male, ECOG 0/1: 33%/67%, median age of 59 yrs (range: 28-82), median 3 (range: 1-14) prior treatment regimens, and 40% were refractory to prior treatment. Evaluable pts include 7 indolent NHL (iNHL), 11 CLL/SLL, 4 Hodgkin's lymphoma (HL), 2 mantle cell lymphoma (MCL), 1 each of lymphoplasmacytic lymphoma, DLBCL, and atypical hairy cell leukemia. TGR-1202 was well tolerated. Gr$\geq$3 AE's in $>$5% of patients were limited to: dyspnea (7%), neutropenia (15%), rash (7%), and thrombocytopenia (7%). Two DLTs were observed: 1 Gr. 3 rash at 800 mg (pt rechallenged with no recurrence), and 1 Gr. 3 hypokalemia at 1800 mg (pt discontinued due to non-compliance). Notably, no hepatotoxicity has been observed to date. Of the 27 enrolled, 23 were evaluable for efficacy. A significant dose-response relationship was observed. Of the 13 pts treated at $<$ 800 mg QD who completed 2 cycles of treatment, 7 achieved SD. Of 10 pts treated at $\geq$ 800 mg QD: 4/6 CLL pts (67%) achieved a nodal PR, 1/3 Hodgkin's pts (33%) achieved a PR. Nodal reductions occurred rapidly in patients with CLL and were accompanied by marked lymphocytosis. **Conclusions:** TGR-1202 is well tolerated in pts with rel/ref hematologic malignancies with no reported hepatic toxicity and signs of clinical activity at doses $\geq$ 800 mg QD. Enrollment continues in expansion cohorts and at higher dose cohorts. Updated safety, efficacy, PK, and PD data will be presented. Clinical trial information: NCT01767766.

**2514^ Poster Highlights Session (Board #28), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**A phase I/II, first-in-human dose-escalation study of GSK2636771 in patients (pts) with PTEN-deficient advanced tumors.** *Presenting Author: Hendrik-Tobias Arkenau, Sarah Cannon Research Institute UK, London, United Kingdom*

**Background:** GSK2636771 is a potent, orally bioavailable and selective inhibitor of PI3K$\beta$ (0.89 nM), with $>$900-fold selectivity over PI3K$\alpha$/PI3K$\gamma$ and $>$10-fold over PI3K$\delta$. It inhibits AKT phosphorylation and downstream signalling measured as decrease of PRAS40-, GSK3$\beta$-, and RPS6-phosphorylation in PTEN mutant cell lines. **Methods:** An ongoing phase-I/IIa FTIH, open label dose escalation study of GSK2636771, once daily (QD), is being conducted to evaluate safety, pharmacokinetics (PK), pharmacodynamics (PD) and efficacy in pts with advanced tumors deficient in PTEN. The study comprised 3 parts: starting-dose selection, 3+3 dose escalation and phase-2 expansion. Backfill cohorts with mandatory, paired biopsies were opened to evaluate PD. The DLT period was 28 days. **Results:** As of 01/2014, 53 pts (35 m: 18 f, mean 60 yrs) were enrolled into 7 dose escalation (25 -500 mg) and 4 PD cohorts (50-350 mg). In total 5 DLTs (3x hypophosphatemia/ 2x hypocalcemia G3) were observed in 3 pts at 500 mg, defining MTD. AEs $>$20% (all grades) included diarrhoea, nausea, vomiting, fatigue, abdominal pain, anemia and decreased appetite - hyperglycemia was infrequent (4%). $C_{max}$ was reached 4-6 h after single and repeat dosing, with a $t_{1/2}$ of 17-38.6 h across cohorts. Increases in $C_{max}$and AUC(0-24 h) were dose-proportional up to 350 mg, but less than proportional at 400 and 500 mg. Phosphorylated AKT analysis in surrogate tissue among 20 pts across cohorts revealed a $>$50% (18 pts) and $>$80% (12 pts) decrease, 1-10 h post dosing, suggesting target engagement. One pt (prostate) had a RECIST PR and 13 pts had SD, 6 of whom were on study for $\geq$6 months. **Conclusions:** MTD and recommended phase-2 dose of GSK2636771 was 400 mg QD. PD effects on AKT and downstream proteins were observed and early efficacy signals suggest anti-tumor activity in pts with PTEN deficient tumors. Recruitment into the phase-2 part is ongoing. Clinical trial information: NCT01458067.

**2515 Poster Highlights Session (Board #29), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Glyco-optimized trastuzumab-GEX, a novel anti-HER2 monoclonal antibody with ADCC activity: A phase I clinical study in patients with HER2-positive tumors.** *Presenting Author: Hellmut Samonigg, Division of Clinical Oncology, Department of Internal Medicine, Medical University of Graz, Graz, Austria*

**Background:** TrasGEX is a glyco-optimized anti-HER2 antibody. It is designed to fully retain the antigen-binding properties of trastuzumab. It is manifold improved by fully human glycosylation and optimized for its antibody dependent cellular cytotoxicity (ADCC)-mediated anti-tumor efficacy for all FcγRIIIa genotypes as well as for lower HER2 expressing tumors. In vitro studies showed an approximate 10 to 140 fold improvement of ADCC-mediated anti-tumor activity for TrasGEX depending on the level of HER2 expression and of the FcγRIIIa receptor status. **Methods:** This is a phase I, dose-escalation trial of TrasGEX 12 to 720 mg IV flat-dose q3w in patients progressive with advanced or metastatic cancer for whom no effective standard treatment is available and ErbB2 (HER2) positivity (at least 1+). The primary objective of this first-in-human study was to determine the optimal dose and regimen of TrasGEX in the study population. **Results:** A total of 37 patients were treated with up to 720 mg TrasGEX IV flat-dose q3w in 5 cohorts of 3 to 6 patients each and an extension group of 16 patients who received 720 mg. No DLT was observed, the MTD was not reached. Infusion-related reactions (IRR) were the most frequently observed drug-related AEs (51.4%) all but two of grade 1 or 2. Premedication with paracetamol and steroids reduced the frequency and intensity of IRRs. The pharmacokinetic properties were dose-dependent with a maximal half-life of 263 h ± 99 h at 720 mg. One patient with HER2+++ salivary duct tumor developed a CR, two HER2+++ patients reached strong PR (breast: 240 mg, FcγRIIIa allotype: FF, prior trastuzumab non-responder; colon: 480 mg, FV allotype) and 12 (32.4%) showed SD (HER2+ = 4; HER2++ = 3; HER2+++ = 5), of which 40% had been exposed to trastuzumab at earlier therapies. **Conclusions:** TrasGEX at doses of up to 720mg IV q3w was well tolerated. No DLT was observed. The pharmacokinetic properties support a q3w infusion scheme. Evidence of activity was seen in 40.6% of patients, including one CR and 2 PRs in patients with progressive disease at study entry. Clinical trial information: NCT01409343.

**2516 Poster Highlights Session (Board #30), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Phase 1 study of REGN1400 (anti-ErbB3) combined with erlotinib or cetuximab in patients (pts) with advanced non-small cell lung cancer (NSCLC), colorectal cancer (CRC), or head and neck cancer (SCCHN).** *Presenting Author: Kyriakos P. Papadopoulos, START Center for Cancer Care, San Antonio, TX*

**Background:** REGN1400 (R) is a fully human mAb targeting ErbB3. Preclinically, dual inhibition of ErbB3 and EGFR confers augmented antitumor potency. This first-in-human dose escalation trial evaluates safety, tolerability, recommended phase 2 dose (RP2D), pharmacokinetics (PK) and anti-tumor activity of R alone or combined with erlotinib (E) or cetuximab (C) in NSCLC, CRC or SCCHN pts who progressed on prior E or C. **Methods:** This study used a 2-stage 3+3 design. R is administered IV Q2W at doses of 3, 10, or 20 mg/kg. Once safety of a monotherapy R dose level was established, subsequent pts enrolled directly into combination cohorts. Pts tolerating R monotherapy in cycle 1 (2 doses) could receive combination therapy thereafter. E and C are given per label, po QD or IV QW, respectively. **Results:** 22 pts [median age of 61 (range 38-78 yrs); M/F (15/7); ECOG PS 0/1 (5/17)] have been treated with R at 3 (n=8), 10 (n=8), and 20 mg/kg (n=6). Twelve pts received R monotherapy, and 20 pts received R combined with E or C. No protocol defined DLTs were observed. Ten treatment-related AEs (TRAEs) in 4 pts occurred with R monotherapy; 2 pts each had fatigue and vomiting. There were 64 TRAEs in 15 pts during combination therapy including rash (11) diarrhea (8), nausea (4), hypomagnesemia (3), increased AST, dry skin, fatigue and stomatitis (2 each). Four TRAE in 3 pts were grade ≥ 3; stomatitis, increased alk phos and pyrexia. There were 14 SAEs in 8 pts: pneumonia (3) and disease progression (3); and single events including dehydration, fatigue, nausea, pyrexia, respiratory failure, sepsis and vomiting. One pt required E dose reduction after addition of R. A pt with advanced tongue cancer who had progressed on C achieved a PR of 17 weeks duration with R + C. The PK profile of R showed linear and dose proportional kinetics; combination with E or C had no impact on R kinetics. **Conclusions:** R alone or combined with E or C was generally tolerated at the RP2D of 20 mg/kg Q2W. Combination therapy did not appear to potentiate any anti-EGFR related AEs. Enrollment into combination expansion cohorts is ongoing in SCCHN and CRC and will include pts who are naïve to EGFR inhibitors. Clinical trial information: NCT01727869.

**2517 Poster Highlights Session (Board #31), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**A phase 1 study of LJM716 in patients with esophageal squamous cell carcinoma, head and neck cancer, or HER2-overexpressing metastatic breast or gastric cancer.** *Presenting Author: Kerry Lynn Reynolds, Massachusetts General Hospital, Boston, MA*

**Background:** The HER3 receptor is important for maintenance of EGFR- and HER2-driven cancers and targeted therapy resistance. LJM716 is a fully human HER3 monoclonal antibody active in ligand-dependent and -independent preclinical models. **Methods:** This phase 1, first-in-human study is evaluating LJM716 in patients (pts) with squamous cell carcinoma of the head and neck (SCCHN) or esophagus (ESCC) and HER2-overexpressing metastatic breast cancer (MBC) or gastric/gastroesophageal junction cancer (MGC) for which no effective treatment exists. The objective for the dose-escalation part of the study, guided by a Bayesian model with overdose control, was to identify the maximum tolerated dose (MTD), recommended dose for expansion (RDE), and preferred dosing schedule. MTD was based on cycle 1 dose-limiting toxicity (DLT). **Results:** As of October 4, 2013, 54 pts (escalation, n = 24; expansion, n = 30) were enrolled (SCCHN, n = 21; ESCC, n = 15; MBC, n = 10; MGC, n = 8) and treated intravenously for 2 hr at dose levels (DLs) 3, 10, 20, or 40 mg/kg once weekly (QW, n = 48) or 20 mg/kg every 2 wk (n = 6) in 28-day cycles. Twenty-nine pts (54%) had ≥ 3 prior anticancer regimens. LJM716 exposure was approximately dose proportional, with an effective half-life of 10 ± 2 days in 5 evaluable pts, supporting QW dosing. Treatment-related toxicities (≥ 20%, all grades) were diarrhea (39%), chills (24%), infusion-related reactions (24%), and reduced appetite (22%). At ≥ 20 mg/kg QW (n = 48), grade 3/4 events occurred (gastrointestinal disorders [n = 3], hypokalaemia [n =2], asthenia [n = 1], and elevated lipase [n = 1]). One DLT was reported (grade 3 diarrhea and hypokalemia), which resolved after discontinuing LJM716. The MTD/RDE of LJM716 was 40 mg/kg QW. One pt with HER2+ MGC achieved an unconfirmed partial response. pHER3 reduction was seen in 4 of 5 paired tumor biopsies. Minor responses were observed in pts with SCCHN, ESCC, and MBC. Stable disease (SD) was observed in 17 pts (31%), including 1 SCCHN pt with SD > 40 wk. Five pts were on the study > 16 wk. **Conclusions:** LJM716 was well tolerated at DLs up to the RDE of 40 mg/kg QW and demonstrated preliminary evidence of antitumor activity. The study is ongoing. Clinical trial information: NCT01598077.

**2518 Poster Highlights Session (Board #32), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Phase 1 trial of MM-151, a novel oligoclonal anti-EGFR antibody combination in patients with refractory solid tumors.** *Presenting Author: Christopher Hanyoung Lieu, University of Colorado Denver, Denver, CO*

**Background:** MM-151 is a novel oligoclonal anti-EGFR antibody combination designed to overcome key challenges of the EGFR network: ligand redundancy and signal amplification. Preclinical studies confirm MM-151's potent ligand antagonism and signal inhibition. A Phase 1, first-in-human study was initiated to assess the safety, tolerability, pharmacokinetics (PK), immunogenicity and preliminary clinical activity of MM-151 in patients with refractory solid tumors. **Methods:** 57 patients were enrolled on 3 schedules (QW, Q2W, or Q3W) at escalating doses using a standard 3+3 design. Response was assessed per RECIST criteria every 8 weeks. Patients continued on study until disease progression or unacceptable toxicity. **Results:** Results presented are based on preliminary data collected as of Dec. 4, 2013. 57 patients (median age 63 years, 30 male, 27 female) have been enrolled (27 QW, 16 Q2W and 14 Q3W) at escalating dose levels, with 56 evaluable for safety and 31 evaluable for efficacy. The most common tumor types were colorectal cancer (CRC) (26 [46%]), pancreatic cancer (5 [9%]), and NSCLC (6 [11%]). An MTD has not been reached and dose escalation continues. Most adverse events (86%) were CTCAE grades 1 and 2. Infusion related reaction (IRR) was the most common AE (43 [76.8%]); however, this was managed to good effect with premedication and an optimized infusion schedule. The most common non-IRR AEs were comprised of EGFR-pathway toxicities, including rash (45 [80%]), hypomagnesemia (12 [21%]), mucositis (6 [11%]) and diarrhea (13 [23%]). Partial responses were observed in 2 CRC patients and a total of 8 (30% of mCRC) patients had SD for > 4 months (2 of the 8 had SD for 20.1 and 19.8 months, respectively). **Conclusions:** Results to date show that MM-151 has an acceptable safety profile and objective clinical activity in CRC. Clinical trial information: NCT01520389.

**2519 Poster Highlights Session (Board #33), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**A phase 1 dose-escalation study of anti-HER3 monoclonal antibody LJM716 in combination with trastuzumab in patients with HER2-overexpressing metastatic breast or gastric cancer.** *Presenting Author: Seock-Ah Im, Department of Internal Medicine and Cancer Research Institute, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea*

**Background:** TheHER2-HER3 heterodimer, a key driver in HER2-positive tumors, is not completely blocked by available therapies. LJM716 is a fully human anti-HER3 monoclonal antibody (mAb) shown to enhance trastuzumab activity in HER2+ preclinical breast and gastric cancer models. **Methods:** This phase 1, open-label study is currently evaluating LJM716 in combination with trastuzumab in patients (pts) with HER2+ metastatic breast (MBC) or gastric (MGC) cancer who failed previous HER2-directed therapy. The objective for the dose-escalation part of the study was to estimate the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE). **Results:** As of October 4, 2013, 35 pts (escalation, n = 17; expansion, n = 18) were enrolled (MBC, n = 29; MGC, n = 6) and treated intravenously with LJM716 at dose levels (DLs) 3, 10, 20, or 40 mg/kg once weekly (QW) in combination with trastuzumab 2 mg/kg QW. All pts had prior antineoplastic therapy, including 19 (54%) with ≥ 3 regimens. Common treatment-related adverse events (≥ 20%, all grades) were diarrhea (91%), nausea (29%), fatigue (23%), and chills (20%). Grade 3/4 events were observed in 7 pts (20%) at all DLs except 20 mg/kg QW. One dose-limiting toxicity (grade 3 diarrhea) was reported. The MTD/RDE of LJM716 in combination with trastuzumab was 40 mg/kg QW. The pharmacokinetics of LJM716 and trastuzumab was consistent with that of single agents. A reduction in pHER3 was demonstrated in 3 of 4 paired tumor biopsies. Of 30 evaluable pts, 2 partial responses (PRs) were observed: 1 each at 3 mg/kg and 10 mg/kg QW (18 and 40 weeks of exposure, respectively). Both pts with PRs had MBC and documented progression with the most recent prior regimen, which contained trastuzumab. Six additional pts (17%) with MBC demonstrated minor responses (8-27% tumor shrinkage). Twelve pts (40%) with MBC or MGC had stable disease as the best response (> 16 weeks of exposure in 3 MBC pts). **Conclusions:** LJM716 is the first anti-HER3 mAb to demonstrate clinical activity in combination with trastuzumab in trastuzumab-resistant pts. The safety profile of the combination was acceptable up to the highest LJM716 DL tested, 40 mg/kg QW. Clinical trial information: NCT01602406.

**2520^ Poster Highlights Session (Board #34), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Phase I study of the safety and efficacy of INC280 in patients with advanced MET-dependent solid tumors.** *Presenting Author: Yung-Jue Bang, Seoul National University Hospital, Seoul, South Korea*

**Background:** Aberrations in the MET receptor tyrosine kinase pathway occur in various human malignancies (via *MET* amplification, mutation, or overexpression) driving cell proliferation, survival and metastasis. INC280 is a highly selective, oral small molecule MET inhibitor with preclinical activity in human tumor models. This dose escalation study evaluated INC280 in patients (pts) with MET dependent advanced solid tumors. **Methods:** In this Phase (Ph) I study, the primary objective was to determine the MTD or recommended Ph II dose (RP2D), safety and tolerability of INC280; secondary objectives included preliminary antitumor activity and PK. Eligible pts (aged ≥18 years, ECOG PS ≤2) had tumors that were refractory to current therapy or for which no effective therapy exists, and confirmed MET dysregulation (by FISH or IHC). An adaptive Bayesian logistic regression model guided dose escalation in establishing the MTD/RP2D. **Results:** As of December 2, 2013, 33 pts were enrolled in the dose-escalation part of the study (79% male, median age 57 years, 61% PS 0). The most common tumors were hepatocellular carcinoma (HCC; 45%) and colon cancer (21%). Pts were treated in 6 dose cohorts of 100–600 mg BID. DLTs occurred at 200 mg BID, 250 mg BID and 450 mg BID (1 pt each). DLTs were Gr 3 fatigue (2 pts), and Gr 3 serum bilirubin increased. The most frequent drug-related AEs (any grade [Gr]) were decreased appetite (33%), nausea (30%), vomiting (27%), and fatigue (27%). The most common drug-related Gr 3/4 AEs were fatigue (9%), and decreased appetite (6%). INC280 plasma concentration generally increased with dose; mean steady state $AUC_{last}$ and $C_{max}$ following 600 mg BID were 6630 ng/mL and 29800 ng*h/mL, respectively, with a median $T_{max}$of 1.9 h and a mean apparent terminal half-life 3.1 h. Stable disease was reported in 8/33 (24%) heavily pretreated pts. Paired biopsy data showed near-complete phospho-MET shutdown in a colorectal cancer pt at 450 mg BID. **Conclusions:** Oral INC280 BID is well tolerated, and the RP2D is 600 mg BID. Dose expansion is ongoing in pts with NSCLC, HCC, and other tumors. These results suggest INC280 should be further evaluated, and Ph II studies in various solid tumors are ongoing. Clinical trial information: NCT01324479.

**2521^ Poster Highlights Session (Board #35), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Results of the first-in-human phase I trial assessing MSC2156119J (EMD 1214063), an oral selective c-Met inhibitor, in patients (pts) with advanced solid tumors.** *Presenting Author: Gerald Steven Falchook, MD Anderson Cancer Center, Department of Investigational Cancer Therapeutics (Phase I Clinical Trials Program), Houston, TX*

**Background:** MSC2156119J, a selective c-Met inhibitor, suppresses tumor growth in preclinical models. **Methods:** Primary endpoint of this dose-escalation study (3+3 design; NCT01014936): to assess an MTD; secondary endpoints: antitumor activity, safety, pharmacokinetics (PK), and pharmacodynamics (Pd). Pts received 1x/d oral MSC2156119J (21-d cycles; 3 regimens [R]): d1–14 followed by 7-d rest (R1); 3x/wk (R2); or d1–21 (R3). An optimized formulation (OF) was introduced in Aug 2011. **Results:** Up to Nov 25, 2013,126 pts were analyzed (R1=42; R2=45; R3=39). On the initial formulation, doses were escalated from 30–230 mg/d in R1 and 30–115 mg/d in R2; on the OF (R1–3): 30–400 mg/d, 60–315 mg/d, and 300–1400 mg/d. AUC and $C_{max}$ increased with dose; bioavailability was higher with OF. An MTD was not reached. Six pts reported dose-limiting toxicities: asymptomatic G4 lipase and G3 amylase increase (R1; 115 mg/d), G3 nausea and vomiting (R2; 130 mg/d; OF), asymptomatic G3 lipase increase (R2; 60 + 100 mg/d; OF), G3 fatigue (R3; 1400 mg/d; OF), and G3 ALT elevation (R3; 1000 mg/d; OF). Other ≥G3 treatment-related adverse events (trAEs) were G3 peripheral edema (1 pt; R3; 300 mg/d; OF) and G3 AST elevation (1 pt; R3; 1000 mg/d; OF). Most frequent G2 trAEs (R1–3): fatigue (n=8), peripheral edema (n=3), vomiting (n=3), nausea (n=2), asymptomatic lipase increase (n=2), and neutropenia (n=2). 79% of pts had no trAE >G1. Pre- and on-therapy tumor biopsies showed phospho-c-Met inhibition in 19/21 evaluable pts. One pt (esophageal adenocarcinoma) had confirmed partial response (PR); 2 pts (nasopharyngeal and colorectal carcinoma) had unconfirmed PRs. Stable disease (SD) ≥4 mo was seen in 18 pts, incl. 1 pt with SD >32 mo. Based on preclinical PK/Pd models and clinical Pd data, 500 mg was considered biologically active and sufficient to reach ≥95% target inhibition. **Conclusions:** MSC2156119J was well tolerated and showed antitumor activity. Recommended phase II dose (RP2D) is 500 mg 1x/d. Dose escalation was stopped at 2.8xRP2D (1400 mg/d). An MTD was not reached. Additional Pd and biomarker data (c-Met status by immunohistochemistry [IHC] and in situ hybridization) will be presented. Clinical trial information: NCT01014936.

**2522 Poster Highlights Session (Board #36), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**A phase 1b study of combined angiogenesis blockade with nesvacumab, a selective monoclonal antibody (MAb) to angiopoietin-2 (Ang2) and ziv-aflibercept in patients with advanced solid malignancies.** *Presenting Author: Kyriakos P. Papadopoulos, START Center for Cancer Care, San Antonio, TX*

**Background:** Nesvacumab (N) is a selective, human Ang-2 MAb, that potently blocks Ang2 signaling through the Tie2 receptor. Ziv-aflibercept (Z) is a recombinant human fusion protein and a decoy receptor for VEGF-A, VEGF-B, and placental growth factor. In mouse xenograft models, N+Z significantly inhibited tumor growth and angiogenesis compared to either agent alone. **Methods:** This phase 1b dose escalation study seeks to evaluate safety, pharmacokinetic (PK), and pharmacodynamics (PD), to find a recommended phase 2 dose (RD), and to explore antitumor activity of N+Z administered IV Q2W in patients (pts) with advanced solid tumors. Pts were treated at 1 of 5 dose levels of combination treatment [6mg/kg N + 2mg/kg Z (6N/2Z), 12N/2Z, 20N/2Z, 12N/4Z, 20N/4Z]. **Results:** 30 pts [11M/19F; median age 60.5 (range 25-89); ECOG PS 0(5)/1(25)] were enrolled. Two pts experienced DLT: esophageal variceal bleeding (12N/4Z) and prolonged proteinuria (20N/4Z). MTD was not defined. Most common treatment-related AEs (TRAEs) were HTN (19), fatigue (13), proteinuria (8), diarrhea (6), stomatitis (6), and decreased appetite (5). Grade ≥ 3 TRAEs were hypertension (11), proteinuria (2) and fatigue (1). Proteinuria was dose related, but resolved with dose modification. Four pts discontinued treatment due to AE: rectal obstruction, skin ulcers, esophageal variceal bleeding, and fatigue. Two pts achieved PR: 1 pt with CRC previously treated with bevacizumab (32+ wk) and 1 pt with OvCa (19 wks);15 patients achieved disease control with median duration of 29 wks; 7 pts experienced SD ≥16 wks. Across all dose levels, the PK and resulting systemic exposures of both N and Z were not affected by co-administration of the 2 agents. Each agent appeared linear and dose-proportional over the Q2W dosing interval. Total circulating serum Ang2 and VEGF appeared saturated following treatment at all dose levels. **Conclusions:** Co-administration of N+Z in patients with advanced cancer is generally well tolerated. TRAEs were as expected for anti-VEGF therapy. Enrollment into expansion cohorts with a planned dose of 20N/4Z with and without chemotherapy is ongoing. Clinical trial information: NCT01688960.

**2523 Poster Highlights Session (Board #37), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Evaluation of CNS and peripheral antitumor activity of ANG1005 in patients with brain metastases from breast tumors and other advanced solid tumors.** *Presenting Author: Nancy U. Lin, Dana-Farber Cancer Institute, Boston, MA*

**Background:** ANG1005 consists of 3 paclitaxel molecules covalently linked to a proprietary 19 AA peptide that targets the LRP1 receptor. This receptor is highly expressed on endothelial cells of the blood-brain barrier, where it mediates transcytosis, and on multiple tumor cells, where it mediates endocytosis. Thus, ANG1005 is both brain-penetrant and tumor-penetrant due to the LRP1-targeting peptide moiety. **Methods:** Ph I: Patients with advanced solid tumors and brain metastases received ANG1005 by IV infusion q3w at escalating doses of 30-700 mg/m$^2$ (n=56), including 20 patients at 650 mg/m$^2$ (MTD). Study objectives included safety/tolerability and overall tumor response (CNS and peripheral). Ph II: Patients with breast cancer brain metastases received ANG1005 by IV infusion q3w at a starting dose of 650 mg/m$^2$ (n=13) or 550 mg/m$^2$ (n=67). Study objectives included independent CNS and peripheral tumor response evaluations as per RECIST 1.1. **Results:** Safety and tolerability of ANG1005 were consistent with a taxane profile. In the Ph I study, 5/27 (18.5%) patients were observed with an overall PR and 11/27 (41%) with SD at doses ≥420 mg/m$^2$. Eighteen of these patients were evaluated for CNS response and 16 for peripheral response, based on unidimensional measurements. In the Ph II study, 80 patients were dosed, with 61 and 33 patients evaluable for CNS and peripheral tumor response, respectively (Table). Peripheral tumor reductions were observed in various metastatic tumor locations, such as liver, lung, bone and lymph nodes. In the Ph I study, 3 patients showed complete lesion disappearance in some of these organs. **Conclusions:** ANG1005 has shown antitumor activity in both CNS and peripheral metastases. Clinical trial information: NCT00539383.

| Study | Ph I: solid tumors (ANG1005-CLN-02) | | Ph II: breast cancer (CP1005B016) | | | |
|---|---|---|---|---|---|---|
| Dose level | ≥420 mg/m$^2$ | | 550 mg/m$^2$ | | 650 mg/m$^2$ | |
| Best response | CNS | Peripheral | CNS | Peripheral | CNS | Peripheral |
| Sample size | n=18 | n=16 | n=51 | n=29 | n=10 | n=4 |
| CR | 0 | 0 | 0 | 1 (3%) | 0 | 0 |
| PR | 4 (22%) | 4 (25%) | 10 (20%) | 7 (24%) | 4 (40%) | 1 (25%) |
| SD | 10 (56%) | 7 (44%) | 31 (61%) | 16 (55%) | 4 (40%) | 2 (50%) |
| PD | 4 (22%) | 5 (31%) | 10 (20%) | 5 (17%) | 2 (20%) | 1 (25%) |

**2524 Poster Highlights Session (Board #38), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**A first-in-human phase I study of VGX-100, a selective anti-VEGF-C antibody, alone and in combination with bevacizumab in patients with advanced solid tumors.** *Presenting Author: Gerald Steven Falchook, Department of Investigational Cancer Therapeutics (Phase I Program), University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Tumoral escape following VEGF-A inhibition may be due to increased VEGF-C.VGX-100 is a novel fully human IgG1λ neutralizing monoclonal antibody targeting VEGF-C, inhibiting its activation of VEGFR-2 & VEGFR-3 receptors. Combination of VGX-100 with bevacizumab may result in synergistic effects by targeting multiple VEGF signalling pathways that mediate angiogenesis and lymphangiogenesis. **Methods:** An open label phase 1 study(NCT01514123) using a 3+3 design was initiated in patients (pts) with advanced solid tumors, ECOG PS 0-1, and adequate organ function. Pts were treated with escalating doses of intravenous VGX-100 monotherapy or combination VGX-100 + bevacizumab in sequential cohorts of 3-6 pts for assessment of safety, maximum tolerated dose (MTD), PK, anti-VGX-100 antibodies, angiogenic biomarkers, and tumor response. **Results:** 43 pts were enrolled and treated; 19 pts with single agent VGX-100 (1-30 mg/kg, QW) and 24 pts with combination VGX-100 (2.5-20 mg/kg, QW) and bevacizumab (5 or 10 mg/kg, Q2W). Overall, the most common grade 1-2 toxicities were fatigue, rash, nausea, anorexia and hypertension. One dose-limiting toxicity of grade 3 hypertension occurred during cycle 1 in a pt at the lowest combination dose level VGX-100 (2.5 mg/kg) and bevacizumab (5 mg/kg); a grade 3 worsening congestive heart failure in another pt was also reported in cycle 3 at dose level VGX-100 2.5 (mg/kg) and bevacizumab (10 mg/kg). At steady state, weekly doses ≥20 mg/kg of VGX-100 exceeded predicted human circulating VEGF-C levels and efficacy exposures in xenograft models. No binding antibodies to VGX-100 were seen. Infusion related reactions grade 1-2 at VGX-100 doses ≥10 mg/kg were controlled by routine premedication allowing escalation to the maximum planned dose of 30 mg/kg weekly; thus a MTD was not reached. A total of 5 of 42 evaluable pts (12%), achieved a best response of durable stable disease ≥4 months. **Conclusions:** VGX-100 alone and in combination with bevacizumab was well tolerated. PK data support weekly dosing. Further clinical evaluation of VGX-100 in combination with chemotherapy and other targeted agents is warranted. Clinical trial information: NCT01514123.

**2525 Poster Highlights Session (Board #40), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Results from the first-in-human (FIH) phase I study of RO5520985 (RG7221), a novel bispecific human anti-ANG-2/anti-VEGF-A antibody, administered as an intravenous infusion to patients with advanced solid tumors.** *Presenting Author: Manuel Hidalgo, START Madrid, Centro Integral Oncológico Clara Campal, Hospital Universitario Norte Sanchinarro, Madrid, Spain*

**Background:** RO5520985 is a novel bi-specific human IgG1 antibody, acting as a dual- targeting inhibitor of the two key angiogenic factors VEGF-A and Ang-2. RO5520985 led to strong inhibition of angiogenesis with enhanced vessel maturation and demonstrated potent tumor growth inhibition, superior to single pathway inhibitors in a panel of preclinical models. **Methods:** This is a 3-part FIH phase I study: Part 1 explores the safety/ tolerability, PK, PD and anti-tumor activity, to establish the recommended phase 2 dose (RP2D) and schedule, part 2 will assess PD effects in tumor tissues and part 3 the efficacy and safety in patients (pts) with rec. ovarian cancer. Results of part I are presented here, where pts were treated on a bi-weekly (Q2W) or weekly (QW) schedule at escalated dose levels (DLs). A Bayesian logistic regression model with overdose control guided the dose escalation. **Results:** 42 pts (18m/24f) were treated on 7 DLs: Q2W 3mg/kg (1pt), 6 (3), 12 (4), 19 (8), 30 (6); QW 10mg/kg (4), 20 (4), 30 (12). Median age: 63 years (range 25-76). Plasma concentrations (Cmax and AUC) increased proportionally, with low inter-individual variability for both schedules. The elimination $t_{1/2}$ was 7-9 days, based on Q2W. DCE-MRI of tumor lesions demonstrated moderate to significant reduction of vascular characteristics in 22/34 pts; within Q2W sustained effects were associated with 30 mg/kg. DW-MRI showed signs of on treatment necrosis and decreased cell density in 7 pts, particularly at 30 mg/kg. Depletion of circulating targets Ang-2 and VEGF-A was evident and apparently independent of dose and schedule. The most frequent AE of any grade (G) were hypertension (50%), asthenia (36%), headache (29%) and fatigue (19%). Most common AE ≥ G3 was hypertension (19%), predominantly associated with the weekly regimen (QW 30% vs. 9% Q2W). One DLT of pulmonary hemorrhage G5 occurred at 19mg/kg Q2W; a MTD was not reached. The progression-free rate at 8 weeks was 67% (Q2W) and 53% (QW). **Conclusions:** The RP2D and schedule was determined at 30mg/kg Q2W, where RO5520985 demonstrated an acceptable safety profile with favorable PK and PD effects. Clinical trial information: NCT01688206.

**2526 Poster Highlights Session (Board #41), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**A phase 1 first-in-human study of XMT-1107, a polymer-conjugated fumagillol derivative, in patients (pts) with advanced solid tumors.** *Presenting Author: Johanna C. Bendell, Sarah Cannon Research Institute/ Tennessee Oncology, Nashville, TN*

**Background:** Fumagillol derivatives are novel anti-angiogenic agents that inhibit methionine aminopeptidase 2 (MetAP2) rather than directly inhibiting VEGF signaling. Clinical development of fumagillol derivatives (e.g. TNP-470) has been limited by CNS toxicities and short-half life. XMT-1107 is a small molecule fumagillol derivative (XMT-1191) conjugated to PHF (Fleximer), a 70 kDa biodegradable, hydrophilic polymer that does not cross the blood-brain barrier. XMT-1107 is hypothesized to decrease CNS exposure to XMT-1191 and lead to prolonged pharmacokinetic (PK) and pharmacodynamic (PD) effect. **Methods:** This study (NCT01011972) explored the maximum tolerated dose (MTD), recommended phase II dose (RP2D), safety, PK, PD and antitumor activity of XMT-1107 as a single agent in pts with advanced solid tumors. XMT-1107 was given IV every 3 weeks at escalating doses using a 3+3 design. **Results:** 52 pts were enrolled in 14 dose cohorts ranging from 6-770 mg XMT-1191 equivalents/ $m^2$. MTD was not reached. Infusion volume limited the maximum administered dose to 770 mg/$m^2$. One DLT of grade 4 thrombocytopenia was seen at 245 mg/$m^2$; Grade 3 (n=4) and Grade 4 (n=3) thrombocytopenia were seen after Cycle 1 at 105 mg/$m^2$ and above. Grade 3 anemia was reported in 3 pts. 2 pts had Grade 3 transaminase elevation. There were 2 cases of ataxia: Grade 3 at 40 mg/$m^2$ in a pt with multiple CNS metastases evaluated as probably not related to study drug; and Grade 2 at 580 mg/$m^2$ evaluated as possibly related to study drug. Otherwise there were no CNS AEs. Free and conjugated XMT-1191 concentrations increased linearly with XMT-1107 dose. Evidence of MetAP2 inhibition was detectable in leukocytes at all dose levels, with complete inhibition throughout the 21 day cycle in 6/7 pts evaluated for PD at doses above 325 mg/$m^2$. 26 pts had a best response of stable disease with 12 pts stable for at least 4 cycles. **Conclusions:** XMT-1107 is well tolerated without significant CNS toxicity. The PK and PD profile supports once every 3 week intravenous dosing. The safety profile and preliminary antitumor effect supports further development in combination with chemotherapy and/or other anti-angiogenic agents. Clinical trial information: NCT01011972.

**2527 Poster Highlights Session (Board #42), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**A phase 1 dose-escalation study of BBI503, a first-in-class cancer stemness kinase inhibitor in adult patients with advanced solid tumors.** *Presenting Author: Scott Andrew Laurie, Ottawa Hospital Cancer Centre, Ottawa, ON, Canada*

**Background:** Targeting cancer stem cells (CSC) may hold significant therapeutic promise. BBI503 is an orally-administered first-in-class multi-kinase inhibitor with potent activity against CSC. Preclinically, potent anti-CSC and broad-spectrum anti-tumor and anti-metastatic activity was seen *in vitro* and *in vivo*. **Methods:** A first-in-man phase 1 dose escalation studyin patients with advanced cancer was conducted to determine safety, tolerability, RP2D, pharmacokinetics and preliminary anti-tumor activity of BBI503. BBI503 was given orally, continuously, in 28-day cycles until disease progression, unacceptable toxicity, or other discontinuation criteria were met. **Results:** Escalating doses from 10 mg to 450 mg once daily were administered to 26 patients. MTD was not reached. BBI503 was well tolerated, with mild GI adverse events, including grade 1, 2 diarrhea, abdominal cramping, nausea, anorexia. Grade 3 diarrhea was observed in 2 subjects at 450 mg once daily. BBI503 exhibited favorable pharmacokinetics with dose-dependent increases in plasma concentration up to 300 mg once daily. Inhibition of cancer stem cell markers was observed in biopsied tumor tissues. Of 20 evaluable patients, 11 (55%) had stable disease (SD) with a median time to progression of 16 wks. Of those patients with SD, tumor regression and/or prolonged stable disease (≥ 16 weeks) were observed in 10 (50% of all enrolled patients) (see Table). Clinical trial information: NCT01781455.

| Diagnosis | Number of patients evaluable | Number of patients with minor regression or SD ≥ 16 wks. |
|---|---|---|
| Colorectal cancer | 5 | 3 |
| Head and neck cancer | 2 | 2 |
| Hepatocellular carcinoma | 2 | 1 |
| Renal cell carcinoma | 1 | 1 |
| Gastric/GEJ adenocarcinoma | 1 | 1 |
| Pancreatic neuroendocrine | 1 | 1 |
| Non-small cell lung cancer | 1 | 1 |

**2528^ Poster Highlights Session (Board #43), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**A phase I study of the single-agent CDK4/6 inhibitor LEE011 in pts with advanced solid tumors and lymphomas.** *Presenting Author: Jeffrey R. Infante, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN*

**Background:** LEE011, an orally bioavailable, highly specific CDK4/6 inhibitor, causes cell cycle arrest and tumor growth inhibition in multiple preclinical models with intact retinoblastoma protein (pRb+). **Methods:** Pts withpRb+ advanced solid tumors and lymphomas were treated with escalating doses of LEE011 on a 21-of-28-d or continuous schedule. Dose escalation was guided by a Bayesian Logistic Regression Model with overdose control principle. Primary objective: to establish the MTD and/or RP2D of LEE011. Secondary objectives: safety, efficacy, PK, and PD. **Results:** As of Jan 17, 2014, 132 pts were treated; 85 during escalation (50–1200 mg/d) and 47 during RP2D expansion. The following results are from dose escalation (data cut-off: July 2, 2013). Ten DLTs were observed in 10 pts: neutropenia (3 pts); asymptomatic thrombocytopenia (2 pts); mucositis, pulmonary embolism, hyponatremia, QTcF prolongation (>500 ms), and increased creatinine (1 pt each). The MTD and RP2D were declared as 900 and 600 mg/d on 21-of-28-d schedules, respectively. The most common study drug-related AEs (all grades) were neutropenia (40%), leukopenia (36%), nausea (35%), and fatigue (27%). G3/4 AEs included neutropenia (19%), lymphopenia (14%), and leukopenia (12%). Asymptomatic QTcF prolongation (>450 ms) was seen at doses ≥600 mg/d: in 10% of pts at 600 mg/d and in 27% of pts at doses >600 mg/d. Plasma exposure increases were slightly higher than dose proportional; mean $T_{1/2}$ at RP2D was 36.2 h. Paired skin biopsies from 40 pts showed reductions of ≥50% from baseline in Ki67 and phospho-pRb in 55% and 42% of samples, respectively. Among 70 evaluable pts, 2 (2.9%; 600 mg/d) had confirmed PRs: 1 pt with *PIK3CA*-mut, *CCND1*-amp, ER+ breast cancer; 1 pt with *BRAF*/*NRAS*-WT, *CCND1*-amp melanoma. SD for ≥4 and ≥6 cycles was seen in 26% and 14% of pts, respectively. **Conclusions:** LEE011 showed an acceptable safety profile, dose dependent plasma exposure, evidence of target inhibition and preliminary signs of clinical activity. The study expansion is confirming safety and efficacy. Further studies are investigating LEE011 as a single agent (neuroblastoma and malignant rhabdoid tumors) and in combination with other agents (breast cancer and melanoma). Clinical trial information: NCT01237236.

**2529 Poster Highlights Session (Board #44), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**A phase I study of DMOT4039A, an antibody-drug conjugate (ADC) targeting mesothelin (MSLN), in patients (pts) with unresectable pancreatic (PC) or platinum-resistant ovarian cancer (OC).** *Presenting Author: Colin D. Weekes, University of Colorado Cancer Center, Aurora, CO*

**Background:** MSLN is a tumor antigen over-expressed in PC and OC. The ADC DMOT4039A is a humanized IgG1 anti-MSLN monoclonal antibody and anti-mitotic agent, MMAE, that shows anti-proliferative activity in xenograft models. **Methods:** This study evaluated safety, PK, and activity of DMOT4039A (0.2-2.8 mg/kg) given every 3 weeks (q3w) to pts with PC or OC. A traditional 3+3 design was used for dose escalation followed by expansion by disease ($2^{nd}$ line in PC) at the recommended Phase 2 dose (RP2D). Anti-tumor response was evaluated per RECIST 1.1, and serum CA19-9 or CA125. Tumor MSLN expression was determined in archival tissue by immunohistochemistry (IHC). **Results:** As of 5 Dec 2013, 49 pts have enrolled (30 PC; 19 OC), median age 63 (range 39-75), PS 0-1, median number of prior regimens 2 (1-7) in PC, and 5 (1-16) in OC. Pts received a median of 3 (range 1-14) cycles of DMOT4039A. The MTD was 2.4 mg/kg, with 2 DLTs at the maximum dose level of 2.8 mg/kg: hyperglycemia (G3) and hypophosphatemia (G3). The most common related AEs (all grades) were fatigue (49%), nausea (37%), diarrhea (29%), vomiting (27%), decreased appetite (22%), abdominal pain, and constipation (both 20%). The majority of AEs were G1-2. Seven related SAEs (fatigue, hyperglycemia, hypophosphatemia, infection, pyrexia, tachycardia, and vomiting) were observed in 2 pts. ADC exposure was dose-proportional over all dose levels. Four pts (8%) had a confirmed partial response (PR), including 1/19 PC (no IHC sample) and 3/10 OC pts (IHC 2+/3+) treated at the RP2D of 2.4 mg/kg q3w. One PC pt without RECIST response showed > 50% decrease from baseline in CA19-9 levels; 7 OC pts showed > 50% decrease in CA125. MSLN expression was IHC 2+/3+ in 64% of in the PC cohort (25 pts), and 91% in the OC cohort (23 pts), in part due to diagnostic selection for enrollment in expansion cohorts. IHC assessment was unavailable for 2 pts with PC with RECIST / CA19-9 response; all patients with OC with RECIST/CA125 responses were IHC 2/3+. **Conclusions:** DMOT4039A administered at 2.4 mg/kg q3w has a tolerable safety profile and encouraging anti-tumor activity in both PC and OC, supporting further evaluation in these diseases. Clinical trial information: NCT01469793.

**2530 Poster Highlights Session (Board #45), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**A phase 1b study of the cancer stem cell inhibitor BBI608 administered with paclitaxel in patients with advanced malignancies.** *Presenting Author: Matthew Hitron, Boston Biomedical, Inc., Cambridge, MA*

**Background:** BBI608 is an oral first-in-class cancer stemness inhibitor which inhibits the Stat3, β-catenin and Nanog pathways. Preclinically, potent, broad-spectrum anti-tumor and anti-metastatic activity was observed *in vitro* and *in vivo,* alone and in combination with other agents. BBI608 with paclitaxel showed marked synergy *in vivo*. In a phase I study, BBI608 monotherapy was well tolerated with encouraging signs of anti-tumor activity and a RP2D of 500 mg BID. **Methods:** A phase Ib dose-escalation study in patients with advanced cancer was undertaken to determine safety, tolerability, RP2D, and preliminary anti-cancer activity of BBI608 plus weekly paclitaxel. BBI608 was administered in 3 escalating dose cohorts (200 mg BID, 400 mg BID, 500 mg BID) in combination with paclitaxel (80 mg/m$^2$ weekly; 3 of every 4 weeks) until progression of disease, unacceptable toxicity, or other discontinuation criteria was met. **Results:** 24 patients were enrolled. The BBI608 monotherapy RP2D could be given in combination with paclitaxel in full dose. MTD was not determined. No new adverse events were observed, and the safety profile was similar to that of each agent as monotherapy. The most common adverse events included grade 1 and 2 diarrhea, abdominal cramps, nausea, vomiting. Grade 3 events related to protocol therapy occurred in 4 patients and included diarrhea, dehydration, and weakness. No significant pharmacokinetic interactions were observed. Disease control (CR+PR+SD) was observed in 10 of 15 (67%) evaluable patients. Of 5 patients with refractory gastric/GEJ adenocarcinoma enrolled, 2 had PR (48% and 45% regressions), 1 had SD with 25% regression, and 2 (who failed prior taxane) had prolonged SD ≥ 24 wks. Tumor regression or SD ≥ 16 wks was also seen in patients with platinum-resistant ovarian cancer (1 of 2), melanoma (2 of 3), bladder CA (1 of 3) and NSCLC (1 of 1). **Conclusions:** This phase Ib study demonstrated that BBI608 and weekly paclitaxel can be safely combined at full dose. Encouraging anti-tumor activity was observed across several tumor types, particularly in patients with gastric and GEJ adenocarcinoma. Clinical trial information: NCT01325441.

**2531 Poster Highlights Session (Board #46), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**ProGem1: A phase I/II study of a first-in-class nucleotide, Acelarin, in patients with advanced solid tumors.** *Presenting Author: Essam Ahmed Ghazaly, Centre for Haemato-Oncology, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom*

**Background:** Acelarin (NUC-1031) is a first-in-class nucleotide designed to overcome key cancer cell resistance by having nucleoside transporter-independent cellular uptake, activity independent of deoxycytidine kinase and being resistant to cytidine deaminase inactivation. **Methods:** The ProGem1 study objectives were to establish the MTD, PK, safety profile and clinical activity of Acelarin in patients with advanced, rapidly progressing treatment-resistant or refractory solid tumours. Acelarin was administered by 10 minute IV injection on a weekly (D1, 8 and 15 of a Q28 schedule), or twice weekly schedule, for 6 cycles. Acelarin doses ranged from 375 to 1000 mg/m$^2$. Compassionate use was allowed after 6 cycles for those benefiting from treatment. **Results:** To date, 29 patients (pts), with a mean age of 57 yrs (range 35-73 yrs), have been enrolled with: ovarian (5), breast (3), colorectal (3), mesothelioma (3), CUP (3), uterine (3), pancreatic (3), cholangiocarcinoma (2), lung (2), and other (2) primary disease. 26 pts had metastatic disease. Pts had received a mean of 2.6 prior lines of therapy (range 1-7). DLTs were: G3 raised AST in 1/6 at 725mg/m$^2$; G4 thrombocytopenia in 1/6 at 750mg/m$^2$; G4 injection site pain in 1 at 1000mg/m$^2$; and G4 thrombocytopenia in 1/6 at 375mg/m$^2$ twice weekly. The most common (>20%) adverse events (AEs) were grade 1-2, and reversible: thrombocytopenia (22%), fatigue (22%), and hypoalbuminaemia (21%). High intracellular levels of the active anti-cancer agent dFdCTP were rapidly achieved and maintained for 24 hours, confirming Acelarin's ability to bypass the key resistance pathways. Responses evaluated by RECIST were: 5 PR (17%); 13 SD (45%); with an ITT Disease Control Rate (DCR) of 62%; and, an OTA DCR of 90% in patients refractory or resistant to standard chemotherapy. All 6 pts who received ≥2 cycles of Acelarin, and were refractory / relapsed on prior gemcitabine, achieved disease control. Disease control in all patients has been durable (range 3 to >12 months; mean 5.8 months). **Conclusions:** Acelarin is a well tolerated, first-in-class nucleotide that has achieved a high, durable Disease Control Rate (ITT 62%; OTA 90%) in a wide range of advanced refractory / resistant cancers. Clinical trial information: NCT01621854.

**2532 Poster Highlights Session (Board #47), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**First-in-human, pharmacokinetic (PK), and pharmacodynamics (PD) phase I study of Debio1143 (AT-406) in patients with advanced cancer: Final results.** *Presenting Author: Herbert Hurwitz, Duke University Medical Center, Durham, NC*

**Background:** Inhibitors of apoptosis proteins (IAPs) modulate multiple processes, including caspases activation and NF-κB signalling. Expression and/or overexpression of IAPs have been reported for a variety of tumour types and are correlated with tumour growth and resistance to apoptosis induced by standard chemo and radiation therapies. The small molecule Debio 1143 (formerly AT-406) is a potent orally-active IAP antagonist able to promote apoptosis in tumour cells by restoring caspase activity, and modulating NF-κB signalling and TNFα effects in various preclinical models. **Methods:** This first-in-human study in patients with advanced cancer used an adaptive design for dose titration. Debio 1143 was given orally once daily on days 1-5 every 2 or 3 weeks. The starting dose of 5 mg was escalated by 100% in consecutively enrolled single patients until related grade 2 toxicity occurred. This triggered expansion to cohorts of 3 and subsequently 6 patients as well as reduction of dose increments to 50%. The MTD was exceeded when any two patients within the same cohort experienced dose-limiting toxicity (DLT). On days 1 and 5, PK and PD samples were taken. **Results:** Thirty-one patients received doses from 5 to 900 mg. Only one DLT (G3 reversible ALT elevation) was reported at 180 mg. Most common adverse events of any grade deemed related to study drug were fatigue (26%), nausea (23%), and vomiting (13%). Average $t_{max}$ and $t_{½}$ were about 1 and 6 h, respectively. Exposure showed inter-individual variability but increased generally proportionally with dose for doses ranging between 80 mg and 900 mg, without accumulation over 5 days. Degradation of cIAP-1 in surrogate tissue was observed at all doses >80 mg. Plasma MCP-1 increased at 3-6 h post-dose and caspase-cleaved fragment of cytokeratin 18 (M30) significantly increased on day 5. Five patients (17%) had stable disease as best response and 1 patient with metastatic melanoma had an 11% reduction in target lesion dimensions. **Conclusions:** The MTD was not reached and 900 mg was the highest tested dose. Debio 1143 was safely administered, with confirmed on-target PD effects at dose level >80 mg and signs of antitumor efficacy. Clinical trial information: NCT01078649.

**2533^ Poster Highlights Session (Board #48), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**VE-BASKET, a first-in-kind, phase II, histology-independent "basket" study of vemurafenib (VEM) in nonmelanoma solid tumors harboring BRAF V600 mutations (V600m).** *Presenting Author: David Michael Hyman, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Low prevalence of V600m in non-melanoma cancers requires a novel trial design to assess the activity of BRAF inhibitors. We undertook a histology-independent, "basket" study of VEM in BRAFV600m-positive cancers (NCT01524978). Six disease cohorts were prespecified, remaining tumors were enrolled to a 7th "all-comers" cohort. Here we present preliminary efficacy and safety data for the non-small cell lung cancer (NSCLC), cholangiocarcinoma (CLC), and Erdheim-Chester disease (ECD)/Langerhans cell histiocytosis (LCH) cohorts. **Methods:** Multicenter Simon 2-stage adaptive design in adult patients (pts; majority pretreated) with metastatic V600m-positive cancers receiving VEM (960 mg bid) until investigator (INV)-assessed disease progression (PD) or unacceptable toxicity. Primary endpoint is INV-assessed response rate (RR) at week 8 (RECIST v1.1). Secondary objectives include overall RR, clinical benefit rate, duration of response, progression-free survival, overall survival, and safety. **Results:** 95 pts have been enrolled (04/2012-12/2013). Median treatment duration (days, range) was 121 (32-449) in NSCLC, 61 (29-451) in CLC, 168 (39-435) in ECD/LCH. In NSCLC, 8/19 pts had unconfirmed partial responses (uPRs) (wk 8, stage II) and 8/19 pts stable disease (SD). 6 uPRs were subsequently confirmed. At stage I CLC analysis, 4/7 pts had SD, 3/7 pts had PD (wk 8). By wk 24, 2 pts converted to PR. At stage I ECD/LCH analysis, 7 pts were enrolled (1 pt not evaluable for response). A confirmed CR was observed in 1/6 pts and SD in 5/6 pts. By wk 16, 2 pts converted to PR. Moving to stage II, 3 further pts have been enrolled, showing 1 SD and 2 PR at wk 8. All 9 evaluable ECD/LCH pts had shrinkage of target lesions, median change (%, range) from baseline was -18% (5-100) at wk 8 and -30% (7-100) at wk 16. Safety data were consistent with prior pivotal VEM studies. **Conclusions:** Histology-independent trials of rare molecularly defined populations are feasible and yield important signals of activity. VEM has promising activity in pts with V600m-positive NSCLC, CLC, and ECD/LCH. Updated efficacy results from all patients will be provided at the time of ASCO. Clinical trial information: NCT01524978.

**2534 Poster Highlights Session (Board #49), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Next-generation sequencing (NGS) in 936 patients (pts) with advanced cancers to prospectively guide clinical trial selection: The Sarah Cannon Research Institute (SCRI) experience.** *Presenting Author: Todd Michael Bauer, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN*

**Background:** With an increasing number of clinical trials testing new molecularly targeted drugs in pts with specific molecular alterations, there is a growing need for comprehensive molecular profiling in community-based practices where nearly 80% of pts in the United States are treated. In October 2012, SCRI launched an initiative to identify molecular alterations with proven or potential therapeutic significance to match pts to mutation-selective clinical trials. **Methods:** Samples from consenting pts were analyzed using NGS (CLIA/CAP laboratory) to detect hotspot mutations in 35 cancer-related genes (1000x average coverage). Results were reported to the treating physician within 12 calendar days, used to inform treatment decisions, and captured in a database to enable correlation with clinical outcomes. **Results:** As of December 31, 2013, 1040 pts consented; 936 (90%) had sufficient material for NGS. At least one mutation was identified in 420 pts (45%). To date, 206 of the 936 pts (22%) have been prospectively enrolled on clinical trials; 91 of these (44%) had no mutations identified, and 12 pts (6%) had non-actionable mutations. One hundred three pts (50%) had actionable mutations. A total of 50 pts (24%) were enrolled to at least one treatment trial of agent(s) matched to their mutation (table, most common genes shown). The remaining 53 pts were enrolled onto trials not matched to genetic alterations (including immunotherapy, 17; antibody-drug conjugate, 8). Response rates and durations will be presented. **Conclusions:** This first effort to prospectively identify and match pts to clinical trials by NGS in a community practice setting establishes a model to facilitate development of therapies targeting actionable mutations. Nearly half of the pts tested had at least one mutation, and depending on the mutation identified, 10-25% enrolled on a matched trial.

| Actionable mutation | Total pts identified (n) | Pts enrolled on any trial | Pts enrolled on a trial matched to mutation |
|---|---|---|---|
| **KRAS** | 167 | 45 (27%) | 17 (10%) |
| **PIK3CA** | 91 | 30 (33%) | 23 (25%) |
| **BRAF** | 39 | 10 (26%) | 7 (18%) |
| **NRAS** | 26 | 8 (31%) | 3 (12%) |
| **FGFR** | 19 | 8 (42%) | 2 (11%) |
| **MET** | 16 | 5 (31%) | 2 (13%) |

**2535 Poster Highlights Session (Board #50), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Phase 1 dose escalation, food effect, and biomarker study of RG7388, a more potent second-generation MDM2 antagonist, in patients (pts) with solid tumors.** *Presenting Author: Lillian L. Siu, Princess Margaret Cancer Centre, Toronto, ON, Canada*

**Background:** RG7388 is an oral pyrrolidine designed as a potent antagonist of MDM2. Preclinical studies demonstrate p53 activation, tumor growth inhibition, & increased life span in xenograft models. **Methods:** A phase 1 study in solid tumor pts was conducted to determine the maximum tolerated dose (MTD), safety, pharmacokinetics (PK), food-effect (FE) & biomarker (BM) activity of RG7388. Administration schedules of once weekly (qwk) x 3, & daily (3 or 5d) every 28d were evaluated. Following initial accelerated titration, a modified continual reassessment method-escalation with overdose control (EWOC) requiring at least 2 DLT evaluable pts per cohort, was used to guide escalation. Enrolment in BM cohorts was initiated at the prior dose level once EWOC was triggered. PK, baseline p53 & MDM2 status, & serum MIC-1 (a marker for p53 activation) were measured for all pts. The FE cohort consisted of 10 pts in a randomized, 3-way crossover, partial-replicate design. In BM cohorts, tumor biopsies were collected pre-dose & during cycle 1 for analysis of p53 activation, anti-proliferative & pro-apoptotic effects of RG7388. Correlative changes in FLT-PET imaging were also assessed. **Results:** Accrual to dose escalation, FE & core BM cohorts is complete: 46 pts enrolled on the qwk schedule (7 dose levels from 100 - 3200 mg qwk x 3); 49 pts enrolled on the daily schedule: 34 pts treated for 5d at 8 dose levels (100 - 1200 mg daily) & 15 pts treated for 3d at 2 dose levels (1000 & 1600 mg daily). Nausea/vomiting & myelosuppression (more frequent in the daily dosing schedule & associated with PK exposure) were the DLTs. MTD per schedule was: 1600 mg bid qwk x 3; 500 mg bid x 3d & 500 mg qd x 5d. Dose-PK exposure was proportional up to 2,400 mg/d; $t_{½}$: ~ 1 d. No major effect of high-fat food on PK exposure was seen. MIC-1 activation was seen at the lowest dose evaluated. Preliminary BM results suggest that p53 activation is greater with 5d dosing than with other schedules at respective MTDs. Stable disease for 17, 22 & 23+ months has been seen in sarcoma pts. **Conclusions:** RG7388 demonstrates p53 activation which may be dose & schedule dependent and warrants further evaluation. Safety, PK, FE, PD & BM results will be presented. Clinical trial information: NCT01462175.

**2536 Poster Highlights Session (Board #51), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Risks and benefits of phase I liver dysfunction studies: Should patients with severe liver dysfunction be included in these trials?** *Presenting Author: Selena Juarez Stuart, The University of Texas Health Science Center at San Antonio, San Antonio, TX*

**Background:** Liver dysfunction studies on novel oncologic agents are necessary to evaluate effects of metabolism and pharmacokinetics, but data regarding risks and benefits of these trials in cancer patients with liver dysfunction is lacking. Our objective was to evaluate clinical benefit rates (CBR), death on study (DOS) rates, and rates of G3/4 toxicity for patients enrolled on liver dysfunction Phase I studies. **Methods:** We performed a retrospective review of non-pediatric Phase I hepatic dysfunction studies in patients with solid tumors from 2003-2013 at a single institution. We report the CBR, defined as response rate (RR) plus rate of stable disease (SD), rates of DOS from all causes, and rates of drug related G3/4 toxicity. **Results:** We analyzed 10 trials involving a total of 126 patients. In 9 of the 10 studies, patients were stratified based on degree of hepatic dysfunction according to the NCI Organ Dysfunction Working Group (NCI-ODWG) criteria. The most common tumor types were colorectal cancer (37%), hepatocellular carcinoma (18%), pancreatic adenocarcinoma (7%), and lung cancer (5%). Median age was 58 years (23-81). Liver dysfunction was from liver metastases in 61% and underlying cirrhosis in 19%. Therapeutic classes included targeted therapies in 7 trials and cytotoxics in 3 studies. The ORR among all patients was 2% (CR 0%/PR 2%). An additional 21% of patients had SD. The overall DOS rate was 15%. Overall G3/4 toxicity rate was 34% with hematologic toxicity being most common (21%). The CBR, DOS rates, and G3/4 toxicity rates were calculated for each group of patients by degree of liver dysfunction (see Table). **Conclusions:** In patients with severe liver dysfunction, CBR from Phase I studies was <1% while risk of death on study was 25%. Therefore, patients with severe liver dysfunction may not be ideal candidates for these types of trials. Further analysis of the data is needed to identify prognostic factors that further predict risk of death on study.

| Degree of liver dysfunction | # of patients (%) | CBR (%) | DOS rate (%) | #cycles completed median (range) | G3/4 toxicity (%) |
|---|---|---|---|---|---|
| **Normal** | 17 (13) | 53 | 12 | 4 (1-62) | 24 |
| **Mild** | 40 (32) | 30 | 10 | 2 (1-26) | 48 |
| **Moderate** | 48 (38) | 13 | 17 | 1 (1-10) | 33 |
| **Severe** | 20 (16) | <1 | 25 | 1 (1-4) | 15 |

**2537 Poster Highlights Session (Board #52), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**A first-in-class, first-in-human phase I trial of KPT-330 (selinexor), a selective inhibitor of nuclear export (SINE) in patients (pts) with advanced solid tumors.** *Presenting Author: Morten Mau-Soerensen, Department of Oncology, Rigshospitalet, Copenhagen, Denmark*

**Background:** KPT-330 is an inhibitor of Exportin 1 (XPO1) that forces the nuclear retention and activation of over 10 Tumor Suppressor Proteins (TSPs) resulting in tumor cell death in preclinical models. **Methods:** KPT-330 was administered orally for 8-10 doses in a 28-day cycles. Cycle 1 was the DLT period. Pharmacokinetic (PK) analyses were performed. XPO1 mRNA, a pharmacodynamic (PDn) marker of XPO1 inhibition, was assessed in blood. Tumor biopsies were performed. Response was evaluated every 2 cycles (RECIST 1.1). All pts had to have documented progressive disease on study entry. **Results:** 103 pts (59/44 M/F; median age 61 yrs; median treatment regimens: 3; ECOG PS 0/1: 24/79) received KPT-330 across 12 dose levels (3 to 65 mg/m$^2$) in dose escalation and expansion cohorts. 2 DLTs (fatigue, dehydration) at 40mg/m$^2$ on the 10-doses/cycle regimen; 1 DLT (nausea) at 35mg/m$^2$ on the 8-doses/cycle (twice weekly, BIW) regimen were noted. Dosing at 65mg/m$^2$ BIW is ongoing (MTD not reached). Grade 3/4 non-DLT, drug related, adverse events (AEs) in cycle 1 in >2 pts: hyponatremia (9%), fatigue (6%), thrombocytopenia (5%), vomiting (4%), anemia (3%), nausea (3%). The most common grade 1/2 AEs in cycle 1: nausea (63%), fatigue (52%), anorexia (42%) and vomiting (37%). The PK and PDn showed dose-dependent increases in $C_{max}$ / $AUC_{0\text{-}inf}$ and XPO1 mRNA increases. Tumor biopsies showed nuclear localization of TSPs (p53, FOXO3A, IkB) and apoptosis induction. Of 87 response evaluable pts, 3 partial responses were observed in colorectal cancer (KRAS mutant), melanoma (BRAFwt) and ovarian adenocarcinoma (OvCa) pts. Stable disease (SD) was noted in 39 pts, with 12 pts for ≥6 months. Five of 5 evaluable pts with hormone and chemotherapy refractory prostate cancer (HRPC) achieved SD; all pts still on study 70-240+ days. Nine of 13 evaluable pts with squamous head and neck cancer (HNCa) achieved SD with 7 on study 75-290+ days. **Conclusions:** Oral KPT-330 has a manageable toxicity profile and prolonged dosing is feasible. Preliminary signals of durable antitumor activity were observed. The recommended dose for phase 2 is ≥50mg/m$^2$ BIW. Phase 2 studies in HNCa, OvCa, and HRPC are planned. Clinical trial information: NCT01607905.

**2538 General Poster Session (Board #1), Sun, 8:00 AM-11:45 AM**

**Relationships between occurrence of chills and clinical outcome during NGR-hTNF therapy.** *Presenting Author: Alessandra Bulotta, Department of Oncology, Istituto Scientifico San Raffaele, Milan, Italy*

**Background:** NGR-hTNF, a selective antivascular agent, quickly and transiently modulates the release of systemic cytokines/chemokines. Intravenous infusion of NGR-hTNF is characterized by onset of an early on-target adverse effect consisting of short-lived chills **Methods:** The impact of the onset of chills over treatment on the clinical outcome was assessed by a pooled analysis of individual patient data from 7 phase II trials. Dataset included 336 patients who had received NGR-hTNF 0.8 $\mu$g/m$^2$ every 3 weeks (q3w) or weekly (q1w) as single agent (mesothelioma, colon and liver cancer) or combined with doxorubicin (ovarian cancer, sarcomas and SCLC) or with platinum-based regimen (NSCLC). In all trials, tumor response by RECIST criteria was assessed q6w until disease progression. To mitigate guarantee-time bias, onset of chills was treated as a time dependent covariate in Cox models fitted to estimate unadjusted and adjusted hazard ratios (HR). Endpoints of interest were progression free survival (PFS) and overall survival (OS). Median follow-up time was 26.9 months **Results:** 204 patients (61%) experienced chills on treatment, while 132 (39%) did not, with rates of all-grade events ranging from 40% to 76% among different trials (p=0.008). According to severity, 64% of patients had grade 1, 34% grade 2 and 2% grade 3. By timing of chills appearance, 88% occurred over the first six weeks and 12% later. Incidence was higher with q1w than with q3w dosing schedule (70% vs 56%; odds ratio, 1.78; p=0.02). Baseline characteristics (chills vs no-chills groups): median age, 63 vs 61; male, 58% vs 42%; PS ≥ 1, 67% vs 33%; prior lines ≥ 1, 66% vs 34%. Among baseline factors, logistic regression analysis retained only previous treatment associated with higher incidence of chills (odds ratio, 2.0; p=0.003). Onset of chills, used as a time-varying covariate, significantly correlated with improved PFS (HR=0.79; 95% CI, 0.69-0.91; p=0.001) in multivariable analysis adjusted for baseline factors and stratified on trial. Occurrence of chills remained also independently associated with better OS (HR=0.88; 95% CI, 0.79-0.99; p=0.03) **Conclusions:** Early onset of chills on treatment with NGR-hTNF may be associated with more prolonged clinical benefit Clinical trial information: NCT00994097 and others.

**2539 General Poster Session (Board #2), Sun, 8:00 AM-11:45 AM**

**Phase I trial of FOLFIRI in combination with sorafenib and bevacizumab in patients with advanced gastrointestinal malignancies.** *Presenting Author: Joleen Marie Hubbard, Mayo Clinic, Rochester, MN*

**Background:** Sorafenib inhibits various pro-angiogenesis pathways including PDGFR-B, a factor associated with resistance to anti-VEGF therapy. A previous phase II trial in patients with chemorefractory metastatic CRC demonstrated a 63% disease control rate with a combination of bevacizumab (BEV) and sorafenib. This phase I trial sought to determine the MTD of BEV and sorafenib combined with standard cytotoxic therapy for advanced gastrointestinal (GI) cancers. **Methods:** Patients with advanced GI malignancies appropriate for irinotecan-based therapy were enrolled (14 with CRC, 3 gastroesophageal). A standard 3 + 3 design was used with 3 escalating sorafenib dose levels (DL): (1) 200 mg po daily, days 3-7, 10-14; (2) 200 mg po twice daily, days 3-6, 10-13; and (3) 200 mg po twice daily, days 3-7, 10-14. FOLFIRI: irinotecan 180 mg/m$^2$ d1, leucovorin 400 mg/m2 d1, 5-fluorouracil (FU) bolus 400 mg/m$^2$ d1, 5-FU infusion 2400 mg/m$^2$d1-2 and BEV 5 mg/kg d1. 1 cycle = 14 days. **Results:** Seventeen pts were enrolled, median age of 56 (range 32 and 81). Two pts were replaced, as they did not complete DLT evaluation, leaving 15 evaluable pts. Four evaluable pts at DL1 and 6 pts at DL2 had no DLTs. At DL 3, the first cohort of 3 pts did not experience any DLTs. In the second cohort of 3 pts, 2 pts experienced DLTs (asymptomatic G3 hypophosphatemia, G3 dehydration and diarrhea). MTD was determined to be DL2: sorafenib 200 mg PO twice daily, days 3-6, 10-13 combined with FOLFIRI and BEV at standard doses. Of the 15 evaluable pts, 4 pts had PR, 8 pts had SD as best response, 1 pt had PD, and 2 pts discontinued treatment prior to first tumor assessment. The median number of cycles was 12 (range 1 - 46). Three pts with CRC had disease control > 12 months. **Conclusions:** The MTD of this regimen is sorafenib 200 mg PO twice daily, Days 3-6,10-13 combined with standard doses of FOLFIRI and BEV. Dual VEGF inhibition combined with cytotoxic therapy may provide prolonged disease stabilization for select patients with advanced GI malignancies. Clinical trial information: NCT01383343.

**2540 General Poster Session (Board #3), Sun, 8:00 AM-11:45 AM**

**Phase 1 first-in-human (FIH) study of nesvacumab (REGN910) a fully human and selective angiopoietin-2 (Ang2) monoclonal antibody (MAb): Results from hepatocellular carcinoma (HCC) cohort.** *Presenting Author: Robin Kate Kelley, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

**Background:** Nesvacumab (N) is an Ang2 selective, human MAb that potently blocks signaling through the Tie2 receptor, inhibiting tumor angiogenesis and growth. In mouse xenograft models of human solid tumors, N inhibits tumor growth. In the dose-escalation (DE) portion of this trial [JCO 31, 2013 (suppl; abstr 2517)] anti-tumor activity (significant decline AFP) was observed in a patient (pt) with HCC, prompting expansion in this indication. **Methods:** Safety and anti-tumor activity are reported from all pts with HCC treated in the FIH trial in DE and expansion phases combined. In DE, single agent N was administered IV Q2W at 1 of 5 dose levels starting at 1 mg/kg; HCC expansion at 2 doses, 12, and 20 mg/kg Q2W, were studied. **Results:** 15 pts with HCC were enrolled: [11M/4F; median age 69 (range 24-82); ECOG PS 0=6/1=9; prior sorafenib 60%]. Dose levels were: 1 (n=1), 12 (n=6) and 20 mg/kg (n=8). Median number of doses administered was 8 (range 1-23). No pts experienced protocol defined DLTs. Most common adverse events (AEs) (all/related) were fatigue (8/5), diarrhea (5/0), decreased appetite (4/2), dizziness (4/0), nausea (4/2), abdominal pain (3/1), vomiting (3/1), back pain (3/0) and dyspnea (3/0); 9 grade ≥3 events reported in 7 pts, of which 3 events were assessed as treatment related: abdominal pain, infusion-related reaction, and retinal detachment, each reported in a single pt. One pt treated with 20 mg/kg experienced a non-severe lower GI bleed, assessed as not treatment related. No objective responses were observed. Two pts experienced a ≥ 50% decline in AFP (1 pt >90%). Nine of 15 pts achieved best response of SD (median duration 24 wks); 6 pts achieved SD for ≥ 20 wks. Notably, 5 of 8 pts treated at 20 mg/kg achieved best response of SD; median duration of 40 wks. **Conclusions:** Single-agent N up to 20mg/kg Q2W was generally tolerated in pts with HCC, with primarily mild and moderate AEs, independent of dose. SD occurred in 60% of pts across doses, with prolonged SD at highest dose. The safety profile supports combination with chemotherapy and/or other anti-angiogenic agents. Expansion in pts with HCC receiving N in addition to sorafenib is ongoing. Clinical trial information: NCT01271972.

**2541 General Poster Session (Board #4), Sun, 8:00 AM-11:45 AM**

**Pharmacodynamic activity of the AKT inhibitor AZD5363 in patients with advanced solid tumors.** *Presenting Author: Paul Elvin, AstraZeneca Oncology Innovative Medicines, Macclesfield, United Kingdom*

**Background:** AZD5363 is an ATP competitive small molecule inhibitor of AKT1, AKT2 and AKT3 and is currently in phase 1 and 2 clinical trials in breast, gynaecological and prostate cancer. In pre-clinical tumour xenograft models, AZD5363 inhibited the phosphorylation of AKT substrates PRAS40 and GSK3$\beta$ in tumour tissue. **Methods:** Tumour biopsies were obtained from patients with advanced solid tumours in Western and Japanese phase 1 studies. Pharmacodynamic activity of AZD5363 in formalin fixed paraffin embedded tumour tissue was measured by immunohistochemistry (IHC) for total and phospho-AKT, phospho-PRAS40 and phospho-GSK3$\beta$ using commercially available antibodies. IHC was quantified by H-score (sum of % tumour cells with 0=negative; 1=weak; 2=moderate; 3=strong staining) based on the results from 3 sections for each antibody. Inhibition of PRAS40 phosphorylation in hair follicles obtained 4 hours after dosing was measured by immunofluorescence and quantified by image analysis. **Results:** Paired tumour biopsies at baseline and after approximately 2 weeks dosing were obtained from patients on continuous and intermittent dosing schedules. Inhibition of GSK3$\beta$ and PRAS40 phosphorylation of >30% or >50% respectively was seen in 4/7 (GSK3$\beta$) and 2/8 (PRAS40) tumours at tolerated doses of AZD5363. Phospho-AKT was increased in 4/7 (AKT-Thr308) and 4/5 (AKT-Ser473) tumours commensurate with the mechanism of action of AZD5363. Hair follicle PRAS40 phosphorylation was reduced by >50% in 22/71 patients and showed evidence of an exposure related response with an IC50 of 2$\mu$M total plasma concentration. Blood glucose also demonstrated an exposure response relationship with maximum glucose concentration correlating with drug plasma $C_{max}$. **Conclusions:** Inhibition of AKT substrate phosphorylation in tumour biopsies from advanced cancer patients with a range of solid tumours was qualitatively comparable to that observed in preclinical models showing tumour growth inhibition at clinically achievable exposures. Clinical trial information: NCT01226316; NCT01353781.

**2542 General Poster Session (Board #5), Sun, 8:00 AM-11:45 AM**

**A first-in-human study of AMG 780, an angiopoietin-1 and -2 (ANG1/2) inhibitor, in patients (pts) with advanced solid tumors.** *Presenting Author: Afshin Dowlati, Case Western Reserve University and University Hospitals Seidman Cancer Center, Cleveland, OH*

**Background:** AMG 780 is a fully human monoclonal antibody binding Ang1/2, thereby inhibiting their interaction with Tie2. This first-in-human study evaluated AMG 780 in advanced solid tumors. **Methods:** Pts (≥ 18 yrs) received open-label AMG 780 IV Q2W until pts progressed, developed intolerable toxicities, or withdrew consent. Doses (0.1, 0.3, 0.6, 1.2, 2.5, 5, 10, 20, 30 mg/kg) were escalated in a 3 + 3 design. Primary endpoints were dose-limiting toxicities (DLTs), treatment-emergent adverse events (AEs), and pharmacokinetics (PK). Secondary endpoints included tumor response per RECIST and tumor vascularity ($K^{trans}$, IAUC) measured with DCE-MRI. The profile of circulating angiogenic factors was an exploratory endpoint. **Results:** 44 pts were enrolled (n = 3 – 9 per cohort; 25 males; mean age [SD] = 61 [9] yrs). Three DLTs occurred (0.6 mg/kg, gr 3 thrombocytopenia; 10 mg/kg, gr 3 proteinuria; 30 mg/kg, gr 3 pericardial effusion; all n = 1). The most frequent AEs were hypoalbuminemia (n = 16; gr ≥ 3, n = 1), peripheral edema (n = 13; gr ≥ 3, n = 0), fatigue (n = 12; gr ≥ 3, n = 1), and decreased appetite (n = 12; gr ≥ 3, n = 0). The most common gr ≥ 3 AEs were blood alkaline phosphotase increase (n = 4) and hyponatremia (n = 3). No treatment-related deaths occurred. At 30 mg/kg, a maximally tolerated dose was not identified. PK was nearly dose-linear. Mean terminal half-life was 8 – 12 days. Steady state was reached after three doses. Of 31 evaluable pts, six pts had stable disease (SD); one pt had SD lasting > 6 months. Twenty pts had progressive disease. Of 16 pts with DCE-MRI data, $K^{trans}$ for 6 pts and IAUC for 5 pts decreased > 20% at week 5 postdose relative to baseline. No $K^{trans}$or IAUC responses occurred prior to reaching the 0.6 mg/kg cohort. Levels of soluble vascular cell adhesion molecule-1 (sVCAM-1) and placental growth factor (PLGF) levels increased and soluble kinase insert domain receptor (sKDR) decreased with higher AMG 780 doses. Circulating angiogenic factors did not correlate with tumor response. **Conclusions:** Results suggest that AMG 780 IV Q2W is tolerable up to 30 mg/kg. Based on safety and PK, additional trials of AMG 780 at 20 – 30 mg/kg monotherapy or combined with targeted agents or chemotherapy are warranted. Clinical trial information: NCT01137552.

**2543 General Poster Session (Board #6), Sun, 8:00 AM-11:45 AM**

**A comparative study of circulating biomarkers of anti-VEGF therapy in phase II trials in advanced hepatocellular carcinoma (HCC) patients (pts).** *Presenting Author: Lipika Goyal, Massachusetts General Hospital Cancer Center, Boston, MA*

**Background:** Sorafenib, a multikinase inhibitor of VEGFR, remains the only approved systemic therapy in HCC. Several other anti-VEGFR agents have either failed or continued in phase III trials. Despite the extensive efforts in developing antiangiogenic agents in HCC, no biomarker currently exists for appropriately selecting patients with HCC for antiangiogenic therapy. We performed a comparative study of circulating biomarkers in single arm, phase II studies of sunitinib, cediranib and ramucirumab in pts with advanced HCC. **Methods:** Clinical trial design and outcomes have been previously reported (PMID 19470923, 23362324, 24088738). Peripheral blood was obtained prior to and at various time points after treatment and was analyzed for circulating biomarkers using multiplex ELISA. **Results:** A total of 54 pts were analyzed in this study: sunitinib (S) (n=33), cediranib (C) (n=12), and ramucirumab (R) (n=9). Compared to baseline, monotherapy with all three agents increased the Day 14 circulating levels (Day 14 level/baseline level) of PlGF (S, 3.1; C, 3.4; R, 3.5) and VEGF (S, 2.1; C, 1.3; R, 2.0) and decreased those of soluble VEGFR2 (S, 0.7; C, 0.8; R, 0.7). In exploratory correlative studies, high baseline and on-treatment levels of soluble VEGFR1 – an endogenous inhibitor of VEGF and PlGF – were associated with poor outcomes for all three treatments. Other biomarkers, including angiogenic molecules and inflammatory cytokines, showed differential kinetics and no significant associations with clinical outcomes. **Conclusions:** Exploratory studies from phase II trials of pts with advanced HCC who received sunitinib, cediranib, or ramucirumab suggest that circulating PlGF, VEGF, and sVEGFR2 are potential pharmacodynamic and response biomarkers of anti-VEGF therapy. They also show that soluble VEGFR1 may be a useful biomarker of resistance to anti-VEGF therapy. These biomarker candidates need to be validated in large prospective studies.

**2544 General Poster Session (Board #7), Sun, 8:00 AM-11:45 AM**

**A phase 1b study of the anticancer stem cell agent demcizumab (DEM), pemetrexed (PEM), and carboplatin (CARBO) in pts with first-line nonsquamous NSCLC.** *Presenting Author: Mark James McKeage, University of Auckland, Auckland, New Zealand*

**Background:** Delta-like ligand 4 (DLL4) activates the Notch pathway and is important for cancer stem cell (CSC) survival. DEM is a humanized $IgG_2$ anti-DLL4 antibody that has been shown to inhibit tumor growth, decrease CSC frequency & cause dysfunctional sprouting of new vessels resulting in an antiangiogenic effect in human tumor xenograft models. **Methods:** Pts received DEM (2.5, 5 or 7.5 mg/kg), PEM 500 mg/m$^2$ & CARBO (AUC = 6) every 3 weeks followed by maintenance DEM or PEM (7.5 mg/kg cohort) every 3 weeks until progression. The objectives were to determine the MTD, safety, efficacy, immunogenicity, pharmacokinetics & biomarkers of Notch signaling. **Results:** Thirty-two pts were enrolled; 6 received 2.5 mg/kg, 20 received 5 mg/kg & 6 received 7.5 mg/kg of DEM. Related AEs in > 20% of pts were: nausea (53%), fatigue (47%), hypertension (41%), vomiting (34%), edema (28%), neutropenia (25%), & increased B-type natriuretic peptide (BNP) (22%). Increased BNP values are an early indicator of the cardiac effects of DEM & mildly elevated values are being used to initiate cardioprotective therapy with an ACE inhibitor or carvedilol. Two pts receiving 5 mg/kg developed reversible pulmonary hypertension & heart failure on days 167 and 183, respectively. As a result, DEM treatment was limited to 63 days in subsequent cohorts. One of 28 (4%) evaluable pts had a RECIST CR, 12 (43%) had a PR and 11 had SD. The Kaplan Meier estimated median progression free survivals for the 2.5, 5 and 7.5 mg/kg pts were 4.8, 6.3 and 4.4 months, respectively. Five pts who discontinued the study for a reason other than progression (3 continued to receive CARBO & PEM off-study) were progression-free through Day 223+, 243+, 457+, 497+, 680+ and a sixth pt (who continued to receive CARBO & PEM off-study) progressed at Day 850. **Conclusions:** DEM, CARBO & PEM was generally well tolerated with nausea, fatigue & hypertension being the most common drug related toxicities. The duration of DEM therapy is being limited to 63 days due to cardiopulmonary toxicity which was observed following more prolonged administration. Encouraging early clinical activity has been observed. Enrollment is ongoing and updated results will be presented. Clinical trial information: NCT01189968.

**2545 General Poster Session (Board #8), Sun, 8:00 AM-11:45 AM**

**Effect of sulfasalazine (SSZ) on cancer stem-like cells (CSCs) via inhibiting xCT signal pathway: Phase 1 study in patients with gastric cancer (EPOC 1205).** *Presenting Author: Kohei Shitara, National Cancer Center Hospital East, Kashiwa, Japan*

**Background:** CD44 is an adhesion molecule expressed in cancer stem-like cells (CSCs). Our group recently reported that CD44 splice variant (CD44v) is expressed in CSCs and interacts with xCT, a glutamate-cystine transporter, keeping high levels of the intracellular reduced glutathione (GSH). Thus, CSCs with a high expression of CD44v have an enhanced capacity for GSH synthesis and defense against reactive oxygen species (ROS), resulting in resistance to various therapeutic stresses. Sulfasalazine (SSZ) as an xCT inhibitor suppressed CD44v-dependent tumor growth and increased sensitivity to cytotoxic drugs in vivo study. **Methods:** A phase 1 dose escalation study in patients with advanced gastric cancer was conducted to determine the optimal dose. SSZ was given fourth-daily oral administration with 2 weeks as one cycle. A 3+3 escalation was used to evaluate a MTD. Tumor tissues were obtained pre- and post SSZ administration to evaluate expression of CD44v and intra-tumor level of GSH by immunohistochemistry and boron doped diamond microelectrode, respectively. **Results:** Eleven patients were dosed from 8 g to 12 g/day; median age: 71 years (61-78); median number of prior chemotherapies: 3 (1-4). There was two DLT of grade 3 anorexia and nausea among patients who were treated with 12 g/day. One additional patients required frequent dose interruption with grade 2 anorexia and nausea. Therefore 12g/day was judged as MTD. No DLT was observed among patients with 8g/day. Patients with high CD44v expression patientss achieved reduced expression of CD44v after the administration of SSZ for 2 weeks as well as decreased level of GSH. The individual variability of SSZ exposure was explainable in terms of the genotypes of ABCG2 and NAT2 which influence SSZ pharmacokinetics. **Conclusions:** Optimal dose of SSZ was considered as 8g/day. Down regulation of CD44v expression and decreased level of GSH migh be a pharmacodynamic marker of drug-on-target effect and mode of action of SSZ for CSCs, which warrants further investigation for combination with chemotherapy or other targeting agents. Clinical trial information: UMIN000010254.

**2546 General Poster Session (Board #9), Sun, 8:00 AM-11:45 AM**

**A phase I extension study of BBI608, a first-in-class cancer stem cell (CSC) inhibitor, in patients with advanced solid tumors.** *Presenting Author: Derek J. Jonker, The Ottawa Hospital Research Institute, Ottawa, ON, Canada*

**Background:** BBI608, an orally-administered first-in-class cancer stemness inhibitor, blocks CSC self-renewal and induces cell death in CSC as well as non-stem cancer cells by inhibiting Stat3, $\beta$-catenin, and Nanog pathways, and has shown potent anti-tumor and anti-metastatic activities preclinically. In a phase 1 study, BBI608 demonstrated tolerability as well as signs of anti-cancer activity in patients with solid tumors. This phase 1 extension study evaluated a formulation designed for pivotal trials to determine pharmacokinetics (PK) in patients with advanced cancer. **Methods:** Day 1, patients received a single 500mg dose of the original BBI608 formulation (DP1). Day 4 and 8, a higher strength capsule designed for pivotal trials (DP2A) was given with fasting then fed conditions. DP2A was then administered daily until disease progression or unacceptable toxicity. Endpoints were safety, PK and preliminary anticancer activity. **Results:** DP2A was evaluated in 24 patients. No significant difference in plasma exposure between DP1 and DP2A, and no significant food effect were observed. Nine patients received BBI608 DP2A 4 h apart (DP2A-4h) only, and 15 patients received BBI608 DP2A 500 mg bid 12 h apart (DP2A-12h). Despite PK equivalence to DP1, DP2A-4 h was associated with higher frequency of gastrointestinal (GI) adverse events (AE) than observed in the prior study, including diarrhea, abdominal cramps, nausea/vomiting, anorexia, and fatigue. In contrast, DP2A-12 h had fewer GI AE and was selected for the extension study. Among 15 patients receiving DP2A-12h, prolonged stable disease was observed in 2 of 7 non-CRC patients (ovarian cancer-16 wk and anal squamous cancer-32 wk) and among 8 CRC patients enrolled, disease control was observed in 67% evaluable for response (4/6), with progression free survival and overall survival at 17 weeks and 39 weeks, respectively. **Conclusions:** The recommended dosing regimen for BBI608 in pivotal trials was determined to be about 500 mg bid q12 h. Signs of anticancer activity were observed in patients with CRC, anal squamous carcinoma, and ovarian cancer. Clinical trial information: NCT01775423.

**2547 General Poster Session (Board #10), Sun, 8:00 AM-11:45 AM**

**Characterization of isolated, uncomplicated neutropenia–related to the CDK4/6 inhibitor palbociclib.** *Presenting Author: Angela DeMichele, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA*

**Background:** Palbociclib (P), an oral, selective, reversible CDK4/6 inhibitor induces transient G1 arrest in hematopoietic stem/progenitor cells (HSPC), without DNA damage or apoptosis in preclinical studies. In patients (pts) with advanced malignancy, P had activity in several tumor types, but neutropenia was dose-limiting. We sought to characterize the incidence and patterns of myelosuppression to determine if the mechanisms observed preclinically were reflected in the clinical experience. **Methods:** Data from 2 phase 2 studies of single agent P in pts with advanced RB+ tumors (UPenn, NCT01037790) and liposarcoma (MSKCC, NCT01209598) were analyzed. Dose (125 mg P), schedule (3 wks on/1 wk off) and safety assessments (baseline, weekly cycle 1 and d 1 of subsequent cycle) were identical. Both trials required P be held for > grade (Gr) 3 myelosuppression until resolved to < Gr 2. **Results:** 140 patients with breast (36%), sarcoma (21%), germ cell (21%), colon (13%), gastric (7%) tumors were enrolled. Neutropenia, anemia and thrombocytopenia rates in cycle 1 by Gr are shown. Mean absolute neutrophil count was 4.98, 4.24, 2.15, 1.62 and 1.86 at weeks 1, 2, 3, 4 and 5, respectively, reflecting time to nadir. Time to Gr3 neutropenia was 3 wks in 11%, 4 wks in 30%, 5 wks in 14%. Recovery occurred after brief dose delay. Neutropenia led to dose interruption in 19% of pts in cycle 1 and 8% had Gr3 neutropenia on day 1/cycle 2. Despite the high rate of Gr 3/4 neutropenia (39%), only 1 episode of neutropenic fever occurred (in setting of disease progression), with no infections or use of G-CSF. Mucositis was rare and <Gr2. Concurrent Gr3 anemia or thrombocytopenia were rare (6% and 15% respectively). **Conclusions:** Frequent, isolated and uncomplicated neutropenia in patients receiving P is consistent with preclinically observed quiescence but not death of HSPC and little effect on differentiated myeloid cells. The lack of clinical morbidity or pancytopenia suggests that P-induced neutropenia is short lasting, reversible and may be managed conservatively. PK data will be reported to confirm the relationship between ANC and drug exposure. Clinical trial information: NCT01037790, NCT01209589.

| Grade | Neutropenia | Anemia | Thrombocytopenia |
|---|---|---|---|
| 2 | 31% | 28% | 14% |
| 3 | 36% | 4% | 9% |
| 4 | 3% | 0 | <1% |

**2548 General Poster Session (Board #11), Sun, 8:00 AM-11:45 AM**

**Association of hypertension and proteinuria with overall survival in solid-tumor patients treated with anti-VEGF drugs in the MARS study.** *Presenting Author: Vincent Launay-Vacher, Service ICAR - Pitie-Salpetriere Hospital, Paris, France*

**Background:** MARS is a multicentric, noninterventional, prospective study which first reported the high prevalence of both baseline and de novo hypertension (HTN) and proteinuria (Pu) in patients receiving bevacizumab (Bev) or sunitinib (Su) (Gligorov J et al. SABCS 2013; Ray-Coquard I et al. ASCO GI 2014; Ray-Coquard I et al. ASCO GU 2014; Goldwasser F et al. ECC 2013; Launay-Vacher V et al. ASCO 2013). **Methods:** It included 1,124 patients, all naive of any previous anti-VEGF treatment. A First Renal Assessment was performed before the anti-VEGF was started with periodic follow-up for 1 year (Renal Follow-up Plan). Univariate (UA) and multivariate analyses (MA) tested the associations of HTN and Pu, at baseline or de novo, with overall survival (OS) (pre-planned). **Results:** De novo Pu was not associated with reduced OS, in any group. De novo Pu was a statistically significant prognostic factor for better OS in Bev-treated CRC, both in UA and MA. Baseline Pu was prognostic of reduced OS in Bev-treated LC, in UA but not in MA. HTN, either at baseline or de novo, was not found to be associated with OS, in any group. **Conclusions:** HTN was not associated with OS in our study, even in RCC Su-treated patients. De novo Pu, determined with a urinary dipstick, which is neither invasive nor costly, could be an easily accessible prognostic factor of better OS in Bev-treated CRC. Bev treatment in LC patients experiencing de novo Pu should be discussed since it can be prognostic of poorer OS.

| | UA | | | | | MA | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | BC + Bev (n=402) | CRC + Bev (n=195) | RCC + Su (n=112) | LC + Bev (n=101) | OC + Bev (n=79) | BC + Bev (n=402) | CRC + Bev (n=195) | RCC + Su (n=112) | LC + Bev (n=101) | OC + Bev (n=79) |
| **Baseline** | | | | | | | | | | |
| **HTN** | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |
| **Pu** | NS | NS | NS | p=0.03 HR=2.46 [1.09-5.54] | NS | NS | NS | NS | NS | NS |
| **De novo** | | | | | | | | | | |
| **HTN** | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |
| **Pu** | NS | p=0.004 HR=0.31 [0.14-0.67] | NS | NS | NS | NS | p=0.01 HR=0.57 [0.39-0.83] | NS | NS | NS |

Abbreviations: HTN: hypertension; Pu: proteinuria; BC: breast; CRC: colorectal; LC: lung; OC: ovarian cancers; RCC: renal cell carcinoma; Bev: bevacizumab; Su: sunitinib; NS: not significant (p>0.05).

**2549 General Poster Session (Board #12), Sun, 8:00 AM-11:45 AM**

**Correlation between phase 2 clinical trial design and subsequent phase 3 outcome.** *Presenting Author: Annette E. Hay, NCIC Clinical Trials Group, Kingston, ON, Canada*

**Background:** Randomized phase 2 (RP2) trials have been postulated to better predict phase 3 (P3) outcome than single arm trials. The aim of this study was to determine which characteristics of P2 trials that led to the conduct of P3 trials are associated with a positive P3 outcome. **Methods:** Randomized P3 trials testing systemic therapy in patients with malignancy, published in English from 2007 to 2012, were identified through a Medline search. Those of superiority design which cited P2 trials contributing to development of the experimental arm were included. Detailed information regarding design and outcome of P2 and P3 trials was extracted in duplicate. Discrepancies were adjudicated by a third investigator. Positivity was defined as statistical difference between arms for primary endpoint in P3. P2 trials reporting that a pre-stated numeric or statistical target had been met were deemed positive. Statistical analysis was performed using the Generalized Estimating Equation model correlating P2 features with P3 outcome, accounting for any P3 duplication. **Results:** Of 189 eligible P3 trials 19% were in hematologic malignancies and 81% in solid tumors. The primary outcome was positive in 79 (42%). These were supported by 336 P2 trials (range 1 - 9 per P3 trial); 66 of which were RP2s (29 selection, 21 control, 3 discontinuation, 7 phase 2/3 and a combination of these in 6). RP2 trials were not associated with P3 positivity (see Table, p = 0.44). Positive P2 outcome correlated with positive P3 outcome (p = 0.031). P2 trial features found not to be predictive of P3 outcome included primary endpoint, sponsorship, sample size, similarity in patient population and therapy. **Conclusions:** We did not find RP2 more predictive than single arm trials. When designing P2 trials consideration should be given to the increased resources required to conduct RP2 studies and anticipated gain for a given disease.

| 336 phase 2 trials | | | | | | | |
|---|---|---|---|---|---|---|---|
| 66 randomized phase 2 | | | | 270 single-arm phase 2 | | | |
| 35 positive | | 31 not positive* | | 102 positive | | 168 not positive* | |
| P3 positive 14 (40%) | P3 negative 21 (60%) | P3 positive 8 (26%) | P3 negative 23 (74%) | P3 positive 50 (49%) | P3 negative 52 (51%) | P3 positive 61 (36%) | P3 negative 107 (64%) |

* Numeric or statistical target not stated or not met.

**2550^ General Poster Session (Board #13), Sun, 8:00 AM-11:45 AM**

**Final results from the phase I study expansion cohort of Debio0932, an oral HSP90 inhibitor, in patients with solid tumors.** *Presenting Author: Pierre Fumoleau, Centre Georges François Leclerc, Dijon, France*

**Background:** Debio 0932 is an oral second-generation heat shock protein 90 (HSP90) inhibitor that has shown promising anti-tumor activity against a broad range of tumors in pre-clinical models. Here we report the results of the expansion part of a phase I study in patients with advanced solid tumor or lymphoma. **Methods:** 30 patients with solid tumor comprising 15 NSCLC patients were enrolled. Patients received the treatment schedule derived from results of the dose-escalation phase, i.e. 1000 mg Debio 0932 QD. PK samples were taken on day 1 and 29. CYP 450 and transporter polymorphism was explored through Affymetrix DMET chip. **Results:** The safety population analysis considered 39 patients of which 30 enrolled into the expansion phase and additional 9 patients treated at 1000 mg QD during the dose-escalation phase of the study. Adverse events (AEs) and the frequencies are reported in the Table. The main reason for treatment withdrawal was progressive disease. Although no objective tumor responses were seen, 25% of patients evaluable for response achieved disease stabilization including long lasting episode. Moreover, one partial metabolic response (PMR) and 5 (41.7%) stable metabolic response (SMR), were observed in the 12 NSCLC evaluable patients. Debio 0932 was rapidly absorbed and subjected to first-pass metabolism. Large inter-individual variability in PK was observed but without evidence of food effect. No obvious relationship between PGx and PK was evidenced. **Conclusions:** Debio 0932 mono-therapy at recommended dose of 1000mg was generally well tolerated and showed signs of activity in patients with advanced NSCLC and can be administered in fed state. A phase I-II study of Debio 0932 in combination with standard of care in NSCLC is ongoing. Clinical trial information: NCT01168752.

| | ALL N=39 | NSCLC N=15 |
|---|---|---|
| **Mean age (range) (yrs)** | 56 (22-74) | 57 (35-70) |
| **Gender M/F [N(%)]** | 23 (59%) / 16 (41%) | 8 (53%) / 7 (47%) |
| **Predominant cancer types (%)** | Lung-NSCLC 38.5% Colorectal 15.4% Kidney 12.8% | |
| **≥ 3 Previous treatment regimes (%)** | 79% | 80% |
| **Days on treatment (range)** | 63 (10-264) | 66 (20-264) |
| **Most frequent AEs (%)** | . | . |
| **Diarrhoea** | 72 % | 80 % |
| **Nausea** | 64 % | 53 % |
| **Decreased appetite** | 62 % | 60 % |
| **Vomiting** | 59 % | 67 % |
| **Asthenia** | 54 % | 47 % |
| **Best overall tumor response (%)** | . | . |
| **SD** | 25 % | 14 % |
| **PD** | 75 % | 86 % |

**2551 General Poster Session (Board #14), Sun, 8:00 AM-11:45 AM**

**Pharmacodynamic assay for evaluation of first-in-class pyruvate kinase-M2 activators in tumors.** *Presenting Author: Payal Khanna, Leidos Biomedical Research Inc., Fredrick National Laboratory for Cancer Research, Frederick, MD*

**Background:** A new class of compounds targets conversion of enzymatically inactive dimeric pyruvate kinase-M2 (PKM2) to an active tetramer complex as a mechanism to tilt the balance between glycolysis and oxidative phosphorylation and reverse the metabolic advantage acquired by tumor cells. The dimer PKM2, which is also a transcription factor, diverts glucose to macromolecular biosynthesis. We developed a pharmacodynamic (PD) assay for PKM2 modulation and evaluated in vivo target engagement using an allosteric PKM2 activator (PKM2a). **Methods:** An experimental PKM2a [N-(4-(4-(2-methoxyphenyl)piperazine-1-carbonyl)phenyl)quinoline-8-sulfonamide] (Kung et. Al., Chem & Biol 2012) was synthesized at NCI. The PD response was determined in H1299 xenografts (n=3/group) dosed daily at 6, 20, and 60 mg/kg for 10 days; tissue samples were collected 2, 6, 24, and 48 hrs post dose 1, 3, and 10. Tumor volumes were recorded biweekly until 27 days after treatment was stopped. A sandwich immunoassay was developed that detects monomer/dimer but not tetrameric PKM2. The assay showed >80% lower PKM2 levels in tumor cell lines treated in vitro with the PKM2a. **Results:** PD analysis showed that the majority of PKM2 (60-80%) was detected in the nuclear fraction of tumor lysates. Compared to controls, nuclear accumulation was decreased by 30-60% between 24 and 48 hrs post dose 10 in the 60 mg/kg treatment group. Changes observed at lower doses or at earlier time points were not significant. Marginal decreases in mean tumor volume (<18%, p=NS) was observed in the 60 mg/kg dose group on 4 and 8 days after treatment. **Conclusions:** Our results show that PKM2 monomers/dimers accumulated in the nuclear fraction suggesting that they may play a role as transcription factors in the model we tested. PKM2 modulation was evident only at the highest dose tested after multiple administrations, and a delayed PD response was consistent with the marginal efficacy observed in this study. Together, these results suggest that sustained modulation of PKM2 with higher doses may be required to reverse the metabolic fate of cancer cells. Importantly, our PD assay provides a critical tool to guide translational studies of PKM2a.

**2552 General Poster Session (Board #15), Sun, 8:00 AM-11:45 AM**

**Risks and benefits of phase 1 oncology trials, 2001 through 2012.** *Presenting Author: Yoko Korenaga Fukuda, MedStar Washington Hospital Center, Washington, DC*

**Background:** The primary objective of phase I clinical trials is to evaluate the tolerability and pharmacokinetics of a new agent. Phase I trials in oncology remain ethically controversial. Our previous analysis from year 1991 through 2002 reported a response rate of 10.6 percent and a toxicity-related death rate of 0.49 percent. An increasing number of molecular targeted agents are under investigation and these results may not reflect current phase I oncology trials. **Methods:** We reviewed all non-pediatric phase 1 oncology trials sponsored by the Cancer Therapy Evaluation Program at the National Cancer Institute between January 1, 2001 and December 31, 2012. We report the rates of response to treatment, of stable disease, of grade 4 toxic events, and of treatment-related deaths. **Results:** We analyzed 286 trials, comprising 8314 participants. All 8314 participants were evaluated for toxic events, whereas 6604 participants were evaluated for response. The overall response rate (complete and partial response) and disease control rate (complete and partial response and stable disease) were higher than in the previous analysis. (13.2 percent vs 10.6 percent, p-value $<$ 0.0001, 52.6 percent vs 34.1 percent, p-value $<$ 0.0001, respectively.) 1651 participants (19.86 percent) experienced at least one grade 4 toxic event that was at least possibly related to the treatment. The overall rate of death at least possibly related to the treatment was 0.99 percent. The overall rates of death due to toxic events and grade 4 toxic events were both higher than in the previous analysis. (1.02 percent vs 0.49 percent, p –value $<$ 0.0001, 19.86 percent vs 14.3 percent, p-value $<$ 0.0001, respectively.) All p-values reported are 2-sided. **Conclusions:** The rates of response and toxicity in non-pediatric phase 1 oncology trials were higher than in the previous analysis and more than 50 percent of patients achieved at least stable disease. The higher disease control rate may be due to greater use of cytostatic molecularly targeted agents. More toxic-related deaths were reported, but this may be because of the change in serious adverse events reporting requirements by the FDA. Rate of death that was probably or definitely related to the treatment remained stable at about 0.2 percent.

**2553 General Poster Session (Board #16), Sun, 8:00 AM-11:45 AM**

**Integrated nonclinical and clinical risk assessment to obviate the need for a dedicated QTc study of ixazomib citrate (MLN9708) in cancer patients (pts).** *Presenting Author: Neeraj Gupta, Takeda Pharmaceuticals International Co., Cambridge, MA*

**Background:** Ixazomib citrate is an investigational oral proteasome inhibitor in phase 3 (P3) clinical development. It is expected to have a favorable cardiac safety profile based on weak in vitro inhibition of the hERG channel ($IC_{50}$ 59.6 $\mu$M) and in vivo nonclinical data. To confirm, serial PK-matched triplicate electrocardiograms (ECGs) were collected in phase 1 (P1) dose-escalation studies to characterize the effect of the active moiety ixazomib (Ix; MLN2238) on QTc intervals and potentially obviate the need for a dedicated QTc study. **Methods:** Data from 245 pts in 2 IV (0.125–3.11 mg/m$^2$, N=125, solid tumor and lymphoma pts) and 2 oral (0.24–3.95 mg/m$^2$, N=120, multiple myeloma pts) P1 studies were included. Mean (range) age was 56.5 (23–86) years; 43% were female. Centrally read 12-lead digital ECGs were used to derive heart rate (HR)-corrected QT intervals using Fridericia's method (QTcF). Relationship between Ix plasma concentration (C) and QTcF was analyzed using linear mixed effects models with fixed effects for day and time to account for circadian variation. **Results:** A safety margin of $>$1700-fold was calculated between the hERG $K_i$ (24.9 $\mu$M) and unbound day 15 $C_{max}$ (14.6 nM) at the fixed P3 dose of 4 mg. Non-clinical dog telemetry studies showed no QT prolongation, or changes in ECGs, HR, or waveform intervals at doses up to 4.2 mg/m$^2$. Linear models relating Ix C to QTcF and RR were developed from clinical data acquired over a wide C range (26% of data $>$mean $C_{max}$ at P3 dose). Ix has no clinically meaningful effect on cardiac repolarization based on the model-predicted mean change in QTcF from baseline, consistent with outlier analyses (Table). There was no relationship between C and RR interval suggesting Ix has no effect on HR. **Conclusions:** Ixazomib citrate has no clinically meaningful impact on QTc or HR. Integrating preclinical cardiac electrophysiology data and clinical C-QTc modeling of P1 data represents an efficient approach in oncology drug development that may obviate the need for a dedicated QTc study.

| QTc mean change from baseline (P3 dose), ms (90% CI) | 0.07 (-0.22–0.36) |
|---|---|
| **QTcF outlier analysis (N=1023), %** | |
| >480 ms | 0.7 |
| >500 ms | 0 |
| Change from baseline >30 ms / >60 ms | 1.6/0 |

**2554 General Poster Session (Board #17), Sun, 8:00 AM-11:45 AM**

**First-in-human, first-in-class phase 1 study of a novel oral multi-AGC kinase inhibitor AT13148 in patients (pts) with advanced solid tumors.** *Presenting Author: Rajiv Kumar, Drug Development Unit at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, UK, London, United Kingdom*

**Background:** Aberrant signaling through the AGC kinases is implicated as a critical driver of multiple cancers. AT13148 is a novel multi-AGC kinase inhibitor, which potently inhibits AKT, P70S6K, PKA and ROCKI/II. Following promising in vivoantitumor activity through mechanisms distinct from specific AKT inhibitors, a phase I trial was initiated. **Methods:** Pts with advanced solid tumors were enrolled onto study using a standard 3+3 dose escalation strategy. AT13148 was given orally on days (D) 1, 3 and 5 of every week, in 28-day cycles. The starting dose was 5mg, with a 4-week dose limiting toxicity (DLT) period. Pharmacokinetic (PK) parameters were assessed after a run-in dose (D1-7) and at cycle (C)2 D1. Pharmacodynamic (PD) biomarkers for AKT signaling were analyzed in tumor, platelet rich plasma (PRP) and hair follicles at multiple timepoints. **Results:** 14 pts were treated with AT13148 (7M: 7F; 4 ECOG 0, 10 ECOG 1). Median age 57y. Median duration of treatment was 40 days (range 25-76). AT13148 was well tolerated with no drug-related toxicities observed. No DLTs have been observed in 9 evaluable pts in 3 completed dose levels (5, 10 and 20mg). PK analysis in 3 pts at 20mg AT13148 demonstrated $C_{max}$ between 18-50nmol/L , with $T_{max}$ of 4h. The average $T_{1/2}$was 24h resulting in a 2 fold increase in exposure on cycle 2. Preliminary PD data in PRP showed no modulation of pAKT, pGSK3$\beta$ or pP70S6K at the first 2 dose levels i.e. 5 and 10mg cohorts. 2 pts currently remain on study in the 20mg cohort. **Conclusions:** AT13148 was well tolerated and showed no drug-related toxicities at 5, 10 and 20mg doses. Preliminary PK and PD data are in keeping with early phases of dose escalation. Dose escalation will continue until a MTD is established. Clinical trial information: NCT01585701.

**2555 General Poster Session (Board #18), Sun, 8:00 AM-11:45 AM**

**A phase I study of ARQ 197 in combination with temsirolimus in patients (Pts) with advanced solid tumors.** *Presenting Author: Amy M. Braden, University of Wisconsin, Madison, WI*

**Background:** Disregulated c-Met activity is implicated in tumor progression and metastasis. Phosporylation of c-Met leads to activation of the PI3K/AKT/mTOR pathway. Preclinical studies demonstrate that combined inhibition of c-Met and mTOR is effective. ARQ 197 (tivantinib) is an inhibitor of c-Met and Temsirolimus selectively inhibits mTOR. This study is designed to determine the maximum tolerated dose (MTD), dose-limiting toxicities (DLTs), adverse events (AEs), clinical activity, and pharmacokinetic (PK) parameters of this combination. **Methods:** This open label phase I study utilizes a 3+3 dose escalation of ARQ 197 (120mg-480mg bid) and Temsirolimus (20-25mg IV weekly) followed by dose expansion at MTD. ARQ 197 is primarily metabolized by CYP2C19. Separate cohorts for dose escalation are incorporated for poor and extensive metabolizers. Cycles are 28 days, except cycle 1 which is 35 days, to evaluate PK interactions. **Results:** 14 pts (median age 60.5 [range 29-71]; 8 male:6 female) were enrolled. The most common malignancies were colorectal (4 pts), ovarian (2 pts) and renal cell carcinoma (2 pts). 3 pts were unevaluable per protocol. 11 evaluable patients were on study a median of 55.5 days (range 15-296). After 3 evaluable subjects there was no DLT at dose level (DL) 1. At DL2, there were 2 DLTs. 1 pt received $<$75% of drug due to grade (gr) 3 hypophosphatemia and gr 3 diarrhea but had baseline diarrhea. A 2$^{nd}$pt had gr 4 neutropenia and gr 3 mucositis. DL 1 was expanded with 3 additional pts without DLT. An amendment with stricter eligibility criteria was approved by CTEP and dose was re-escalated to DL2. 2 additional pts have been treated without DLT. Dose escalation will continue if 1 additional pt at DL2 does not have DLT. The most common AEs at least possibly related to therapy included: fatigue (gr 1-2 in 9 pts), anemia (gr 2 in 7 pts, gr 3 in 1 pt), nausea (grade 1-2 in 8 pts) and diarrhea (gr 1-2 in 6 pts, and gr 3 in 1 pt). 1 pt with ovarian cancer had a confirmed partial response, a decline in CA 125 and remained on study for $>$ 9 months. **Conclusions:** ARQ 197 in combination with Temsirolimus appears to be well-tolerated at biologically active doses. Dose escalation and PK analysis is ongoing. MTD expansion is planned. Clinical trial information: 9145.

**2556 General Poster Session (Board #19), Sun, 8:00 AM-11:45 AM**

**Predicting success in regulatory approval from phase I results.** *Presenting Author: Laeeq Malik, Institute for Drug Development at Cancer Therapy and Research Center, University of Texas Health Science Center, San Antonio, TX*

**Background:** Drug development in oncology is resource intensive and has a high failure rate. In this exploratory analysis, we aimed to identify the characteristics and outcomes of Phase I studies associated with future Food and Drug Administration (FDA) approval or non-approval. **Methods:** Published Phase I studies of anticancer agents between 2000 and 2013 were retrospectively identified by searching PubMed, relevant oncology journals, and the oncologic drugs advisory committee website. Phase I trials of supportive drugs, radiopharmaceuticals, endocrine agents, vaccines, Ib combination studies and agents without Phase III evaluation were excluded. We then examined trial characteristics and outcomes associated with future FDA-approval or non-approval. Fisher's Exact and Chi-square tests were used to compare the potential predictive measures. Responses were classified according to the description in the published study (RECIST or WHO criteria). **Results:** Phase I results of 88 new agents treating a total of 4423 subjects met the eligibility criteria (54 approved and 34 non-approved by the FDA). The median number of patients in Phase I trials of approved and non-approved agents were 44.5 and 32 respectively. A total of 423 subjects had complete responses (CR) and 342 had partial responses (PR). Higher number of PRs ($P<0.001$), PR rate ($P=0.003$) and longer PR duration ($P=0.001$) were predictive of regulatory success. A positive trend toward higher regulatory success was observed for studies with larger study size ($P=0.053$), higher CR rate ($P=0.049$), and number of patients with stable disease ($P=0.047$). **Conclusions:** Approved anticancer agents in hematological and solid organ malignancies demonstrated a higher number, rate and duration of PRs in Phase I trials than non-approved agents. This information might be useful as part of the decision process regarding which agents proceed to later stages of drug development.

**2557 General Poster Session (Board #20), Sun, 8:00 AM-11:45 AM**

**A phase 1 study of phospholipid ether [$^{131}$I]-CLR1404 in patients with advanced solid tumors.** *Presenting Author: Sam Joseph Lubner, University Wisconsin Carbone Cancer Center, Madison, WI*

**Background:** Preclinical data suggest that tumor cells of many types selectively accumulate and retain phospholipid ethers. To capitalize on this, a radiolabeled phospholipid ether [$^{131}$I]-CLR1404 was developed with the goal of improving tumor imaging specificity and as a novel approach to therapy. Experiments with [$^{131}$I]-CLR1404 in mouse models demonstrated safety and efficacy. We conducted a phase 1 study of escalating doses of [$^{131}$I]-CLR1404 in patients with advanced solid tumors. The primary objective of this study was to determine a recommended dose of [$^{131}$I]-CLR1404 for treating advanced solid malignancies. The secondary objectives were to expand the safety and pharmacokinetic profile, determine anti-tumor activity, and obtain tumor imaging with [$^{131}$I]-CLR1404. **Methods:** Patients were first given a dosimetric dose followed by a treatment dose 1-2 weeks later in an algorithmic escalation design. Toxicity follow up included q 7 day lab and clinical assessment. Patients had single photon emission computed tomography (SPECT) scans to assess [$^{131}$I]-CLR1404 biodistribution. **Results:** Twelve patients were enrolled (7 male, 5 female, age range 40-70) at 3 open centers. Two patients withdrew from study before receiving drug; 10 patients (3 colon, 2 breast, 2 prostate, 2 esophagus, 1 ovarian) received protocol therapy. The per-protocol dose-limiting toxicities (DLT) were grade 4 thrombocytopenia (PLT) and grade 4 neutropenia (ANC) at 37.5mCi/m$^2$. For further safety analysis, an intermediate dose level was opened at 31.25 mCi/m$^2$; 2 DLTs (grade 4 PLT, grade 3 ANC with fever) were encountered. Clinical activity was shown with 4 patients with stable disease (SD) up to 6 months. SPECT imaging confirmed selective [$^{131}$I]-CLR1404 accumulation in known tumors. **Conclusions:** At a dose of 31.25 mCi/m$^2$, DLTs were low PLT and ANC. Studies exploring the mechanism(s) of action of [$^{131}$I]-CLR1404 toxicity are ongoing to minimize myelosuppression. Disease-specific studies are also underway to identify patients most likely to benefit from [$^{131}$I]-CLR1404 monotherapy. In this study, there was evidence of [$^{131}$I]-CLR1404 anti-tumor activity (4 pts with SD) and sustained uptake in tumors by SPECT imaging. Clinical trial information: NCT01495663.

**2558 General Poster Session (Board #21), Sun, 8:00 AM-11:45 AM**

**A phase 1 multicenter open-label dose-escalation study of BMS-936561 (MDX-1203) in clear cell renal cell carcinoma (ccRCC) and B-cell non Hodgkin lymphoma (B-NHL).** *Presenting Author: Taofeek Kunle Owonikoko, The Winship Cancer Institute of Emory University, Atlanta, GA*

**Background:** BMS936561 is a fully human monoclonal anti-body conjugate targeting the CD70 transmembrane cell-surface protein highly expressed in ccRCC and B-NHL. The study was designed to determine the safety profile and maximum tolerated dose (MTD) of BMS-936561 in this patient population. **Methods:** This phase 1 study employed an accelerated titration design followed by a 3+3 dose escalation to evaluate the safety, maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of BMS-936561. Patients with advanced ccRCC or B-NHL, $\leq$ 3 prior chemotherapy regimens, ECOG performance status 0-2 were treated with escalating doses of BMS-936561 (0.5mg/kg, 1mg/kg, 2mg/kg, 4mg/kg, 8mg/kg, 15mg/kg) by IV infusion every 21 days in a 42 day cycle up to 17 cycles. Dose limiting toxicity (DLT) was defined as any of the following adverse events (AEs): $\geq$ Grade 4 anemia, leukopenia, thrombocytopenia, neutropenia or any other $\geq$ Grade 3 events according to NCI CTCAE 3.0 during the first cycle. **Results:** There were 26 patients enrolled into the escalation (16) and expansion cohorts (10): median age: 63 y, range 48-74; gender: 18M/8F; race: 25W/1AA. BMS-936561 was tested at doses ranging from 0.1 to 15 mg/kg without a defined MTD. There was DLT of grade 3 hypersensitivity in 2/16 (13%) subjects treated at the 15 mg/kg dose cohort. The most commonly reported AEs included fatigue (85%), nausea (54%), decreased appetite (39%), anemia, dyspnea (35% each), constipation, peripheral edema (31% each), vomiting (27%), cough, skin hyperpigmentation, thrombocytopenia (23% each). Delayed toxicities characterized by facial edema and/or pleural or pericardial effusions were observed in 6/16 (38%) subjects treated at the 15mg/kg dose. All treatment emergent grades 3-4 serious AEs occurred in subjects treated at the 15 mg/kg dose. No deaths were attributed to BMS-936561. Exploratory efficacy analysis by investigator assessment showed a best response of stable disease in 18 of 26 patients (69%) without any apparent correlation with the administered dose. **Conclusions:** BMS936561 is well tolerated over a wide range of doses in patients with advanced ccRCC and B-NHL. Clinical trial information: NCT00944905.

**2559 General Poster Session (Board #22), Sun, 8:00 AM-11:45 AM**

**Population pharmacokinetics (PK) and exposure–neutropenia relationship of *nab*-paclitaxel (*nab*-P) in patients (pts) with solid tumors.** *Presenting Author: Nianhang Chen, Celgene Corporation, Summit, NJ*

**Background:** *nab*-P is a solvent-free, human albumin–stabilized formulation of paclitaxel (P) with a distinct clinical efficacy and safety profile in several indications (lung, breast, and pancreatic cancers) compared with solvent-based paclitaxel (sb-P). This study characterized the population PK and the exposure–neutropenia relationship with *nab*-P in pts with solid tumors. **Methods:** Plasma and blood concentrations of paclitaxel and neutrophil data were collected from 150 pts with various solid tumors over the *nab*-P dose range of 80 to 375 mg/m$^2$. Data were analyzed using nonlinear mixed-effect modeling or logistic regression. **Results:** Population PK of *nab*-P was described by a 3-compartment model with saturable distribution and elimination. The rapid disappearance of circulating P was driven by its fast distribution to peripheral compartments; maximum rate for saturable distribution (325,000 mg/h) was 40-fold greater than that for saturable elimination (8070 mg/h). Albumin was a significant covariate of P elimination ($P < 0.001$), while total bilirubin, creatinine clearance, body weight, body surface area, age, sex, and tumor type had no significant or clinically relevant effect. Neutropenia development was driven by systemic P exposure. The probability of experiencing a $\geq$ 50% reduction in neutrophils was best correlated to the duration of time above the drug concentration of 720 ng/mL. At a given exposure level, neutropenia development was positively correlated with increasing age but not significantly influenced by hepatic function, tumor type, sex, or dosing schedule. **Conclusions:** *nab*-P causes more rapid and deeper tissue penetration and slower elimination of paclitaxel compared with sb-paclitaxel. Rapid decline of paclitaxel concentration below the threshold of 720 ng/mL is associated with less-frequent neutropenia. The covariate analysis supports exposure-matched dose adjustments in patients with moderate to severe hepatic impairment and suggests that no dose adjustments are needed in patients with mild to moderate renal impairment.

**2560 General Poster Session (Board #23), Sun, 8:00 AM-11:45 AM**

**A phase I study of metformin and chemotherapy in solid tumors.** *Presenting Author: Athena Kritharis, Tufts Medical Center, Boston, MA*

**Background:** Metformin has recently received increased attention because of its potential antitumorigenic effects on a number of cancers. It activates AMP-related pathways leading to inactivation of mTOR and suppression of its downstream effectors, crucial for cancer growth. Data also suggests reduced incidence of cancer and better response to chemotherapy with metformin. We conducted a prospective phase I study to assess safety of metformin + chemotherapy in pts with solid tumors. **Methods:** We conducted delayed start randomized trial of non-diabetic pts in 2 stages. In stage 1, we randomized pts to 2 arms: concurrent arm (metformin + chemo) vs. delayed arm (chemo alone). In stage 2, pts in delayed arm were crossed over to receive metformin. Pts received metformin 500mg twice daily + chemotherapy to define DLTs in both stages. Secondary endpoints assessed AEs (CTCAE v.3.0) and response rates (RECIST). Translational correlates included effects of metformin on expression and phosphorylation of AMPK by western blot in PBMCs. **Results:** A total of 100 pts were enrolled (51 in delayed arm vs. 49 concurrent arm). There were 17 tumor types (CRC = 14, breast = 11). 26 chemoregimens were combined with metformin. Rate of DLTs in pts receiving metformin + chemotherapy was 6.1% vs. 7.8% in pts receiving chemotherapy alone (Table). DLTs seen with addition of metformin included those associated with established chemo AEs. No lactic acidosis or hypoglycemia occurred. Restaging showed stable disease in 46% at cessation of metformin. 28% of pts with measurable tumor markers showed improvement. AMPK phosphorylation showed a 4 to 6 fold increase in AMPK phosphorylation after metformin. **Conclusions:** This large phase I study suggests that metformin can be given safely with chemotherapy and offers a platform for future studies. Post-metformin increase in AMPK phosphorylation may potentially explain lack of disease progression in nearly half of our pts. Clinical trial information: NCT01442870.

**DLTs.**

| | Run-in stage Chemo w/out DLT | Stage 1 Chemo + metformin vs. chemo | Stage 2 Chemo + metformin |
|---|---|---|---|
| **Concurrent** | N= 49<br>1=G3 fatigue<br>**(2%)** | N= 49<br>3=G3 anemia, ↓ albumin, ↑ ALT<br>**(6.1%)** | N= 49<br>N/A |
| **Delayed** | N=51<br>2=G3 Thrombocytopenia, HFS<br>**(3.8%)** | N=51<br>4=G3 syncope, dehydration, ↑ bilirubin<br>**(7.8%)** | N=51<br>2=G3 dehydration, vomiting, proteinuria<br>**(3.8%)** |

**2561 General Poster Session (Board #24), Sun, 8:00 AM-11:45 AM**

**Pilot study of sorafenib and biweekly capecitabine in patients with advanced breast and gastrointestinal tumors.** *Presenting Author: Ami P. Jhaveri, Yale Cancer Center, New Haven, CT*

**Background:** Combination of sorafenib (S) and capecitabine (C) has shown clinical activity in single arm and randomized phase II trials of patients (pts) with metastatic breast (B) or GI (G) tumors. We sought an alternative schedule for C and S to reduce toxicity based on studies using the bi-weekly schedule for C and flat-dose administration. Study objectives are to assess safety, dose limiting toxicity (DLT), and maximum tolerated dose (MTD) of bi-weekly C and daily S. Secondary aims are efficacy, overall response rate, and duration of response. **Methods:** 19 pts with metastatic B or G tumors were enrolled to assess MTD and safety of C 1000mg bid flat dosing on days 1-7 and 15-21 of a 28 day cycle and S, 200mg AM/400mg PM given on a continuous basis. DLT definitions were predefined. Responses were defined using RECIST 1.0. **Results:** 19 pts with median age 55 (range 34-79) were treated. 14 pts had metastatic breast cancer; 5 pts had GI cancers. Median # of prior lines of chemotherapy in the metastatic setting was 1 (range 0-7). 2 pts are still on study. Median # cycles on study were 2 (range 1-5). Cycle 1 DLT were grade 3 pain in extremity (2 pts); grade 4 increased lipase (1 pt). Other grade 3/4 toxicities are summarized in Table. 16 pts are evaluable for response (12B, 4G). 2 pts with B tumors had partial response, 5 pts (3B, 2G) had stable disease, and 9 pts (7B, 2G) had disease progression. **Conclusions:** MTD was C 2,000mg 7 days on/7 days off and S 600mg daily. Despite overlapping toxicities of C and S combination, this dosing schedule is well tolerated and has sufficient clinical activity in pts with heavily pretreated metastatic breast and GI cancers to suggest further testing. Clinical trial information: NCT01640665.

**Treatment-related adverse events.**

| Adverse events | Grade 3 #pts | Grade 4 #pts |
|---|---|---|
| **Fatigue** | 5 | 0 |
| **Hand-foot syndrome** | 5 | 0 |
| **Hypophosphatemia** | 4 | 0 |
| **Diarrhea** | 2 | 0 |
| **Pain in extremity** | 2 | 0 |
| **Nausea** | 2 | 0 |
| **Vomiting** | 1 | 0 |
| **Increased alkaline phosphatase** | 1 | 0 |
| **Hypertension** | 1 | 0 |
| **Increased lipase** | 0 | 1 |
| **Hyponatremia** | 1 | 0 |
| **Increased amylase** | 1 | 0 |
| **Anorexia** | 1 | 0 |
| **Rash (maculopapular)** | 1 | 0 |
| **Anemia** | 1 | 0 |

**2562 General Poster Session (Board #25), Sun, 8:00 AM-11:45 AM**

**Phase I/IIa trial of the novel microtubule inhibitor BAL101553 in advanced solid tumors: Phase I completed.** *Presenting Author: L Rhoda Molife, Drug Development Unit at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*

**Background:** BAL101553 is a prodrug of the small molecule BAL27862, a novel microtubule-targeting agent (MTA) with potent activity in tumor models refractory to conventional MTAs. Its anti-cancer activity is related to cytotoxic effects on tumor cells as well as vascular disruption at higher doses. A NSCLC xenograft mouse model demonstrated similar BAL27862 tumor exposure (AUC) at the MTD and a sub-MTD dose, with the lower dose resulting in higher peak intratumoral levels. Phase I objectives of this trial included determination of maximum tolerated dose (MTD) and dose-limiting toxicity (DLT), evaluation of pharmacokinetics, pharmacodynamics (PD) and anti-tumor activity. **Methods:** Eligible patients (pts) with advanced solid tumors, having failed standard therapy, received BAL101553 as a 2-h IV infusion on days 1, 8 and 15 of a 28-day cycle (accelerated dose-escalation). Adverse events (AEs) were assessed by CTCAEv4 grade (G); tumor response was assessed every 2 cycles by RECIST 1.1. **Results:** 24 pts (12 males; median age 54.5 years; range 29-80) were treated at 15, 30, 45, 60 or 80 mg/m$^2$ of BAL101553. At 80 mg/m$^2$, 2 out of 6 evaluable pts experienced a DLT of G2-3 gait disturbance (fully or partially reversible with follow-up ongoing) related to G1-2 peripheral neuropathy. 60 mg/m$^2$ was defined as MTD with 1 DLT observed out of 6 pts (G3 reduced mobility with dizziness). Frequent drug-related AEs up to the MTD included injection site reactions, nausea, vomiting, diarrhea, fatigue, peripheral neuropathy (all G1-2) and asymptomatic hypertension (G2-3, transient during the infusion; responding to nifedipine). 1 confirmed partial response (ampullary cancer, for >2 years) and 5 stable diseases were observed, predominantly at sub-MTD doses. Reproducible exposure to BAL27862 was seen across all dose levels. Comparison of post- to pre-treatment tumor biopsies indicated PD effects on tumor cell proliferation and vascularization. **Conclusions:** BAL101553 is well tolerated up to the MTD of 60 mg/m$^2$. As a lower dose may be preferred (providing cytotoxic and intermediate anti-vascular effects), treatment at MTD and a lower dose is being considered for the randomized Phase IIa part. Clinical trial information: NCT01397929.

**2563 General Poster Session (Board #26), Sun, 8:00 AM-11:45 AM**

**Targeting argininosuccinate synthetase-deficient advanced solid tumors in a phase I trial of ADI-PEG20 plus cisplatin.** *Presenting Author: Siqing Fu, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Besides its selective activity to induce autophagy and caspase-independent apoptosis in argininosuccinate synthetase (ASS)-deficient cancer cells, ADI-PEG20 (pegylated arginine deiminase) synergized with the antitumor activity of cisplatin in vitro and in vivo. Accordingly we conducted a phase I study of ADI-PEG20 plus cisplatin in patients with ASS-deficient advanced solid tumors (NCT01665183). **Methods:** Primary objective was to establish the maximum tolerated dosage (MTD) following a standard 3+3 design. Secondary objectives were safety, antitumor activity and pharmacodynamics and immunogenicity effects. Patients with adequate organ functions, ECOG performance status of 1 or better, and ASS deficient advanced solid tumors were eligible. Dose escalation over 6 dose levels starting at ADI-PEG20 18 mg/m$^2$ IM weekly plus cisplatin 20 mg/m$^2$ IV weekly x 3 every 4 weeks and dose expansion at the MTD were included. Toxicity and efficacy were evaluated according to CTCAE 4.0 and RECIST 1.1, respectively. **Results:** A total of 37 patients with a median age of 62 were enrolled: 26 melanoma (18 cutaneous, 7 uveal, and 1 mucosal), 8 sarcoma, 1 prostate, 1 cervical, and 1 head and neck cancer. The MTD was established at ADI-PEG 36 mg/m$^2$ IM weekly plus cisplatin 30 mg/m$^2$ IV weekly x 3 every 4 weeks. Dose limited toxicities (DLT) included grade 4 neutropenia and neutropenic fever. Antitumor activity showed 2 partial responses (PR, 5%) and 8 stable disease ≥ 4 months (SD≥4 months, 22.2%). In patients with cutaneous melanoma, 2/18 PR (11 %) and 2/18 SD≥4 months (11%) were observed, associated with a median progression-free (PFS) and overall survivals of 2.6, and 5.8 months, respectively. Of 7 uveal melanoma patients, a median PFS of 4.7+ months was observed with 3 still on study, 2 off study but still alive, and 2 off study and dead (survived 11.6 and 1.5 months respectively). **Conclusions:** ADI-PEG 36 mg/m$^2$ IM weekly plus cisplatin 30 mg/m$^2$ IV weekly x 3 every 4 weeks was determined as the recommended phase 2 dosage, which was safe and demonstrated antitumor activity in patients with ASS-deficient advanced solid tumors. Further evaluation in patients with metastatic uveal and cutaneous melanoma is warranted. Clinical trial information: NCT01665183.

**2564 General Poster Session (Board #27), Sun, 8:00 AM-11:45 AM**

**First-in-human study of 4SC-205 (AEGIS), a novel oral inhibitor of Eg5 kinesin spindle protein.** *Presenting Author: Klaus B. Mross, KTB Klinik für Tumorbiologie, Freiburg, Germany*

**Background:** 4SC-205 is a potent small molecule inhibitor of the kinesin spindle protein Eg5 with broad anti-tumour activity in vitro and in vivo. Currently, 4SC-205 is the only oral available Eg5 inhibitor at clinical stage. Oral availability allows for flexible dosing in order to determine an optimal therapeutic window. **Methods:** Patients (pts) with solid tumors were dosed either once weekly (ow) at days 1 and 8 or twice weekly (tw) at days 1, 4, 8, and 11 or continuously (con) within a 21-day cycle. Dose escalation followed a 3+3 design. Primary objectives comprised safety, tolerability, definition of MTD/DLT and pharmacokinetic (PK) characterization. Secondary objectives include assessment of anti-tumour effect, measurement of M30/M65 cytokeratin-18 and pH3 in skin biopsies. **Results:** 56 Pts were enrolled at dose levels of 25mg (N=3), 50mg (N=3), 100mg (N=6), 150mg (N=6) and 200mg (N=13) ow; at 50mg (N=3), 75mg (N=7), and 100mg (N=5) tw; and at 10mg (N=3), 20mg (N=3) and 30mg (N=4) con. DLT was reached at 200mg (ow) and at 100mg (tw). MTD is established at 150mg (ow) and at 75mg (tw). These findings are in line with a dose proportional PK, resulting in similar cumulative AUCs for DLT and MTD for ow and tw dosing, respectively. The most common dose limiting adverse event was neutropenia. Prophylactic treatment with G-CSF at 200mg (ow) did not result in additional benefit. Interim analysis of exposure-toxicity data using a population PK/PD model for neutropenia suggested an opportunity for continuous dosing. Neutropenia occurred at dose level of 30mg (con). A dose-dependent biomarker response was observed in skin biopsies. Response acc. to RECIST was not observed. 28% of patients were stabilized into follow-up after 6 weeks. The maximum treatment duration was > 300 days. Currently, 3 more patients are entrolled in 20mg con. However,the data of 56 patients allows for reliable evaluation. **Conclusions:** 4SC-205 could be safely administered up to 200mg (ow), 100mg (tw) and 30mg (con). Neutropenia was the main dose limiting toxicity. The compound exhibits dose-proportional pharmacokinetics with $t_{1/2}$ ~ 10h. Plasma exposure exceeds average *in vitro* $GI_{50}$ 20x at the highest dose level over a period of 24h. Clinical trial information: NCT01065025.

**2565 General Poster Session (Board #28), Sun, 8:00 AM-11:45 AM**

**Joint cell-line and patient modeling of drug sensitivity reveals novel molecular biomarkers for targeted and conventional chemotherapy.** *Presenting Author: Charles Ferte, Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France*

**Background:** The unresponsiveness to anticancer drugs in patients outlines the need to identify novel and robust biomarkers of response to therapy. The recent release of large molecular cell line datasets labeled for drug sensitivity enables the development of such predictors. Cell line based models poorly reflect the extent of molecular heterogeneity existing at the patient level. We aimed to overcome this limitation by combining cell line with patient data to uncover novel molecular traits associated with drug response at the patient level. **Methods:** We used both patients and cell lines data from the following publicly available datasets: CCLE (1057 cell lines, 24 drugs), Sanger (790 cell lines, 130 drugs) and TCGA (patients: breast cancer, colorectal cancer, lung squamous carcinoma, lung adenocarcinoma, ovarian cancer, endometrial cancer and melanoma). A two-step Elastic Net approach was used to model the drug sensitivity using gene-expression, copy-number alteration, and somatic mutation data. As validation, we used the dataset of 420 cancer patients prospectively enrolled in the ongoing MOSCATO molecular screening program (Gustave Roussy, France). **Results:** As positive control, we were able to recover all of the recognized landmark biomarkers across drug - tissue combination (e.g. Erlotinib: EGFR mutation in lung adenocarcinoma; Lapatinib: ERBB2 amplification in breast cancer; Vemurafenib: BRAF mutation in melanoma, etc). We uncovered novel molecular traits (copy, number mutations) associated (FDR<20%) with drug response (e.g. erlotinib: CDKN2A deletion in lung adenocarcinoma, lapatinib: CDH1 deletion in breast cancer, etc.). The validation of our framework in the MOSCATO patients' cohort will be presented. **Conclusions:** We provide a comprehensive annotation of mutations and copy-number events predicted to be associated with sensitivity and resistance in 142 anti-cancer drugs and across 7 tumor types. This approach is likely to exert a major impact on precision medicine programs in oncology.

**2566 General Poster Session (Board #29), Sun, 8:00 AM-11:45 AM**

**A phase I and pharmacokinetic study of a weekly dosing schedule of paclitaxel injection concentrate for nano-dispersion (PICN) in patients with advanced solid tumors.** *Presenting Author: Wen Wee Ma, Roswell Park Cancer Institute, Buffalo, NY*

**Background:** PICN is a novel Cremaphor-free composite of paclitaxel nano-particles stabilized with polymer and lipid using NanotectonTechnology. PICN started development with every-3-week schedule of PICN +/- carboplatin (ASCO 2013; #2557). This study aimed to determine the maximum tolerated dose (MTD) and pharmacokinetic (PK) profile of PICN dosed using a weekly schedule. **Methods:** Patients (pt) with solid malignancies and ECOG PS 0-1 were eligible, and the dose escalation was conducted per a '3+3' design. PICN was administered i.v. weekly for 3 weeks then1 week rest (28 days per cycle) at planned dose levels 80, 100, 125 and 150 mg/m$^2$. The 125 mg/m$^2$level was intolerable in pts who previously received multiple lines of chemotherapy (Arm A), and the study was amended to continue dose escalation in pts who previously received 2 or less lines of treatment (Arm B). Only standard anti-emetic premedications were used. Adverse events (AEs) were graded using CTCAE 4.0 and tumor response by RECIST 1.1 **Results:** A total of 22 pts were enrolled from 2 US academic centers and 15 evaluable for dose limiting toxicity (DLT). Number of pts at each level were n=3 at 80, n=6 at 100, n=3 at 125 (Arm A) and n=3 at 125 mg/m$^2$ (Arm B). The DLTs observed were: dose delay for > 7 days for Gr1 ANC at 100 mg/m$^2$; Gr3 fatigue and Gr3 weakness at 125 mg/m$^2$ (Arm A). Anti-tumor efficacy was observed in breast (PR, 80 mg/m$^2$), ovarian (SD for > 12 months; 100 mg/m$^2$), and urothelial (PR; 125 mg/m$^2$) cancers. Previous treatments received in the ovarian pt included platinum(P)/paclitaxel, P/docetaxel and P/gemcitabine; and, P/gemcitabine in the urothelial pt. The dose level of 125 mg/m$^2$(Arm B) was tolerable and enrollment to higher dose levels are underway. PK analysis showed dose-proportional increase in total plasma paclitaxel level. **Conclusions:** When administered on a weekly schedule (3-weeks-on/1-week-off), 100 mg/m$^2$ was the MTD in heavily pretreated pts. 125 mg/m$^2$ was tolerable in pts who received 2 or less previous lines of chemotherapy. Anti-tumor efficacy was observed in breast, ovarian and urothelial cancers. Final PK, toxicity and efficacy data will be reported at the conference. Clinical trial information: NCT01305512.

**2567 General Poster Session (Board #30), Sun, 8:00 AM-11:45 AM**

**A phase I study of pemetrexed in combination with docetaxel in advanced solid tumor patients.** *Presenting Author: Lee D. Cranmer, The University of Arizona Cancer Center, Tucson, AZ*

**Background:** Pemetrexed is an anti-folate targeting the purine and pyrimidine synthetic pathways. Docetaxel is a third generation cytotoxic that modulates microtubule dynamics, inhibiting cell division. Our primary objective is to determine the MTD for the combination in a biweekly regimen in advanced solid tumors. Secondary endpoints include characterizing the adverse events (AEs) profile, anti-tumor activity, and recommended phase 2 dose (RPTD). **Methods:** Pemetrexed and docetaxel were administered on days 1 and 15 of a 28-day cycle. The dose escalation scheme consisted of 7 planned dose levels ranging from 300-600 mg/m$^2$ pemetrexed and 30-60 mg/m$^2$ docetaxel. Cohorts of 3-6 patients were enrolled in each dose level using the classical 3+3 dose escalation design. AEs were classified using CTCAE 3.0. Upon determination of MTD, an expansion phase was implemented to include 12 patients treated at the MTD level. **Results:** 33 advanced solid tumor patients were enrolled; 32 received treatment (1 ineligible). 28/32 patients received at least one prior line of chemotherapy. Three (3) patients were removed from the study before completing one cycle: 1 due to disease progression, 1 refused further treatment, 1 experienced dose-limiting toxicity (grade 3 gastrointestinal AE).Most frequent, treatment-related AEs were fatigue (85%), leukopenia (73%), nausea (69%), elevated aminotransferases (54%–62%), anemia (62%), and neutropenia (62%). MTD was deemed to be 500 mg/m$^2$ pemetrexed and 40 mg/m$^2$ docetaxel. Twenty-six (26) patients were evaluable for response: 19% PR (5: 2 sarcoma, 2 NSCLC, 1 renal cell kidney cancer), 50% SD (13: 7 sarcoma, 4 NSCLC, 1 bladder cancer, 1 thymoma), and 31% PD (8: 6 sarcoma, 2 NSCLC). **Conclusions:** Administration of pemetrexed and docetaxel was feasible without unexpected toxicities. The combination demonstrated preliminary evidence of significant anti-tumor activity in pretreated patients with advanced solid tumors. It may also be a useful alternative doublet in patients with non-squamous NSCLC unable to tolerate platinum. The RPTD is 500 mg/m$^2$ pemetrexed and 40 mg/m$^2$ docetaxel. Given the preliminary anti-tumor activity, the combination deserves further investigation, particularly in sarcoma. Clinical trial information: NCT01172028.

**2568 General Poster Session (Board #31), Sun, 8:00 AM-11:45 AM**

**Aurora-A mitotic kinase and induction of endocrine resistance through downregulation of er$\alpha$ expression in initially er$\alpha$+ breast cancer cells.** *Presenting Author: Mateusz Opyrchal, Roswell Park Cancer Institute, Buffalo, NY*

**Background:** Development of endocrine resistance during tumor progression represents a major clinical challenge in the management of ER$\alpha$+ breast tumors and is an area under intense investigation. Although the underlying mechanisms are still poorly understood, many studies point toward the 'cross-talk' between ER$\alpha$ and MAPK signaling pathways as the key in the development of estrogen-independent growth of initially ER$\alpha$+ and hormone sensitive breast cancer cells. **Methods:** In this study we employed a metastatic, Mcf-7, ER$\alpha$+, breast cancer xenograft model harboring constitutive activation of Raf-1 oncogenic signaling to investigate the mechanistic linkage between aberrant MAPK activity and development of endocrine resistance. Patient samples were tested for expression of Aurora-A. **Results:** In vitro cells showed resistance to endocrine therapies. Development of endocrine resistance was functionally linked to ER$\alpha$ down-regulation both in vitro and in vivo. Because resistant cells also overexpressed Aurora-A kinase, we investigated the causal role of Aurora-A kinase in regulating ER$\alpha$ expression. Inhibition of Aurora-A kinase activity employing a specific inhibitor, Alisertib, resulted in re-expression of ER$\alpha$ and increased sensitivity to endocrine therapies as well as decreased p~SMAD5. The role of SMAD5 was also tested by overexpressing SMAD5 in MCF-7 cells, which led to loss of ER$\alpha$ expression. Aurora-A over-expression in ER$\alpha$+ patient breast tumor tissues was associated with increased risk of recurrence. **Conclusions:** We demonstrate for the first time the causal role of Aurora-A kinase in the development of endocrine resistance through activation of SMAD5 nuclear signaling and down-regulation of ER$\alpha$ expression in ER$\alpha$+ breast cancer cells. This contribution is highly significant for the treatment of endocrine refractory breast carcinomas. Our findings may lead to the development of novel molecular therapies targeting the Aurora-A/SMAD5 axis to eradicate endocrine resistant cancer cells and suppress tumor progression and the onset of distant metastases with consequent clinical benefit to breast cancer patients.

**2569 General Poster Session (Board #32), Sun, 8:00 AM-11:45 AM**

**Phase I: Veliparib with cisplatin (CP) and vinorelbine (VNR) in advanced triple-negative breast cancer (TNBC) and/or *BRCA* mutation-associated breast cancer.** *Presenting Author: Eve T. Rodler, Seattle Cancer Care Alliance, Seattle, WA*

**Background:** Poly(ADP-ribose) polymerase inhibitors (PARPi) have activity in tumors with DNA repair defects, including BRCA 1/2 deficient cancers. CP is synergistic with the PARPi veliparib in xenografts, and has anti-tumor activity in TNBC and BRCA1 deficient breast cancer. VNR shows preclinical synergy with CP and the combination has efficacy in metastatic breast cancer (MBC). We hypothesize that veliparib combined with CP and VNR is active in TNBC and will be most effective in tumors with DNA repair defects. **Methods:** To determine maximum tolerated dose (MTD), pharmacokinetic (PK) and pharmacodynamic profiles, and anti-tumor activity, patients (pts) with TNBC and/or *BRCA1/2*+ MBC received CP 75 mg/m$^2$ day 1, VNR 25 mg/m$^2$days 1, 8 and escalating doses of veliparib (V) orally BID days 1-14, every 21 days for 6-10 cycles followed by maintenance V. **Results:** 45 pts enrolled in 9 cohorts. Treatment was tolerated well; MTD was not reached. 36 pts (80%) had at least 1 prior metastatic regimen (range 1-11). *BRCA* mutation status was: *BRCA1*+ (n=9); *BRCA2*+ (n=3); negative (n=24); unknown (n=9). BID V dose cohorts were: 20 mg (n=4); 30 mg (n=3); 40 mg (n=6); 60 mg (n=8); 80 mg (n=5 ); 120 mg (n=6); 160 mg (n=3); 200 mg (n=7); and 300 mg (n=3). DLT occurred at 40 mg BID in 1 pt with grade (gr) 4 thrombocytopenia, 60 mg BID (gr 4 neutropenia + fever, n=1), and 200 mg BID (gr 3 neutropenia + fever, n=1). Most common adverse events (AEs) were nausea, anemia, fatigue, mainly gr 1/2. Most common gr 3/4 AEs were neutropenia (n=13), anemia (n=11), thrombocytopenia (n=6). Of 38 evaluable pts, 21 (55%) responded (2 CR, 19 PR), 13 (34%) had SD, and 4 had PD, as best response. One pt with CR remains on trial for 42+ cycles. Response was 73% in *BRCA* 1/2+ pts (6/11 PR; 2/11 CR), 53% in *BRCA*1/2- pts (11/21 PR) and 33% in unknown status pts (2/6 PR). Analyses of PK and correlative predictors of response will be presented. **Conclusions:** Veliparib at the recommended phase II dose of 300mg BID combined with CP and VNR is well tolerated. *BRCA* mutation carriers and pts with sporadic TNBC, including heavily pretreated pts, responded. We plan to investigate the contribution of veliparib to cisplatin-based therapy in a randomized trial. Clinical trial information: NCT01104259.

**2570 General Poster Session (Board #33), Sun, 8:00 AM-11:45 AM**

**Final results of a phase 1 study of single-agent veliparib (V) in patients (pts) with either BRCA1/2-mutated cancer (BRCA+), platinum-refractory ovarian, or basal-like breast cancer (BRCA-wt).** *Presenting Author: Shannon Leigh Huggins-Puhalla, University of Pittsburgh Cancer Institute, Magee-Womens Hospital of UPMC, Pittsburgh, PA*

**Background:** Veliparib (V) (ABT-888) is a potent, oral PARP 1/2 inhibitor with preclinical and clinical efficacy in BRCA+ malignancies. As there are known similarities between BRCA+ cancers, serous ovarian cancer, and basal-like breast cancer, we postulated potential for V activity in these groups also. We sought to establish the maximum tolerated dose (MTD), dose-limiting toxicities (DLT), pharmacokinetic (PK) and pharmocodynamic properties, and preliminary efficacy of chronically-dosed V. **Methods:** A 3+3 dose-escalation phase I trial was performed. Nine dose levels ranging from 50 mg BID to 500 mg BID dosed continuously were enrolled to determine a maximum tolerated dose (MTD) and recommended phase II dose (RP2D). A biopsy cohort in BRCA+ patients was enrolled at the RP2D. Correlative studies included assessment of BRCA reversion mutation analysis, DNA repair pathway analysis, and BRCA promoter methylation status. **Results:** A total of 88 pts (60 BRCA+ and 28 BRCA-wt) were enrolled to date. DLTs occurred at the following dose levels: BRCA+: gr 3 nausea/vomiting at 400 mg BID, gr 2 seizure at 500 mg BID; BRCA-wt: gr 2 seizure at 400 mg BID. The RP2D was established at 400 mg BID. The most common all-grade toxicities were nausea, fatigue, and lymphopenia. PK was linear and non-saturable with t ½ of 5.2 h. Fifty-two BRCA+ patients (28 ovary, 13 breast, 11 other) were evaluable for response. In BRCA+ patients at all dose levels, the ORR (CR+PR) was 23% with a clinical benefit rate (CBR; CR + PR + stable disease) of 58%. At the MTD and RP2D, 28 BRCA+ patients were evaluable, with an ORR of 40%, and a CBR of 68%. Twenty-four BRCA-wt pts (21 breast and 3 ovary) were evaluable for response, and the ORR was 4% with a CBR of 38%. **Conclusions:** Single-agent V is well-tolerated with evidence of anti-tumor activity seen in both BRCA+ and BRCA-wt tumors comparable to other single agent PARP inhibitors. Evidence of potential dose responsiveness was observed. Correlative studies from archival tissues and mandatory biopsy cohort, with final data to be presented, will provide early insights on potential mechanisms of response and resistance. Clinical trial information: NCT00892736.

**2571 General Poster Session (Board #34), Sun, 8:00 AM-11:45 AM**

**Intraoral JP4-039 to ameliorate irradiation-induced mucositis in tumor-bearing Fanconi anemia (FA) mouse model.** *Presenting Author: Ashwin Shinde, University of Pittsburgh Cancer Institute, Pittsburgh, PA*

**Background:** The DNA repair defect in Fanconi anemia (FA) patients makes radiotherapy of head and neck cancers a challenge due to mucositis as a dose limiting toxicity. We tested intraoral delivery of mitochondrial-targeted antioxidant, JP4-039, in a novel F15 emulsion, to reduce mucositis in fractionated irradiated FA mice with orthotopic tumors. **Methods:** *Fancd2*$^{+/+}$, *Fancd2*$^{+/-}$, and *Fancd2*$^{-/-}$mice from C57BL/6J background with palpable tumors, measureable by calipers, were irradiated to single 28 Gy or 8 Gy x 4 daily fractions to the oral cavity. Subgroups of mice (N=4/group) received intraoral JP4-039/F15 (100 ul containing 4 mg/ml of drug) 10 minutes prior to irradiation, F15 alone or irradiation alone. Tumor size was measured daily. Five days after the last radiation dose, mice were sacrificed, and tumors and tongue tissue removed for histopathology. Statistical analysis was performed using Students t-test, with a p-value $<$ 0.05 considered significant. **Results:** Intraoral JP4-039/F15 prior to irradiation significantly decreased oral cavity ulceration ($p < 0.001$). Following 8 Gy x 4, F15-JP4-039 treated *Fancd2*$^{-/-}$ knockout mice had 47.8 $\pm$ 11.1% of the tongue ulcerated compared to 81.7 $\pm$ 11.6% ulceration in untreated mice ($p < 0.001$). Results in JP4-039/F15 treated irradiated heterozygotes and wild-type *Fancd2*$^{+/+}$ mice (34.1 $\pm$ 21.2 or 16.9 $\pm$ 12.6% ulceration, respectively) were also improved compared to untreated irradiated mice (88.3 $\pm$ 8.0 or 76.3 $\pm$ 17.2% ulceration, respectively) ($p <$ 0.001 for all groups). F15 alone did not reduce ulceration. JP4-039/F15 treated FA mice had increased ulceration compared to *Fancd2*$^{+/+}$ mice (47.8 $\pm$ 11.1% and 16.9 $\pm$ 12.6% respectively, $p < 0.0001$). Both single fraction and fractionated radiation treatment controlled tumors at 5 days in *Fancd2*$^{+/+}$, *Fancd2*$^{+/-}$, and *Fancd2*$^{-/-}$ mice (0.4 $\pm$ 0.3, 0.05 $\pm$ 0.05, or 0.1 $\pm$ 0.1 mm$^3$, respectively) compared to nonirradiated controls (2.1 $\pm$ 0.4, 1.9 $\pm$ 0.5, or 3.1 $\pm$ 0.1 mm$^3$, respectively, $p < 0.027$). Tumor size was comparably reduced in all irradiated groups. **Conclusions:** Intra oral JP4-039 protects normal tissue in irradiated FA mice without associated tumor protection.

**2572 General Poster Session (Board #35), Sun, 8:00 AM-11:45 AM**

**Early phase I study of the PARP inhibitor veliparib (ABT-888) alone or in combination with carboplatin/paclitaxel (CP) in patients with varying degrees of hepatic or renal dysfunction: A study of the NCI-Organ Dysfunction Working Group (ODG).** *Presenting Author: Hussein Abdul-Hassan Tawbi, University of Pittsburgh Cancer Institute, Pittsburgh, PA*

**Background:** PARP inhibitors are promising anti-cancer agents with clinical activity as single agents or in combination with chemotherapy. Alteration of hepatic or renal function could affect the pharmacokinetic (PK) characteristics of veliparib (V) and thus, impact adversely on its safety. We conducted a multi-center Phase I study through the NCI-Organ Dysfunction Working Group (ODG) to determine: (1) the maximum tolerated dose (MTD) of V in combination with CP in pts with varying degrees of renal or hepatic dysfunction; and (2) the PK of V. **Methods:** Pts with advanced solid malignancies, ECOG PS 0-2, and normal bone marrow were enrolled to the following cohorts: normal (N); moderate (R2; CrCL= 30-59mL/min), severe (R3; CrCL<30mL/min) renal dysfunction, and hemodialysis (R4); mild (H2; bilirubin(B)<1.25x ULN), mild with transaminase elevation (H3; B<1.25x ULN and ALT/AST(T)>3xULN), moderate (H4; B>1.25-2xULN and T<10xULN), and severe (H5; B>2-5xULN and T<10xULN) hepatic dysfunction. Pts with both renal and hepatic dysfunction were excluded. All pts received a single 80 mg oral dose of V for extensive PK sampling 1 week prior to the initiation of combination therapy. V dose escalation up to 80 mg PO BIDx5d followed the standard "3+3" design within each cohort with C AUC 6 and P 175 mg/m$^2$ on d3 of a 21-d cycle. C and P were dose-adjusted to the degree of organ dysfunction following FDA dosing guidelines. DLTs were defined based on myelosuppression or worsening organ function. **Results:** A total of 59 pts were enrolled of which 45 were evaluable: N: 13, R2: 11, R3: 6, H2: 7, H3: 3, H4: 4. All pts enrolled on DL1 and DLminus1 of H4 experienced DLTs closing accrual to this cohort and H5. PK data on V and its inactive metabolite M8 were available on all pts treated with a single fixed dose V. **Conclusions:** V combined with CP is not safely deliverable in pts with moderate to severe hepatic dysfunction, though V PK appeared unaffected by hepatic dysfunction. Renal dysfunction did result in increased V and M8 exposure. These data will guide potential dose reductions in pts with hepatic or renal dysfunction. Clinical trial information: NCT01366144.

**2573 General Poster Session (Board #36), Sun, 8:00 AM-11:45 AM**

**Phase 1/2 study of oral rucaparib: Final phase 1 results.** *Presenting Author: Rebecca Sophie Kristeleit, University College London Cancer Institute, London, United Kingdom*

**Background:** Rucaparib is a potent, oral PARP inhibitor (PARPi) that induces synthetic lethality in homologous recombination deficient (HRD) tumors (e.g. BRCA mutation). The primary objectives of the Phase 1 portion were to define the MTD, RP2D and PK of continuous rucaparib. **Methods:** A 3+3 dose escalation design was used. Intra-patient dose escalation was allowed. Patients (pts) aged ≥18 with advanced solid tumors that had progressed on standard treatments were recruited. Measurable disease was not required. Rucaparib was taken orally QD or BID continuously. Plasma PK assessments included full profile and trough levels. **Results:** Phase 1 is complete with 56 pts (median age 51 yrs [range 21-71]; 51 female; 29 ECOG PS=0; 27 breast cancer (BC), 20 ovarian/peritoneal cancer (OC), 9 other tumor) enrolled in 10 dose cohorts (40 QD-840 mg BID). 600 mg BID was identified as the optimal RP2/3D based on maximum exposure, manageable toxicity and promising clinical activity. Exposures exhibited dose proportional kinetics up to the RP2/3D with low inter- and intra-pt variability, an important attribute for uniform flat dosing strategies. At 360 mg BID, 1 pt had a DLT of Grade (G) 3 nausea, with no others at higher dose levels. The incidence and severity of myelosuppression, a known PARPi effect, was dose-dependent with ~50% of pts at the RP2/3D having at least one G2 or G3 event (% G2/G3): anemia (29%/29%), thrombocytopenia (0/14%), neutropenia (29%/0). All G3 events were post-Cycle 1 and were successfully managed with dose reduction. Treatment-related AEs (mostly G1/2) reported in ≥10% of all pts include fatigue (30%), nausea (30%), vomiting (23%), diarrhea (13%), anorexia (11%). No G4 AEs have occurred. RECIST and/or CA-125 responses occurred at doses ≥ 300 mg QD (2 CRs, 7 PRs, 3 CA-125). At these doses, disease control rate (CR+ PR + SD≥24 weeks) was 70% (7/10) in gBRCA OC pts. At the RP2/3D, 4/5 (80%) OC (3/4) and BC (1/1) pts had a RECIST or CA125 response. All responders had a BRCA 1/2 mutation. Responses were seen in platinum-sensitive and platinum-resistant OC pts. **Conclusions:** Rucaparib has a desirable PK profile and is well tolerated with promising clinical benefit in OC, BC, and pancreatic cancer. Three studies are ongoing in OC pts (ARIEL2, ARIEL3, Phase 2 portion of this trial). Clinical trial information: NCT01482715.

**2574 General Poster Session (Board #37), Sun, 8:00 AM-11:45 AM**

**A phase 1 dose-escalation study of veliparib with bimonthly FOLFIRI in patients with advanced solid tumors.** *Presenting Author: Jordan Berlin, Vanderbilt-Ingram Cancer Center, Nashville, TN*

**Background:** Veliparib (V; ABT-888), a potent, competitive poly (ADP-ribose) polymerase (PARP)-1 and -2 inhibitor enhances the activity of irrinotecan (IRI). This study seeks to establish the maximum tolerated dose (MTD) and recommended Phase 2 dose (RPTD) of V in combination with bimonthly FOLFIRI. **Methods:** Solid tumorpatients (pts; ≤3 prior DNA-damaging regimens) were administered V BID (days 1-5; 15–19) and FOLFIRI in three parts (P) : (P1) IRI 150 mg/m$^2$; (P2) IRI 180 mg/m$^2$ with 5-FU 400 mg/m$^2$ bolus; or (P3) IRI 180mg/m$^2$. All regimens included folinic acid 400 mg/m$^2$, immediately followed by 5-FU 46-hour continuous infusion. Dose escalation began with V 10 mg BID in P1 and 100 mg BID in P2 and P3. Two expansion cohorts were evaluated in gastric or colorectal cancer pts with no prior PARP inhibitor therapy. **Results:** 96 pts (median age 54.5 years; range, 24–77) were enrolled in cohorts from 10–300 mg BID V. Tumor types were: other (n=30); gastric (n=20); pancreatic (n=14); ovarian, breast, and colorectal (each, n=9). 88 pts discontinued: 83 due to progressive disease; 2 withdrew consent; and 3 other. Most common AEs (>40% pts) were diarrhea (61%), nausea (60%), neutropenia (59%), vomiting (48%), fatigue (47%), anemia and alopecia (each, 41%). Grade 3/4 AEs (>30 pts) were neutropenia (47%), nausea (38%), and diarrhea (34%). Four DLTs occurred: neutropenia (n=3; P1, 160 mg and 270 mg BID V; P2, 100 mg BID V); and gastritis and vomiting (P1, 270 mg BID V). 12 pts (gastric, n=3; ovarian, breast, pancreatic, and other, each n=2; colorectal, n=1) achieved a partial response and 1 (ovarian) a complete response. V exposure was approximately dose-proportional in combination with FOLFIRI. FOLFIRI PKs were comparable with or without V administration, indicating the lack of drug-drug interaction. **Conclusions:** V in combination with chemotherapy was generally well-tolerated without drug-drug interactions. Ovarian and breast cancer pts experienced the greatest anti-tumor activity with an objective response rate of 33% and 22%, respectively. The RPTD was 200 mg BID V with bimonthly FOLFIRI (IRI 150 or 180 mg/m$^2$ without 5-FU bolus). This study supports further evaluation of V in combination with FOLFIRI in specific tumor types. Clinical trial information: NCT01123876.

**2575 General Poster Session (Board #38), Sun, 8:00 AM-11:45 AM**

**Phase I dose-escalation study of an oral administration of the pan-histonedeacetylase inhibitor abexinostat combined with a fixed dose of doxorubicin in patients with solid tumors.** *Presenting Author: Arnaud Scherpereel, University Hospital of Lille Nord de France, Lille, France*

**Background:** Preclinical data indicate that abexinostat enhances sensitivity to DNA-damaging agents, such as doxorubicin, particularly when administered 48h before infusion. A phase I dose-escalation study of abexinostat in combination with doxorubicin was performed in candidate patients to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT), and establish the recommended phase II dose (RP2D). **Methods:** Abexinostat was given 4 consecutive days weekly, 3 out of 4 weeks, and fixed doxorubicin dose of 25 mg/m$^2$ was administered on day 3 of each weekly abexinostat schedule, for a maximum of 6 cycles. **Results:** 35 patients were included and treated: 23 in the dose-escalation phase in cohorts receiving abexinostat 30 to 75 mg/m$^2$ bid, and 12 in the confirmation phase at the RP2D. In the dose-escalation phase, MTD was 75 mg/m$^2$ bid with 3 DLTs 2 grade 4 thrombocytopenia, 1 grade 2 neutropenia >7 days. In the confirmation phase (RP2D 60 mg/m$^2$ bid), there were 4 DLTs (33% patients): 2 grade 4 thrombocytopenia, 1 grade 3 fatigue, 1 failure to restart treatment due to prolonged grade 2 neutropenia. Most abexinostat-related adverse events were grade 1 or 2 (79%), with 18% grade 3 and 3% grade 4; they were mostly hematological (51%), gastrointestinal (23%), or general disorders (10%). Preliminary pharmacokinetics of the combination showed no interaction between the two drugs. Preliminary efficacy results on 27 evaluable patients showed 3 partial responses (2 at C4 and 1 at C6) and 12 stable disease with median duration of 2 cycles (range C2-C6) as best response. 13 patients received the combination for at least 4 cycles and 11 patients completed 6 cycles. **Conclusions:** Combination of abexinostat 60 mg/m$^2$ bid 4 consecutive days weekly, 3 out of 4 weeks, with doxorubicin at 25 mg/m$^2$ on the third day of each abexinostat cycle appears to be well tolerated in patients with advanced solid tumors. Preliminary efficacy results were observed at different dose levels. Clinical trial information: ISRCTN55052510.

**2576 General Poster Session (Board #39), Sun, 8:00 AM-11:45 AM**

**A phase I trial of pazopanib and vorinostat: The role of *TP53* mutations.** *Presenting Author: Ming-Mou Hou, Chang Gung Memorial Hospital, Taoyuan, Taiwan*

**Background:** VEGF inhibition-mediated tumor hypoxia promotes invasive growth by transcriptional activation of hypoxia-induced factors mediated by tumor hypoxia. Accordingly, we conducted this phase 1 study of pazopanib plus vorinostat to overcome resistance to antiangiogenesis (NCT01339871). **Methods:** Primary objective of this phase I trial was to define the maximum tolerated dosage (MTD) and the safety profile following a zone-based, modified 3 + 3 dose escalation design (12 dose levels). Toxicity and efficacy were evaluated according to CTCAE 4.0 and RECIST 1.1. **Results:** A total of 78 evaluable patients enrolled. Six patients (7.7%) experienced dose-limiting toxicity (DLT): 2 hypertension, 2 diarrhea, 1 thrombocytopenia, and 1 skin rash. The most frequent drug-related grade 2 or higher adverse events were thrombocytopenia, neutropenia, fatigue, hypertension, diarrhea, and vomiting in 39 patients (50%). Pazopanib plus vorinostat (800 mg/200 mg [4A], 600 mg/300 mg [4B], 400 mg/400 mg [4C] PO daily) in zone 4 were defined as the MTDs, with dose reduction in 67%, 33% and 57% of patients, respectively. The dose level 4B was chosen for further evaluation. Four patients (5.1%) achieved partial response (PR) and 9 patients (11.5%) experienced stable disease for at least 6 months (SD≥6months). This cohort of patients showed a median progression-free survival (PFS) of 2.2 months (95% CI, 1.8-2.6) and a median overall survival (OS) of 8.3 months (95% CI, 6.2-10.4). Further evaluation revealed that patients with *TP53* mutations (n=10) showed a median PFS of 3.5 months and a median OS of 12.7 months (95% CI, 2.2-23.2), compared favorably with 2.0 months (95%CI, 1.9-2.1; $p$=0.08), and 7.5 months (95%CI, 5.0-9.4; $p$=0.12) in those with *TP53* mutation undetected (n=21), respectively. In 13 patients who achieved PR/SD≥6months, 4 patients had *TP53* mutations, 2 undetected, and 7 unknown. **Conclusions:** Dose level 4B (pazopanib 600 mg PO daily plus vorinostat 300 mg PO daily) was considered as the recommended phase II dosage. Antitumor activity in patients with advanced solid tumors was demonstrated. Early clinical evidence indicated that further evaluation of the efficacy and safety of this regimen, and role of *TP53* mutations in treatment sensitivity is warranted. Clinical trial information: NCT01339871.

**2577 General Poster Session (Board #40), Sun, 8:00 AM-11:45 AM**

**Phase I study of pazopanib (PAZ) in combination with abexinostat (ABX) in patients (Pts) with metastatic solid tumors.** *Presenting Author: Rahul Raj Aggarwal, University of California, San Francisco, San Francisco, CA*

**Background:** PAZ is a tyrosine kinase inhibitor of VEGFR, PDGFR, and C-KIT approved for use in renal cell carcinoma (RCC) and soft tissue sarcoma (STS). ABX is a potent pan-HDAC inhibitor (HDACi). Pre-clinical models suggest that epigenetic modulation with an HDACi potentiates PAZ's efficacy and prevents the outgrowth of a resistant phenotype. We therefore designed a Phase I clinical trial combining ABX with PAZ in pts with advanced solid tumors. **Methods:** The primary objective was to determine the maximal tolerated dose (MTD) of PAZ plus ABX in pts with advanced solid tumor malignancies. Secondary objectives included pharmacokinetics (PK) and efficacy. Altered histone acetylation post treatment denoted HDACi activity and served as pharmacodynamic (PD) markers in peripheral blood mononuclear cells. PAZ was dosed daily and ABX on days 1-5, 8-12, 15-19 of a 28-day cycle, at a starting dose of 400 mg/day and 45 mg/m$^2$ orally twice daily for PAZ and ABX respectively. **Results:** 22 patients with advanced solid tumors were enrolled. There were five dose-limiting toxicities (DLTs) (fatigue: N = 2, thrombocytopenia: N = 2; grade 2 elevated AST with fever: N = 1). The MTD was PAZ 600 mg/day + ABX 30 mg/m$^2$ BID. The most common grade ≥ 3 drug regimen-related adverse events observed include thrombocytopenia (12%), fatigue (12%), and diarrhea (8%). 3 of 15 evaluable pts (20%) (including 2 RCC pts) had a confirmed objective partial tumor response, including one pt with prior progression in single agent PAZ. 5 out of 17 evaluable pts (29%) have experienced disease stabilization or better for ≥ 6 months. PK and PD analyses are ongoing. An alternate dosing schedule is being explored with ABX administered on D1-4, 8-11,15-18 of a 28-day cycle. The current dose level is 45 mg/m$^2$ BID and PAZ at 600 mg/day with no DLTs observed thus far (N = 2). **Conclusions:** This is the first trial to explore the combination of ABX with PAZ in RCC and other solid tumor malignancies. The optimal dosing schedule may be ABX taken 4 days/week but requires further investigation. Encouraging preliminary evidence of anti-tumor activity was observed including in a pt with prior disease resistance to PAZ monotherapy. An expansion cohort with 20 pts in RCC and sarcoma is planned. Clinical trial information: NCT01543763.

**2578 General Poster Session (Board #41), Sun, 8:00 AM-11:45 AM**

**A phase 1 trial and pharmacokinetic study of RRx-001, a novel ROS-mediated pan-epigenetic agent.** *Presenting Author: Tony R. Reid, University of California, San Diego, La Jolla, CA*

**Background:** RRx-001 the first of a new class of pan-epigenetic anticancer agents, binds hemoglobin and drives RBC-mediated redox reactions under hypoxia. RRx-001 inhibits HDACs and Dnmt1 and 3a expression, affecting multiple aspects of cancer cell-cycle regulation and survival, including caspase activation, cyclin-dependent kinase activities, and p53 gene expression. The objectives of this dose-escalation trial were to investigate safety, DLTs, and PK of RRx-001. **Methods:** Eligible patients had advanced solid tumors; ECOG PS 0-2; adequate bone marrow function. In a 3+3 escalation design, RRx-001 was administered IV for up to 6h weekly for 8 weeks to patients in successive dose-escalating cohorts. Tumor response (CT, PET-CT, biopsy) was determined every 4 or 8 weeks. Subjects were evaluable if they had a baseline CT scan and at least one follow up scan after at least one dose of RRx-001. **Results:** 25 pts were dosed over 6 cohorts (10, 16.7, 24.6, 33, 55, 83 mg/m$^2$). Tumor types were pancreas (3), CRC (11), head and neck (4), melanoma (1), cholangiocarcinoma (1), ovarian (1), lung (2) and HCC (1) and oligodendroglioma (1). RRx-001 was well tolerated with no DLTs and no formal MTD was established. No RRx-001-induced systemic toxicities were observed. The only drug-related AE across all cohorts was acute and transient injection-site pain and vasodilation, moderate in severity and generally managed by lengthening infusion time, using peripheral venous access and corticosteroids. 20 pts were evaluable for response per protocol criteria, 1 with partial response (parotid adenoid cystic carcinoma), durable for one year. 9 pts (45%) had stable disease of ≥ 4 months. OS for all pts was 16.8 months. PK analysis of the GSH adduct was not representative of exposure to RRx-001. Two pts became responsive to previously failed FOLFIRI post RRx-001, as shown by changes in CEA and by imaging. As responses were seen in all cohorts, 33 mg/m$^2$ was selected as the Phase 2 dose. **Conclusions:** RRx-001 was well tolerated with infusion-site pain as the only observed AE to date. Toxicities normally associated with anticancer agents were absent. Single agent activity and a renewed response to previously failed chemotherapy was observed. Clinical trial information: NCT01359982.

**2579 General Poster Session (Board #42), Sun, 8:00 AM-11:45 AM**

**Effects of aprepitant on the pharmacokinetics of controlled-release oral oxycodone in cancer patients.** *Presenting Author: Yutaka Fujiwara, Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan*

**Background:** Oxycodone is a $\mu$-opioid receptor agonist widely used in the treatment of cancer pain. The predominant metabolic pathway of oxycodone is CYP3A4-mediated N-demethylation to noroxycodone, while a minor proportion undergoes 3-O-demethylation to oxymorphine by CYP2D6. The aim of this study was to investigate the effects of the mild CYP3A4 inhibitor aprepitant on the pharmacokinetics of orally administered controlled-release (CR) oxycodone. **Methods:** This study design was an open-label, single-sequence with two phases in cancer patients with pain who continued to be administered orally with multiple doses of CR oxycodone every 8 or 12 hours. Plasma concentration of oxycodone and its metabolites were measured up to 8 hours after administration as follows; on day 1, CR oxycodone was administered alone; on day 2, CR oxycodone was administered with aprepitant (125 mg, at the same time of oxycodone dosing in the morning). The steady-state trough concentrations (Css) were measured from day 1 to day 3. **Results:** Aprepitant increased the area under the plasma concentration-time curve ($AUC_{0\text{-}8}$) of oxycodone by 25% ($p<0.001$) and of oxymorphine by 34% ($p<0.001$), as well as decreased the $AUC_{0\text{-}8}$ of noroxycodone by 14% ($p<0.001$). Moreover, aprepitant increased Css of oxycodone by 57% ($p=0.001$) and of oxymorphine by 36% ($p<0.001$) and decreased Css of noroxycodone by 24% ($p=0.02$) at day 3 compared to day 1. **Conclusions:** Aprepitant increased the exposure levels of oxycodone by inhibiting its CYP3A4-mediated N-demethylation. Clinical trial information: UMIN000003580.

**2580 General Poster Session (Board #43), Sun, 8:00 AM-11:45 AM**

**A presurgical study of oral silybin-phosphatidylcholine in patients with early breast cancer.** *Presenting Author: Matteo Lazzeroni, European Institute of Oncology, Milan, Italy*

**Background:** Silybin-phosphatidylcholine (Siliphos) is an orally bioavailable complex of silybin, a poorly absorbable polyphenolic flavonolignan derived from milk thistle and endowed with potential anticancer activity in preclinical models. The purpose of the window of opportunity trial (code n. R621-IEO661/511) was to determine the tissue distribution of silybin-phosphatidylcholineand its effect on cell proliferation and other biomarkers in breast cancer (BC) patients. **Methods:** Twelve BC patients received silybin-phosphatidylcholine, 2.8 g daily for 4 weeks prior to surgery. Silybin levels were measured before (SIL) and after (TOT SIL) enzymatic hydrolysis by HPLC-MS/MS in biological samples (plasma, urine, BC tissue and surrounding normal tissue). Fasting blood samples were taken at baseline, before the last administration (end) and 2 hours after. **Results:** All patients were fully compliant and completed the treatment program. No toxicity was observed. SIL and TOT-SIL were undetectable in baseline samples. Median SIL and TOT-SIL concentrations after supplementation are shown in the table. Median TOT-SIL concentration was higher in the tumor as compared to the adjacent normal tissue (P=0.018). Despite a high between-subject variability, plasma SIL levels significantly correlated with the low concentration in normal tissue (Spearman coefficient=0.690, P=0.027). **Conclusions:** We show for the first time that oral silybin-phosphatidylcholine can attain biologically relevant breast tumor tissue levels and high blood concentrations of silybin. These results provide the basis for future clinical studies of Siliphos in breast carcinogenesis prevention. Circulating and tissue biomarkers of activity will be presented at the conference.

**Median (Q1-Q3) concentrations after supplementation.**

| | Urine*-final ng/mL | Plasma-end ng/mL | Plasma-end-2h ng/mL | Breast-K ng/g | Breast-N ng/g |
|---|---|---|---|---|---|
| **TOT-SIL** | 6,676 (3,766-14,515) | 901 (651-1,481) | 14,538 (13,147-16,828) | 131 (35-869) | 11 (0-34) |
| **SIL** | 144 (62-349) | 69 (13-59) | 5,847 (4,526-6,454) | 33 (4-58) | 0 (0-4) |

* Creatinine normalization; end: before the last administration; end-2h: 2 hours after the last administration; K: cancer tissue; N: normal tissue.

**2581 General Poster Session (Board #44), Sun, 8:00 AM-11:45 AM**

**Phase 1 study assessing dovitinib (TKI258) on the pharmacokinetics of caffeine, diclofenac, omeprazole, and midazolam in patients with advanced solid tumors.** *Presenting Author: Ding Wang, Josephine Ford Cancer Center/Henry Ford Health System, Detroit, MI*

**Background:** Dovitinib (TKI258) is an oral tyrosine kinase inhibitor targeting kinases involved in tumor cell proliferation and survival, including FGFR, VEGFR, PDGFR, c-KIT, and FLT3. In vitro, dovitinib induced CYP1A2, CYP2C9, and CYP2C19 activity and increased the mRNA level of CYP3A4. Here, we evaluated the impact of dovitinib on the pharmacokinetics (PK) of caffeine, diclofenac, omeprazole, and midazolam, the probe drugs metabolized by these cytochrome P450 isoforms. **Methods:** Patients (pts) ≥ 18 years of age with advanced solid tumors were given a cocktail of oral caffeine (100 mg), diclofenac (25 mg), omeprazole (20 mg), and midazolam (2 mg) on days 1 and 13, and dovitinib (500 mg oral once daily, 5 days on/2 days off) starting on day 2. Blood PK samples for each probe were collected predose and for 24 hours after drug cocktail dosing. Area under the curve (AUC) and maximum concentration ($C_{max}$) values were log-transformed and analyzed with a linear mixed-effects model. Following the drug-drug interaction phase, pts were allowed to continue dovitinib at the same dose and schedule. **Results:** Of 58 pts screened, 39 were treated, of which 28 and 26 pts were evaluable for PK analysis for drug interaction with caffeine and the remaining probe drugs, respectively. Dovitinib decreased the exposure (AUC and $C_{max}$) of caffeine and omeprazole, decreased the $C_{max}$of diclofenac, but increased the exposure of midazolam (Table). The most common adverse events regardless of study drug relationship were diarrhea (69%), fatigue (69%), nausea (64%), and vomiting (62%). **Conclusions:** Dovitinib is a strong inducer of CYP1A2, a moderate inducer of CYP2C19, and has limited impact on CYP2C9. Different from in vitro data, dovitinib is a moderate inhibitor of CYP3A4/5 in humans. Clinical trial information: NCT01596647.

| | Dovitinib + drug:drug alone Geometric mean ratio (90% CI) | | | |
|---|---|---|---|---|
| | **Caffeine** | **Omeprazole** | **Diclofenac** | **Midazolam** |
| **Enzyme tested** | CYP1A2 | CYP2C19 | CYP2C9 | CYP3A4 |
| **$AUC_{last}$** | 0.04 (0.03-0.05) | 0.39 (0.28-0.56) | 1.07 (0.86-1.34) | 2.63 (2.25-3.08) |
| **$AUC_{inf}$** | 0.06 (0.04-0.08) | 0.39 (0.28-0.55) | 1.19 (0.94-1.50) | 2.91 (2.31-3.66) |
| **$C_{max}$** | 0.20 (0.17-0.24) | 0.49 (0.35-0.70) | 0.65 (0.47-0.90) | 1.52 (1.33-1.75) |

**2582 General Poster Session (Board #45), Sun, 8:00 AM-11:45 AM**

**Analysis of impact of post-treatment biopsies in phase I clinical trials.** *Presenting Author: Randy F. Sweis, University of Chicago, Chicago, IL*

**Background:** It is commonly believed that post-treatment biopsies for pharmacodynamic biomarkers (PD-BM) positively impact drug development. We sought to determine the utility of PD-BM in phase I trials, based on their impact on subsequent studies. **Methods:** We identified publications on phase I clinical trials in oncology that incorporated a biomarker by searching PubMed using a broad search algorithm. Articles were restricted to 2003-2006 in order to allow adequate time for publication of subsequent trials citing the phase I trial. Articles covering pediatric populations, hematologic malignancies, topical/local therapies, gene therapy, immunotherapy, or radiation therapy were excluded. Characteristics of identified trials were analyzed and trials that included post-treatment biopsies were selected for further analysis. Citing articles were identified using PubMed and Google Scholar, and those articles were then reviewed. Fisher's exact test was used to compare groups. Statistics were carried out using JMP 11.0.0. **Results**: We identified 2,136 publications on phase I trials in oncology from 2003 to 2006. The use of any biomarker, as defined by our search algorithm was found in 200 (9.4%) publications, including 22 with a PD-BM. None of those PD-BM studies included a pre-specified statistical plan for the biomarker analysis. Only one study described performance characteristics of the assay. The number of reported biomarker tests ranged from 1-12, but no study included a correction for multiple testing. A statistically significant result on the PD-BM was reported in 3 (14%) studies, which was more likely to occur in industry-sponsored studies (P=0.04). A biomarker conclusion and statement of impact on future studies was found in 17 (77%) and 9 (41%) studies, respectively. Articles reporting subsequent phase 2/3 trials cited 19 (86%) of these PD-BM studies, but none used prior biomarker results in regard to phase 2/3 dose or schedule. Only a minority of the citing publications (8, 36%) mentioned the prior PD-BM studies. **Conclusions:** The impact of post-treatment biopsies for pharmacodynamic biomarkers is of uncertain value for subsequent drug development. This issue requires further evaluation, given the risk and cost of such studies.

**2583 General Poster Session (Board #46), Sun, 8:00 AM-11:45 AM**

**Pazopanib (P) and cisplatin (CDDP) in patients with advanced solid tumors: A UNICANCER phase I study.** *Presenting Author: Veronique Dieras, Institut Curie, Paris, France*

**Background:** P is an effective anti-angiogenic agent currently investigated in a wide variety of tumors outside its authorized indication. In a dose-escalation phase I study, we investigated the safety and tolerability of combining P with CDDP. **Methods:** Patients (pts) with metastatic refractory solid tumors eligible for CDDP chemotherapy were treated with oral P given once daily, in fasted condition, starting 8 days (d) before the first CDDP infusion. CDDP was given every 3 weeks (q3w) in a 1-hour iv infusion. Five dose levels (DL) were planned to investigate the occurrence of dose limiting toxicities (DLT) over cycle 1 and 2, and to determine the maximum tolerated dose (MTD). **Results:** 35 pts were enrolled with median age of 59 y., PS≤1. Tumor types were: ovary (8), H&N (5), sarcoma (5), breast (4), colorectal (4), choroidal melanoma (3), other (6). DLs explored are shown in the Table. MTD was confirmed at DL1. An inverted schedule (IS) was added at the MTD starting with CDDP followed by P to explore PK interaction. DLT were 2 Grade (G) 3 ALAT elevation, one associated with G4 hyponatremia (DL1 and DL2 respectively), 2 G3 thrombopenia + neutropenia (DL2), 1 G2 neutropenia (DL2), 2 G3 pulmonary embolism (DL1 and IS). Mean number of 21d-cycles was 3 for CDDP and 4.7 for P. 15 pts discontinued treatment for unacceptable toxicity, 5 pts are still under treatment. 2 complete (DL2) and 2 partial responses (DL1 and DL2) were achieved. Mean (CV% for interindividual variability) CDDP clearance was 13.6 L/h (27%) and not influenced by P. However, mean of P clearance was 0.78 L/h (69%) at d-1 (before CDDP), 24.5% lower at d1 (CDDP + aprepitant), and 30% lower at d2 (aprepitant), likely due to competitive inhibition of P metabolism and efflux by aprepitant. The plasma P exposures observed at 400 mg (at d-1) were similar to those observed at 800 mg of P during the first-in-man phase 1 [Hurwitz et al]: 676.2 μg.h/mL (47%) vs. 743.3 μg.h/mL (76%), respectively. A nonsignificant trend of higher P AUC was observed in patients with DLT. **Conclusions:** Despite activity observed in some patients, the potential to combine P and CDDP appears limited due to the safety profile and the PK interactions within the combination. Clinical trial information: NCT01165385.

| DL | P mg/d | CDDP mg/m² | n |
|---|---|---|---|
| **1** | 400 | 75 | 13 |
| **-1** | 400 | 60 | 3 |
| **2** | 600 | 75 | 6 |
| **-2** | 200 | 75 | 4 |
| **IS** | 400 | 75 | 9 |

**2584 General Poster Session (Board #47), Sun, 8:00 AM-11:45 AM**

**Evaluation of pharmacokinetic (PK) drug-drug interactions (DDI) between trebananib (AMG 386) and paclitaxel (PTX) in patients (pts) with advanced solid tumors.** *Presenting Author: Jennifer Robinson Diamond, University of Colorado Cancer Center, Aurora, CO*

**Background:** Trebananib (AMG 386) is an investigational peptide-Fc fusion protein that inhibits angiogenesis by preventing the interaction between angiopoietin-1/2 and Tie2. In a phase 3 study, trebananib 15 mg/kg QW plus PTX improved progression-free survival in women with recurrent ovarian cancer compared with placebo plus PTX. PTX was chosen because it is a standard of care in ovarian cancer, and both PTX and trebananib are dosed weekly. This open-label phase 1b DDI study evaluated PK of PTX with/without trebananib. **Methods:** Pts with advanced solid tumors who were candidates for PTX treatment, had evaluable/measurable disease per RECIST v1.1, and ECOG performance status ≤2 received PTX 80 mg/m$^2$ IV QW (3 wks on/1 wk off) beginning wk 1 and trebananib 15 mg/kg IV weekly QW beginning wk 2 until disease progression, unacceptable toxicity, or withdrawal of consent. Intensive PK sampling occurred in wks 1 (PTX only), 6 (PTX+trebananib), and 8 (trebananib only). CT/MRI was performed every 8±1 wks. The primary endpoint was $C_{max}$/AUC of PTX with/without trebananib. **Results:** Thirty-five pts were enrolled. Most had ovarian (n=11) or bladder cancer (n=9). Mean PTX $C_{max}$ and $AUC_{inf}$ were similar with/without trebananib, and mean trebananib $C_{max,ss}$ and $AUC_{tau,ss}$ were similar with/without PTX (Table). All pts had ≥1 adverse event (AE), most commonly fatigue (any grade/grade 3 or 4, 57%/14%), nausea (54%/3%), peripheral edema (51%/6%), and peripheral neuropathy (46%/3%). 34% of pts discontinued trebananib due to AEs. Among 26 pts with measurable disease, 5 had partial response and 8 had stable disease (per RECIST) as best response. **Conclusions:** There was no evidence of clinically meaningful PK DDI between trebananib and PTX. Toxicity was as anticipated for the combination of trebananib plus weekly PTX; no new toxicity signals were identified. Clinical trial information: NCT01992341.

**PK of paclitaxel and trebananib.**

| | Week 1 PTX alone | | | Week 6 PTX + trebananib | | |
|---|---|---|---|---|---|---|
| **Paclitaxel** | **n** | **Mean** | **SD** | **n** | **Mean** | **SD** |
| **$C_{max}$, ng/mL** | 33 | 2,290 | 896 | 30 | 2,970 | 932 |
| **$AUC_{inf}$, ng•h/mL** | 33 | 5,200 | 1,590 | 29 | 6,240 | 1,820 |
| | **Week 6 PTX + trebananib** | | | **Week 8 Trebananib alone** | | |
| **Trebananib** | **n** | **Mean** | **SD** | **n** | **Mean** | **SD** |
| **$C_{max,ss}$, μg/mL** | 31 | 359 | 98.2 | 28 | 366 | 90.6 |
| **$AUC_{tau,ss}$, mg•h/mL** | 31 | 15.4 | 5.64 | 28 | 17.0 | 6.97 |

**2585 General Poster Session (Board #48), Sun, 8:00 AM-11:45 AM**

**Clinical pharmacokinetic (PK)/pharmacodynamic (PD) model for Debio 1143, a novel antagonist of IAPs in cancer treatment.** *Presenting Author: Elisabeth Rouits, Debiopharm International SA, Lausanne, Switzerland*

**Background:** Inhibitors of apoptosis proteins (IAPs) modulate multiple processes, including caspase activation and NF-kB signaling. Expression and/or overexpression of IAPs have been reported for a variety of tumor types and are correlated with tumor growth and resistance to apoptosis induced by standard chemo and radiation therapies. The small molecule Debio 1143 is an orally-active IAP antagonist able to promote apoptosis in tumor cells. **Methods:** In a first-in-human Phase I study in patients with advanced cancer, Debio 1143 was given orally once daily on days 1-5 every 2 or 3 weeks. Ten dose levels ranging from 5 mg to 900 mg were explored. Blood samples were taken on days 1-5 for PK (Debio 1143) and PD assessments (IAPs levels, blood markers of apoptosis and inflammation) with rich sampling at day 1 and day 5. A population PK model was built within NONMEM 7.2. Further to a graphical PK vs PD check, population PK/PD models were explored. **Results:** The PK of Debio 1143 was well described by a two-compartment model with two absorption pathways. Debio 1143 bioavailability appeared to decrease after repeated administrations, suggesting a possible time-dependent PK. Graphically, markers of target engagement (cIAP1 PBMCs levels) and apoptosis (caspase-3 generated cytokeratine-18 fragments plasma levels [CK18-M30]) showed changes with Debio 1143 PK. cIAP1 levels could be fitted using an indirect response model where the elimination of cIAP1 was stimulated by Debio 1143. The CK18-M30 data was best fitted by a model with a delayed effect, onsetting after the first day. Simulations of d14q21 treatment predicted a clear decrease in cIAP1, with small differences between 100 mg and 200 mg dosing. A CK18-M30 increase ranging from 20 to 200% is predicted at day 14 after 200 mg qd. **Conclusions:** Debio 1143PK is compatible with oral administration q5d21. A clear relationship between PK and markers of target engagement or apoptosis was evidenced over the dose range explored. Findings from the q14d21 simulations indicate a promising PK/PD relationship for such schedule. Results from ongoing studies including PK/safety and PK/efficacy exploration will also feed the model to support Debio 1143 treatment optimization.

**2586 General Poster Session (Board #49), Sun, 8:00 AM-11:45 AM**

**Pharmacokinetics of the BCL2-targeted DNA interference (DNAi) nanoparticle PNT2258 in patients with recurrent or refractory non-Hodgkin lymphoma.** *Presenting Author: Wael Harb, Horizon Oncoloy Center, Lafayette, IN*

**Background:** PNT2258 contains PNT100, a DNA interference (DNAi) oligonucleotide encapsulated in a lipid nanoparticle. PNT2258 targets the BCL2 gene and is undergoing evaluation in patients with r/r NHL (NCT01733238). PNT2258 exhibits single-agent anti-tumor effect (50% ORR) in patients with r/r follicular or diffuse large B-cell lymphoma. The study also evaluated pharmacokinetic (PK) parameters in this target population, as reported here. **Methods:** Patients received 120 mg/m$^2$of PNT2258 IV on days 1-5 of a 21-day cycle. The concentrations of PNT2258 (measured as total PNT100) were determined pre-infusion and at 30, 60, 90, 120 and 150 minutes and at 24 hours by a validated hybridization-ligation bioanalytical method that measured PNT100 content using a complementary template probe followed by visualization by ELISA. **Results:** No free PNT100 was found in the plasma samples and detergent solubilization of intact PNT2258 in plasma was required to release encapsulated PNT100, indicating the stability of the PNT2258 liposome in serum. PNT2258 infusion resulted in minimal inter-patient variability when measuring encapsulated PNT100 concentrations on days 1 and 4. Day 4 plasma concentrations were consistently higher than day 1 levels without evidence of cumulative toxicity. Preliminary data indicate a serum half-life ($t_{½}$) of 9-12 hours. AUC exposure levels on days 1 and 4 were 87300 and 208000 ng.hr/ml, respectively, and additional day 4 values include $T_{max}$ = 2.39 hr (SD 0.22 hr), $C_{max}$ = 13,800 ng/ml (SD 10,000 ng/ml) and $R_{AUC\ Days\ 1\text{-}4}$ = 10.1. **Conclusions:** Pre-clinically, levels of > 22,377 ng.hr/ml PNT2258 resulted in activity in WSU-DLCL2 xenograft models. Clinical PK data confirm serum levels of the BCL2-targeted oligonucleotide that were 4-9 times greater than what was required to exhibit anti-tumor effect in the preclinical models. The data provided in this abstract indicate that the BCL2-targeted DNAi oligonucleotide PNT2258 is the first of this new class of therapeutic to provide systemic exposure, a manageable clinical safety profile and measureable anti-tumor effect warranting further clinical development. Clinical trial information: NCT01733238.

**2587 General Poster Session (Board #50), Sun, 8:00 AM-11:45 AM**

**Population pharmacokinetic (PK) analysis from phase 1 and 2 studies of the HER3 inhibitor patritumab in patients with advanced non-small cell lung cancer (NSCLC) or solid tumors.** *Presenting Author: Satoshi Yoshiba, Daiichi Sankyo Co., Ltd., Tokyo, Japan*

**Background:** Patritumab is a fully human antibody specific to HER3, a HER family receptor implicated in tumor resistance to anticancer treatment. In order to support patritumab dose recommendations, a population PK model was developed for phase 1 and 2 patritumab studies to characterize its PK and identify influencing factors. **Methods:** Population PK analysis was performed using data from the international phase 1b/2 HERALD study of patritumab (18 mg/kg every three weeks [q3w] or 18 mg/kg loading dose followed by 9 mg/kg q3w maintenance dose) in combination with erlotinib in EGFR treatment-naïve patients with advanced NSCLC after failure of ≥1 prior chemotherapy. Data from an open-label, phase 1 study of patritumab (9 mg/kg q3w or 18 mg/kg q3w) in Japanese patients with advanced solid tumors were also included. The effects of gender, baseline body weight (BW), creatinine clearance, eGFR, and albumin as covariates for clearance (CL), and gender and baseline BW as covariates for volume of central compartment (Vc) were investigated. PK simulations were performed to compare interpatient variability of patritumab exposure following fixed or BW-based dosing. **Results:** In total, 833 serum concentrations from 145 patients (136 NSCLC, 9 solid tumor) were included in the analysis. Serum patritumab concentrations were described by a two-compartment intravenous model with first-order elimination. Linear PK were observed at doses of 9 mg/kg and 18 mg/kg. CL, Vc, and volume of peripheral compartment were estimated as 0.0238 L/h, 3.62 L, and 2.50 L, respectively. BW and baseline albumin were significant covariates of CL ($p<.05$) and BW was a significant covariate of Vc ($p<.05$). PK simulations showed that BW-based dosing reduces interpatient variability in exposure compared with fixed dosing. **Conclusions:** Results showed that Vc was approximately serum volume and that CL was relatively low, indicative of a long terminal half-life. BW and albumin were significant factors affecting PK. The analysis supports an 18 mg/kg loading dose and 9 mg/kg q3w maintenance dose, and suggests that BW-adjusted dosing reduces interpatient variability. Clinical trial information: NCT01211483.

**2588 General Poster Session (Board #51), Sun, 8:00 AM-11:45 AM**

**A phase 1b trial of PI3K inhibitor copanlisib (BAY 80-6946) combined with the allosteric-MEK inhibitor refametinib (BAY 86-9766) in patients with advanced cancer.** *Presenting Author: Ramesh K. Ramanathan, TGen - Virginia G. Piper Cancer Center at Scottsdale Healthcare, Scottsdale, AZ*

**Background:** Dual inhibition of the PI3K and MAPK signaling pathways is a promising strategy for optimal anticancer therapy. In this phase 1b trial we determined the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of the combination of the pan-PI3K inhibitor copanlisib (C) and the allosteric-MEK inhibitor refametinib (R). **Methods:** Eight dose cohorts combining increasing doses and varying schedules of C (0.2-0.8 mg/kg IV; 3W on/1W off and QW) and R (30 mg and 50 mg bid po; continuous or 4 days on/3 days off) on 28-day cycles were studied. PK of C was assessed on Days 1 and 15 and PK of R on Days 14 and 15. In a 15-patient mutation-selected expansion cohort in mixed solid tumors, plasma samples are being assessed for tumor mutations (N-RAS, K-RAS, B-RAF, and PI3KCA) in circulating DNA by BEAMing and paired tumor biopsies undergoing biomarker analyses (including pERK and pAKT). **Results:** The study has completed accrual, with 49 patients treated in the dose escalation part of this study, of which 44 were evaluable for safety and efficacy. DLT's included Grade 3 AST or ALT elevation (n=2), hyperglycemia (1); hypertension (2); diarrhea (2), mucositis (2) and rash (1). The most common drug-related adverse events (>20%) in the dose escalation part were: diarrhea, nausea, hyperglycemia, fatigue, rash, anorexia, and hypertension. The MTD and RP2D for the C + R combination were: C 0.4 mg/kg IV QW and R 30 mg bid po. These doses are below the MTDs of either compound alone: C 0.8 mg/kg IV 3wks on/1 wk off and R 50 mg bid or 100 mg qd po. PK exposures of R and C were not affected by concomitant administration. Clinical activity included one PR in a patient with endometrial cancer, and stable disease lasting >4 cycles in 9 patients. Treatment discontinuations were due to disease progression (n=13), drug or tumor-related adverse events (n=24), or patient/physician discretion (n=12). Preliminary signals of antitumor activity have been observed in the fully accrued expansion cohort. **Conclusions:** The C+R combination was generally well tolerated with the MTD and RP2D below the individual tolerated doses of either compound. Preliminary evidence of clinical efficacy has been observed. Clinical trial information: NCT01392521.

**2589 General Poster Session (Board #52), Sun, 8:00 AM-11:45 AM**

**Phenformin combines with selumetinib in targeting KRAS mutant non-small cell lung cancer cells with alternative LKB1 status.** *Presenting Author: Jun Zhang, Winship Cancer Institute of Emory University, Atlanta, GA*

**Background:** Combining with docetaxel, the MEK inhibitor selumetinib holds the promise in treating KRAS mutant non-small cell lung cancer (NSCLC). However, a previous co-clinical trial based on genetically engineered mouse model (GEMM) suggested that concomitant loss of LKB1 might confer primary resistance. Since LKB1 inactivation was recently shown to sensitize NSCLC cells to the metabolism drug phenformin, which may also activate AMPK in LKB1 wild-type NSCLC, we therefore investigated whether phenformin could enhance the therapeutic effect of selumetinib in KRAS mutant NSCLC with different status of LKB1. **Methods:** NSCLC cell lines harboring RAS/RAF mutations that were tested with selumetinib were identified from literature to study the correlation of LKB1 status with selumetinib sensitivity. Then, the isogenic derivatives of A549 cell line namely $A549^{LKB1}$ (stably expressing wild-type LKB1) and $A549^{pBabe}$ (empty vector, LKB1 deficient) were used for actual studies of selumetinib, phenformin, their combination and dosing sequence. Phenformin was also investigated in GEMM derived cell lines 634 ($Kras^{G12D/wt}/p53^{-/-}/LKB1^{wt/wt}$) and t2 ($Kras^{G12D/wt}/p53^{-/-}/LKB1^{-/-}$). **Results:** 29 NSCLC cell lines were identified which showed concomitant LKB1 mutation significantly correlated with selumetinib resistance (IC50>1uM, p=0.0025). Consistently, $A549^{LKB1}$ cells were more sensitive to selumetinib. In contrast, $A549^{pBabe}$ (as well as t2) cells showed stronger response to phenformin. Their synergism was observed in both the proliferation and colony formation assays, and confirmed via CalcuSyn calculation. While phenformin helped induce much more robust apoptosis in $A549^{pBabe}$ cells, it also activated AMPK and potently enhanced the inhibition of S6 phosphorylation by selumetinib in $A549^{LKB1}$cells. Interestingly, when the drugs were applied sequentially in single agent, selumetinib followed by phenformin was ~ 3 folds more efficient in inducing apoptosis than the reverse order. **Conclusions:** Phenformin may synergize the anti-tumor effect of selumetinib in KRAS mutant NSCLC irrespective of the LKB1 status. Their combination offers a potential new therapy for this subtype of NSCLC.

**2590 General Poster Session (Board #53), Sun, 8:00 AM-11:45 AM**

**Tyrosine kinase inhibitors and QTc intervals: A class effect.** *Presenting Author: Jacqueline S.L. Kloth, Erasmus MC-Cancer Institute, Department of Medical Oncology, Rotterdam, Netherlands*

**Background:** Tyrosine kinase inhibitors (TKIs) are reported to be associated with prolongation of the QTc interval on the ECG. QTc interval prolongation increases the risk for life threatening arrhythmias. However, studies evaluating the effects of TKIs on QTc intervals are limited and consist of small patient numbers. **Methods:** We screened all patients from 4 centers in the Netherlands and Italy, who were treated with TKIs. To evaluate the effects of TKIs on the QTc interval we investigated ECGs prior to and during treatment with sunitinib, vemurafenib, sorafenib, pazopanib, imatinib, erlotinib, lapatinib or gefitinib. All ECGs were reviewed by a single cardiologist (CN). Outcomes of this study were quantitative change in QTc interval (ΔQTc) after start of TKI treatment and chance of becoming a high risk individual, defined as QTc ≥ 470 milliseconds (ms), adjusted for risk factors such as for $K^+/Ca^{2+}$levels, co-medication, age, gender and co-morbidity. **Results:** A total of 363 patients had ECGs taken prior to and during TKI treatment and were therefore eligible for the analyses (see Table). In the entire group, start of TKI resulted in a significant increase in QTc interval ($QTc_{baseline}$ = 401 ms *vs* $QTc_{treatment}$ = 415 ms, p < 0.0001). After correction for possible confounders (site, tumor type, ethnicity, TKI, time between ECGs), sunitinib, vemurafenib, sorafenib, imatinib and erlotinib showed a significant increase in QTc interval after start of treatment (p < 0.01). Especially patients treated with vemurafenib are at increased risk of having QTc ≥ 470 ms (p < 0.05). **Conclusions:** These observations show that most TKIs give rise to a significant increase in QTc interval. In vemurafenib treated patients, the incidence of patients who are at risk for arrhythmias is increased. Therefore, especially in case of combined risk factors, frequent ECG controls in patients treated with TKIs are required.

| | | QTc (ms) | | | N QTc ≥ 470 ms | | ΔQTc ≥ 30 ms |
|---|---|---|---|---|---|---|---|
| TKI | N | Baseline | Treatment | p-value | Baseline | Treatment | N |
| Whole | 363 | 401 | 415 | 0.0001 | 6 | 21 | 76 |
| Sunitinib | 110 | 393 | 406 | 0.0001 | 1 | 3 | 22 |
| Vemurafenib | 67 | 401 | 427 | 0.0001 | 1 | 8 | 23 |
| Sorafenib | 52 | 400 | 410 | 0.0015 | 1 | 2 | 11 |
| Pazopanib | 46 | 402 | 412 | 0.0792 | 1 | 2 | 6 |
| Imatinib | 41 | 410 | 425 | 0.002 | 1 | 1 | 8 |
| Erlotinib | 21 | 412 | 421 | 0.0043 | 0 | 2 | 3 |
| Lapatinib | 16 | 413 | 414 | 0.9822 | 1 | 1 | 1 |
| Gefitinib | 10 | 403 | 409 | 0.92 | 0 | 2 | 2 |

**2591 General Poster Session (Board #54), Sun, 8:00 AM-11:45 AM**

**Cytochrome P450 interacting medication use in adult advanced solid tumor and phase I trial patients.** *Presenting Author: Kari Braun Wisinski, University of Wisconsin Carbone Cancer Center, Madison, WI*

**Background:** Cancer patients often take multiple medications increasing the potential for drug-drug interactions. There is limited data regarding the frequency of cytochrome P450 (CYP) medication use in advanced cancer patients or among subjects enrolling in phase I trials. The objective of this study was to characterize medication use in adult advanced solid tumor patients, including those in phase I trials. **Methods:** We evaluated the electronic health record for medication use in adult patients with advanced solid tumors seen at the University of Wisconsin from 1/2008-7/2011. Two cohorts (metastatic and phase I) were established. Demographics, co-morbidities, and medications were abstracted. Each medication's CYP-interaction was classified using Lexicomp. We also reviewed charts from NCI-sponsored phase I trials from 1/2007- 12/2009 involving CYP interacting drugs. The CYP pathway affected, concurrent and contraindicated medications, and changes in medications for study eligibility were recorded. **Results:** Data from 1,773 patients were analyzed: 1,489 in the metastatic cohort [median age 62 (18-93), 52% female] and 284 in the phase I cohort [median age 59 (18-80), 57% female]. Polypharmacy was seen in both groups (95% phase I vs. 80% metastatic; p<0.001). The majority of the metastatic cohort were taking CYP interacting medications (87% ≥ 1 inhibitor , 45% ≥ 1 inducer and 79% ≥ 1 sensitive substrate). Use of moderate-strong inducers or inhibitors was also common: ≥ 1 inducer (40% and 36%) and ≥ 1 inhibitor (61% and 66%), metastatic and phase I, respectively. Separately, 4 phase I trials were evaluated, involving 294 screened subjects – 3.8% screen failed due to interacting medications. Charts from 74 enrolled subjects revealed 655 concurrent medications (average 8.9/subject). 93 medications were CYP-interacting and 51(69%) subjects were on ≥1 interacting medication. Of the 93 medications: 38 (41%) were stopped and 41 (44%) were changed for study. **Conclusions:** CYP-interacting medication use is common in patients with advanced cancer. Medications are frequently discontinued or changed for enrollment in phase I trials. This has important implications for translating phase I results into practice.

**2592 General Poster Session (Board #55), Sun, 8:00 AM-11:45 AM**

**The pharmacokinetics and safety of idelalisib in subjects with moderate or severe hepatic impairment.** *Presenting Author: Feng Jin, Gilead Sciences, Foster City, CA*

**Background:** Idelalisib (IDELA) is a potent inhibitor of PI3Kδ, which has been shown to be prominently expressed in cells of hematopoietic origin. IDELA is metabolized primarily by aldehyde oxidase to form GS-563117 and to a lesser extent by CYP3A and UGT1A4. The mass balance study of IDELA in healthy subjects showed the radioactive dose administered was recovered mainly in feces (~78%). The objective of this study was to evaluate the PK and safety of IDELA/GS-563117 in subjects with moderate or severe hepatic impairment following administration of a single oral dose of IDELA. **Methods:** Eligible subjects categorized by the Child-Pugh-Turcotte (CPT) classification system with moderate (Class B: CPT score 7-9) or severe (Class C: CPT score 10-15) hepatic dysfunction and matched healthy subjects received a single oral dose of IDELA at 150 mg under fed condition. Blood samples were collected and IDELA/GS-563117 levels were measured. Geometric least-squares mean ratio and 90% confidence interval of PK exposure parameters in the hepatic impairment group(s) versus matched controls were calculated, with clinically relevant exposure change defined as ≥ two-fold increase. Safety assessments were performed throughout the study. **Results:** A total of 32 subjects were enrolled in the study. The majority of subjects were white (87.5%) males (71.9%) and median age was 52 years. Most treatment-emergent AEs and laboratory abnormalities were Grade 1 or 2 in severity. Overall study treatments were generally well tolerated. IDELA $C_{max}$was generally comparable in the subjects with moderate or severe hepatic impairment vs healthy controls, while mean AUC was higher (58% to 60%). GS-563117 exposures were lower in hepatic impaired vs healthy control subjects, likely due to lower formation in the setting of liver impairment. These changes are not considered to be clinically relevant. Exploratory analyses indicated no relevant relationships between the IDELA or GS-563117 plasma exposures and CPT score. **Conclusions:** No clinically relevant changes in IDELA and GS-563117 exposures were observed in subjects with moderate or severe hepatic impairment versus matched healthy subjects. Single oral doses of IDELA 150 mg were well tolerated.

**2593 General Poster Session (Board #56), Sun, 8:00 AM-11:45 AM**

**Drug interaction profile of idelalisib and its major metabolite, GS-563117.** *Presenting Author: Feng Jin, Gilead Sciences, Foster City, CA*

**Background:** Idelalisib (IDELA), a potent PI3Kδ inhibitor in Phase 3 studies for hematological malignancies, is metabolized mainly by aldehyde oxidase to GS-563117 and partially by CYP3A. In vitro, IDELA inhibits Pgp, OATP1B1, and 1B3 and GS-563117 is a time-dependent CYP3A inhibitor. Accordingly, the present study evaluated the effects of IDELA on these transporters/enzyme, and rifampin (RIF), a strong inducer, on IDELA pharmacokinetics (PK). **Methods:** Single oral dose of probe Pgp (digoxin; DIG), OATP1B1/1B3 (rosuvastatin; ROS), and CYP3A (midazolam; MDZ) substrates were given alone or with IDELA 150 mg BID. IDELA 150 mg single dose was given alone or with RIF 600 mg QD. PK of IDELA, GS-563117, and probes were determined (N = 11 to 12). Lack of PK interaction was defined as 90% confidence interval of the geometric mean ratio within 70-143% (combination vs alone). Safety was assessed throughout the study. **Results:** The study enrolled mainly white males (N=24) with median age of 38 years. Upon treatment, most common adverse events (AE) were headache and pyrexia; Gr 3 transaminase increases (5/24 subjects) were reversible. Two subjects had serious AEs after treatment completion. No clinically relevant changes in vital signs/ECGs were noted. IDELA did not affect DIG or ROS PK but increased MDZ plasma exposure, consistent with GS-563117 CYP3A inhibition in vitro. RIF reduced IDELA and GS-563117 exposures, indicating enhanced IDELA metabolism by CYP3A with a strong inducer. **Conclusions:** IDELA does not affect common drug transporters and is a moderate inhibitor of CYP3A due to GS-563117. Strong inducers of CYP3A decrease IDELA exposure.

**PK parameters (mean [%CV]).**

| DIG | DIG | DIG + IDELA | % Geometric least squares means ratio (90% CI) |
|---|---|---|---|
| $C_{max}$ (ng/mL) | 1.6 (18) | 1.9 (19) | 124 (115, 133) |
| $AUC_{inf}$ (ng·h/mL) | 38.0 (28) | 37.0 (28) | 100 (87, 115) |
| **ROS** | **ROS** | **ROS + IDELA** | |
| $C_{max}$ (ng/mL) | 1.6 (52) | 1.9 (67) | 115 (97, 137) |
| $AUC_{inf}$ (ng·h/mL) | 23.1 (32) | 25.7 (59) | 103 (83, 124) |
| **MDZ** | **MDZ** | **MDZ + IDELA** | |
| $C_{max}$ (ng/mL) | 16.6 (29) | 38.1 (14) | 238 (200, 283) |
| $AUC_{inf}$ (ng·h/mL) | 89.1 (36) | 454 (24) | 537 (456, 632) |
| **IDELA** | **IDELA** | **IDELA + RIF** | |
| $C_{max}$ (ng/mL) | 2,150 (24) | 933 (41) | 42 (36, 49) |
| $AUC_{inf}$ (ng·h/mL) | 9,600 (37) | 2,290 (40) | 25 (23, 27) |
| **GS-563117** | | | |
| $C_{max}$ (ng/mL) | 1,990 (39) | 675 (44) | 32 (28, 37) |
| $AUC_{inf}$ (ng·h/mL) | 21,400 (59) | 2,240 (49) | 11 (9, 12) |

**2594 General Poster Session (Board #57), Sun, 8:00 AM-11:45 AM**

**The impact of gastric acid suppression therapy on tyrosine kinase inhibitors in advanced cancer patients.** *Presenting Author: Michael Patvin Chu, Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada*

**Background:** Oral tyrosine kinase inhibitors (TKIs) are used across tumor subtypes. Oral drug absorption is dependent on numerous factors including gastric acidity. Few studies have examined effects of gastric acid suppressants such as proton pump inhibitors (PPIs) on TKI outcomes. This study aims to determine if concurrent PPIs and TKIs impair progression free (PFS) and overall survival (OS) in patients (pts). **Methods:** Advanced/metastatic non-small cell lung cancer (NSCLC) patients receiving erlotinib from 2007 to 2012 and renal cell cancer (RCC) patients receiving sunitinib from 2007 to 2013 were retrospectively reviewed. The review included the Alberta outpatient/retail pharmacy databases. Pts with ≤ 1 week of therapy were excluded. Aside from demographics, pts were identified as concurrently receiving acid suppression if their pharmacy records included a PPI with prescription dates that overlapped by ≥ 20% of TKI treatment duration. PFS and OS were primary endpoints. **Results:** Of 545 NSCLC and 383 RCC pts, 507 and 231 were included, respectively. PPIs given concomitantly with erlotinib was detrimental to both PFS (hazard ratio [HR] 1.71, 95% CI: 1.39-2.11, p<0.0001) and OS (HR 1.29, 95% CI: 1.05-1.59, p=0.016). PPIs also affected sunitinib PFS (HR 1.42, 95% CI: 1.00-2.01, p=0.050) and OS (HR 1.27, 95% CI: 0.88-1.82, p=0.202). In pooled analysis, PPIs negatively impacted TKI PFS (HR 1.60, 95% CI: 1.34-1.91, p<0.0001) and OS (HR 1.34, 95% CI: 1.09-1.57, p=0.003). Considering performance status, acid suppression impaired PFS (HR 1.56, 95% CI: 1.31-1.87, p<0.0001) and OS (HR 1.24, 95% CI: 1.04-1.49, p=0.019) in both RCC and NSCLC. **Conclusions:** Despite limitations of a retrospective study, this large cohort study shows PPIs negatively interact with oral TKIs in NSCLC and RCC pts. Our results lend support that PPIs impair TKI absorption leading to poorer survival. This interaction is not found in electronic drug interaction sources and patients embarking on TKI therapy should be made aware that gastric acid suppressants may limit TKI efficacy. Further investigation as to whether this effect is seen in other TKIs is underway.

**2595 General Poster Session (Board #58), Sun, 8:00 AM-11:45 AM**

**Pharmacokinetics (PK) of eribulin mesylate in cancer patients (pts) with normal and impaired renal function.** *Presenting Author: Antoinette R. Tan, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

**Background:** Eribulin mesylate is a novel microtubule dynamics inhibitor. The effect of renal impairment on eribulin PK was evaluated following a single dose in adult pts with advanced solid tumors no longer responding to standard therapy. **Methods:** This phase 1 sequential cohort study grouped pts by renal function according to the Cockcroft-Gault formula: moderate impairment (creatinine clearance [CrCL]: 30–50 mL/min), severe impairment (CrCL: 15–29 mL/min), or matched-normal (CrCL: ≥80 mL/min). During cycle 1, the iv eribulin mesylate dose on days 1 and 8 were 1.4 mg/m$^2$ and 1.1 mg/m$^2$ for moderate; 0.7 mg/m$^2$ days 1 and 8 for severe; 1.4 mg/m$^2$ days 1 and 8 for normal; the dose for severely impaired pts was based on an interim PK analysis of the moderate group. Blood was collected up to 168 hours after the first dose (cycle 1); PK parameters were calculated by non-compartmental analysis. **Results:** Nineteen pts were enrolled (12 women; median [range] age 70 [33–82] years: moderate, n = 7; severe, n = 6; normal, n = 6). Mean dose-normalized (DN) area under the curve (AUC) was increased for pts with moderate and severe renal impairment when each was compared with pts with normal renal function (ratio for both: 1.49; 90% confidence interval [CI] 0.9, 2.45). The magnitude of increase in DN maximum plasma concentration was 1.31-fold (90% CI 0.84, 2.05) for pts with moderate impairment and 2.02-fold (90% CI 1.27, 3.21) for those with severe impairment. Renal impairment decreased eribulin clearance (CL). Regression analysis of CL and renal function showed a positive correlation with a numerically small slope (0.0184; 90% CI −0.00254, 0.0394), indicating a small effect of renal impairment on eribulin disposition. Simulations of expected AUC values showed that dose reduction to 1 mg/m$^2$ for pts with moderate and severe renal impairment led to similar eribulin exposure as with 1.4 mg/m$^2$ in pts with normal renal function. Similar toxicity profiles were observed between groups and there were no unexpected AEs. **Conclusions:** Renal impairment decreased eribulin clearance and increased eribulin exposure in pts with advanced solid tumors. PK evaluation supports eribulin dose reduction to 1 mg/m$^2$ in pts with moderate and severe renal impairment. Clinical trial information: NCT01418677.

**2596 General Poster Session (Board #59), Sun, 8:00 AM-11:45 AM**

**Choice of starting dose for biopharmaceuticals in first-in-human phase I cancer clinical trials.** *Presenting Author: Aaron Richard Hansen, Princess Margaret Cancer Center, University Health Network, Division of Medical Oncology & Hematology, Department of Medicine, University of Toronto, Toronto, ON, Canada*

**Background:** The conventional paradigm used to set a safe human starting dose (SD) in phase I trials with anti-cancer agents of low molecular weight is derived from 1/10$^{th}$ the severely toxic dose in 10% ($STD_{10}$) of rodents or 1/6$^{th}$the highest nonseverely toxic dose (HNSTD) in nonrodents. There is no consensus on whether this paradigm can be safely applied to biotechnology derived products (BDP). **Methods:** A comprehensive search was conducted to identify all BDP (excluding immune checkpoint inhibitors and antibody drug conjugates) with sufficient nonclinical and clinical data to assess safety of hypothetical use of 1/6$^{th}$ HNSTD from a relevant species in a phase I trial. The HNSTD in nonrodents was compared to the maximum tolerated dose (MTD) or in the absence of the MTD, the maximum administered dose (MAD) in patients. In addition, 1/6$^{th}$HNSTD was compared to the actual SD chosen for the first in human (FIH) trial, which employed a wide range of pharmacologic and toxicologic parameters to set the SD. **Results:** The search identified 23 BDP, of which 21 were monoclonal antibodies. The median ratio of MTD or MAD to the actual FIH SD was 36 (range 8 to 500). The majority of the BDP (21 of 23) were administered without reaching MTD in phase 1 trials. Hypothetical use of 1/6$^{th}$ HNSTD would not have exceeded MTD or MAD for all 23 BDP and would have reduced the median ratio of MTD or MAD to SD to 2.2 (range 1.2 to 10). While use of 1/6$^{th}$ HNSTD would have decreased the number of cohorts to reach MTD or MAD, hypothetical dose escalation of 1/6$^{th}$ HNSTD would have surpassed MTD or MAD for 10 of 23 (43%) BDP after 1 dose doubling. Only 7 of the 23 BDP included pharmacodynamic (PD) markers in animal models; however these markers were useful to determine the maximally biologic active dose in animals. **Conclusions:** Use of 1/6$^{th}$ HNSTD in nonrodents would not have resulted in unacceptable toxicities for the 23 BDP evaluated. Absence of MTD in animals and humans underscores the need to identify and utilize pharmacokinetic (PK) endpoints and PD biomarkers to guide SD selection for FIH phase I cancer trials. This approach could help reduce the number of dose-escalations needed to reach the optimum biological dose in phase 1 studies and limit unnecessary exposure to high drug levels in humans.

**2597 General Poster Session (Board #60), Sun, 8:00 AM-11:45 AM**

**Effect of toxicity-adjusted dose (TAD) of sunitinib on intra-patient variation of trough levels: A longitudinal study in metastatic renal cell cancer (mRCC).** *Presenting Author: Alison Yan Zhang, Crown Princess Mary Cancer Centre, Westmead, Australia*

**Background:** It has been proposed that trough levels of sunitinib (S) + metabolite of >50ng/mL may be associated with better anti-cancer effect. Large inter-patient variations of trough S have been reported in patients (pts) with mRCC at standard doses. However, little is known about the intra-patient variation of S levels over time. **Methods:** Dose and schedule of S was adjusted to ensure grade 1 or 2 toxicity on >10 days (d) of each 42 d cycle. Trough levels of S and its active metabolite, N-desethyl-sunitinib (NdS) were determined by HPLC-mass spectrometry every 6 weeks. Total trough level (TTL) was defined as the sum of S + NdS. Pts achieving a TTL target of >50ng/mL at stable dose were determined. **Results:** 27 pts with mRCC received S for a median of 7 months (range 0.5 to 11 months) with doses ranging from 25 to 87.5mg/day in the dose adjustment period. There was no correlation between dose and S trough level (r=0.14; P=NS). However there was a positive correlation between dose and NdS level (r=0.54; P<0.01), and dose and TTL (r= 0.34; P<0.01). The mean stable dose was 41.8mg (range 25-75mg) usually on a 14/7 schedule. Dose was significantly lower for females (32.5 vs 42.5 mg; P=0.05). Between pts, TTL ranged from 3.61 to 190.8 ng/mL (mean 68.0 ng/mL, coefficient of variation 42.3%). In contrast, mean intra-patient variability of TTL in pts at stable dose was 16.2% (range 0.4% to 32.2%). 24/27 patients (88.9%) reached the target TTL >50 ng/mL using the TAD protocol. **Conclusions:** Using a novel TAD protocol almost 90% of pts achieved the target TTL. This study demonstrates that individuals on stable dose had negligible variation in trough level over time and has implication for therapeutic drug monitoring. The study is ongoing to correlate TTL at stable dose with outcome. Clinical trial information: NCT01711268.

**2598 General Poster Session (Board #61), Sun, 8:00 AM-11:45 AM**

**Comparison of chemosensitivity testing of CETCs and spheroids in cancer patients with solid tumors.** *Presenting Author: Katharina Pachmann, Transfusion Center Bayreuth, Bayreuth, Germany*

**Background:** In vitro chemosensitivity testing of circulating epithelial tumor cells (CETCs) provides real-time information about the sensitivity of the tumor cells present in the patient and correlates with treatment success. Nevertheless, a fraction of CETCs can survive after conventional chemotherapy and grow into distant metastasis. A subpopulation of CETCs with proliferation activity has the ability to form spheroids in suspension culture. Spheroids exhibit stem cell-like properties and may be responsible for chemo therapeutic resistance. Therefore, the aim of our study was the comparison of the efficacy of chemo therapeutics on CETCs and on spheroids originated from the same individuals. **Methods:** The enumeration of CETCs collected from patients with solid tumors in clinical stage 1-4 were performed using the maintrac method. Subsequently, viable CETCs were cultured in suspension culture system allowing for spheroid formation. To evaluate the cytotoxic effect CETCs and spheroids were exposed to anticancer drugs in short time culture in different concentrations and for different periods of time. **Results:** Theresponse to chemotherapeutics was different between CETCs and spheroids. In contrast to CETCs, spheroids from the same patients were significantly more chemoresistant. Whereas active drugs led to membrane permeability in single CETCs with subsequent staining of the nuclei with propidium iodide, the same drugs led to disintegration of tumorspheres with destruction of part of the cells but often part of the cells in the spheres were able to survive. Epirubicin and, interestingly, and especially salinomycin, a polyether ionophore antibiotic isolated from *Streptomyces albus*, showed the best effects. Docetaxel, cyclophosphamide and 5-Fluoruracil showed almost no cytotoxic effects onto the cells in the spheres. **Conclusions:** Our results show, for the first time that stem cells circulating in peripheral blood, capable of forming spheroids are way more resistant to anticancer drugs than the remnant circulating tumor cells. We, furthermore, demonstrate that salinomycin efficiently destroys spheroids cultured from CETCs, strengthening its role as promising anti-cancer therapeutic.

**2599 General Poster Session (Board #62), Sun, 8:00 AM-11:45 AM**

**Effect of food on the pharmacokinetics (PK) of olaparib after oral dosing of the capsule formulation.** *Presenting Author: Ignace Vergote, Division of Gynecologic Oncology, University Hospitals Leuven, Leuven, Belgium*

**Background:** The oral PARP inhibitor olaparib is well tolerated at doses ≤400 mg bid (capsule formulation) and has shown efficacy in patients (pts) with BRCA-mutated ovarian cancer (Ledermann et al ASCO 2013). This is the first study to evaluate the effect of food on olaparib PK. **Methods:** InPart A of this open-label, randomized, crossover Phase I trial (NCT01851265), adult pts with refractory/resistant advanced solid tumors received a single oral dose of olaparib 400 mg (8 x 50 mg capsules) in each of 3 prandial states, after (1) an overnight fast (2) a high-fat meal and (3) a standard meal (5–14 days' washout between doses). Blood samples were taken pre-dose and regularly up to 72 h post-dose. Part B was an extension phase to further evaluate safety, where pts completing Part A could receive continuous dosing with olaparib 400 mg bid (capsules) whilst deriving clinical benefit. AE data were collected in both phases. **Results:** 32 pts (ECOG PS 0/1: n=30; PS 2: n=2) entered the study (female, 84%; median age, 59.5 y; most common tumor types, ovarian [44%], breast [19%], rectal [13%]). 30 pts contributed to statistical analysis (2 pts were excluded: n=1, previous gastric surgery; n=1, withdrawal after first dose [grade 1 vomiting]). The effect of food was similar for both meals. The rate of absorption was slower in the presence of food ($t_{max}$ delayed by ~2 h) resulting in little impact on $C_{max}$ whilst the extent of absorption (AUC) was increased by ~20% in the fed state. AE data from Part A were consistent with the known safety profile of olaparib. Part B is ongoing. **Conclusions:** The PK of olaparib following oral dosing of the capsule formulation is affected by food. Olaparib capsule doses should be taken on an empty stomach. Clinical trial information: NCT01851265.

| PK parameter | Fed GIsmean (n) | Fasted GIsmean (n) | GIsmean ratio (fed:fasted) | 90% CI for GIsmean ratio |
|---|---|---|---|---|
| **High-fat meal** | | | | |
| $C_{max}$ (μg/ml) | 6.2 (27) | 6.2 (30) | 1.01 | 0.93 – 1.10 |
| AUC (μg.h/ml) | 69.6 (27) | 58.0 (29) | 1.20 | 1.09 – 1.32 |
| $t_{max}$ (h) | 4.03 (27)* | 1.72 (30)* | 2.79† | 2.24 – 3.50† |
| **Standard meal** | | | | |
| $C_{max}$ (μg/ml) | 6.7 (29) | 6.2 (30) | 1.09 | 1.01 – 1.19 |
| AUC (μg.h/ml) | 69.2 (27) | 58.0 (29) | 1.19 | 1.08 – 1.32 |
| $t_{max}$ (h) | 4.00 (29)* | 1.72 (30)* | 2.00† | 1.53 – 2.40† |

Abbreviations: GIsmean, geometric least squares mean. *Median. †Median of food effect and 90% CIs, calculated using the Hodges–Lehmann estimator.

**2600 General Poster Session (Board #63), Sun, 8:00 AM-11:45 AM**

**Evaluation of the potential for QT/QTc interval prolongation for therapeutic biotechnology products.** *Presenting Author: Sarah J Schrieber, U.S. Food and Drug Administration, Silver Spring, MD*

**Background:** The implementation of the 2005 ICH E14 has included clinical evaluation of QTc prolongation for Therapeutic Biotechnology Products (TBPs). The ability of monoclonal antibodies (mAbs) to cause a QT effect via indirect mechanisms was uncertain. Therefore, we compiled a database of TBPs under development to assess the study designs and outcomes to guide future FDA regulatory recommendations on evaluation of the QT/QTc interval prolongation potential for TBPs. **Methods:** FDA reviews for QT/QTc study reports of TBPs were collected. Therapeutic drug class and molecular weight, study design features, ECG data analyses, study results, and regulatory recommendations were compiled and analyzed. **Results:** Fifteen TBPs with completed QT/QTc studies were identified including 13 mAbs and 2 antibody drug conjugates (ADCs). The study designs were varied by study population (patients vs. healthy subjects), dosing (single vs. multiple dosing), and active control (moxifloxacin was used in 2 studies). No large QT/QTc interval changes were observed for any of the mAbs evaluated. **Conclusions:** The available data suggest that mAbs are unlikely to cause QT/QTc interval prolongation. This finding supports our proposal that no dedicated QT assessment is necessary and clinical ECG monitoring may follow ICH E14 guidelines under negative 'thorough QT' (TQT) scenario except in cases where off-target cardiac-related adverse events are observed for specific mAbs. Conclusions cannot be made on the potential QT effect for other TBPs at this time, and the recommendations for well-designed QT studies to generate useful data for this assessment will continue.

**2601 General Poster Session (Board #64), Sun, 8:00 AM-11:45 AM**

**Results of a phase I trial combining ridaforolimus (mTOR inhibitor) and MK-0752 (Notch inhibitor) in patients with advanced solid tumors.** *Presenting Author: Sarina Anne Piha-Paul, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** The PI3K/AKT/mTOR signaling pathway is aberrantly activated in a variety of cancers. Ridaforolimus (R) is an mTOR inhibitor with activity in a broad range of cancers. MK-0752 inhibits the Notch receptor through its significant inhibition of gamma secretase and has evidence of antiangiogenic effects. R + MK-0752 may lead to complementary blockade of the PI3K pathway. **Methods:** The primary objective of this Phase I dose-escalation study (NCT01295632) was to define the dose limiting toxicities (DLTs) and maximum tolerated dose (MTD); a secondary objective was assessment of antitumor activity. Patients (pts) received a 5-day lead-in of R as monotherapy before beginning combination dosing. Rising doses of R were orally administered 5 days/week. MK-0752 dosing was fixed at 1800 mg given orally once per week. **Results:** For the 28 treated pts R doses were escalated from 20 to 30 mg/d. The MTD was determined to be 20 mg qd R 5 days/week + 1800 mg weekly MK-0752 (dose level 1). Among the 14 evaluable patients at the MTD, one DLT was reported: Grade 2 stomatitis, second episode. Among the 8 evaluable patients in dose level 2 (R=30mg), three DLTs were reported: 1 patient each with Grade 3 stomatitis, Grade 3 diarrhea, and Grade 3 asthenia. Other ≥G3 treatment-related adverse events (AEs) at the MTD were anemia (2 pts), stomatitis (2pts), diarrhea (1 pt), fatigue (1 pt), ALT elevation (1 pt), AST elevation (1 pt), hypokalemia (1 pt), hemoglobin decreased (1 pt) and hypophosphatemia (1 pt) (all Grade 3). The most common treatment-related Grade 2 toxicities at the MTD were: stomatitis (3 pts) and diarrhea (2 pts). One pt (squamous cell carcinoma [SCC] of the head/neck) had confirmed partial response (PR). Stable disease (SD) ≥6 mo was seen in 2 pts with SCC of the head/neck, including 1 pt with SD > 20 mo. **Conclusions:** The combination of R + MK-0752 shows activity in SCC of the head/neck (3/14). This combination resulted in disease responses though there were tolerance issues. The most common drug-related AEs occurring in >20% of patients treated at the MTD were diarrhea (32%), stomatitis (32%) and decreased appetite (32%) with 42% of patients experiencing Grade 3 drug-related AEs of any kind at this dose. Clinical trial information: NCT01295632.

**2602 General Poster Session (Board #65), Sun, 8:00 AM-11:45 AM**

**Pharmacokinetics of MEDI4736, a fully human anti-PDL1 monoclonal antibody, in patients with advanced solid tumors.** *Presenting Author: David Fairman, MedImmune, Cambridge, United Kingdom*

**Background:** MEDI4736 is a human immunoglobulin G1 kappa (IgG1$\kappa$) monoclonal antibody directed against human programmed death ligand 1 (PD-L1). MEDI4736 blocks inhibitory interaction of PD-L1 with the PD-1 (CD279) and B7-1 (CD80) molecules, and enhances T-cell activation. The primary objectives of this analysis were to assess the pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of MEDI4736 in patients with advanced solid tumors. **Methods:** Data were collected from a Phase 1 study (NCT01693562) designed to evaluate safety, tolerability and PK following 0.1, 0.3, 1.0, 3.0, and 10 mg/kg every 2 weeks (Q2W) and 15 mg/kg every 3 weeks (Q3W) intravenous (IV) doses of MEDI4736. A total of 32 patients provided evaluable data. PK, ADA and soluble PD-L1 (sPD-L1) as PD were measured using validated electrochemiluminescence assays in human serum. Data analysis was performed using Phoenix Winnonlin and NONMEM software. **Results:** Area under the curve (AUC) increased more than dose-proportionally over the dose range of 0.1 to 10 mg/kg Q2W and approached linearity at ≥3 mg/kg Q2W. Soluble PD-L1 was fully suppressed over the entire dosing interval with doses ≥ 0.3 mg/kg Q2W. MEDI4736 PK profiles were best described using a 2-compartment model with both linear and nonlinear (target mediated) clearances. The linear clearance, volume of distribution and concentration at half maximal elimination ($K_M$) were 240 mL/day, 3.6 L and 0.4 $\mu$g/mL, respectively. The half-life was ~23 days at doses ≥ 3 mg/kg Q2W. Greater than 99% target saturation (soluble and membrane bound) is expected at ≥40 $\mu$g/mL of MEDI4736. PK simulations indicate that following 10 mg/kg Q2W, >90% patients are expected to maintain PK exposure ≥40 $\mu$g/mL throughout the dosing interval. Three of 31 patients were ADA positive with an impact on PK and PD in 1 subject. Based on preclinical/clinical PK, PD, and safety data, a dose of 10 mg/kg Q2W was selected for the ongoing expansion phase. **Conclusions:** MEDI4736 exhibited non-linear (dose-dependent) PK and yielded dose-dependent sPD-L1 suppression. Evidence of ADA impacted exposure in 1 (3%) patient. A monotherapy dose of 10 mg/kg Q2W is currently being evaluated in multiple tumor types in the expansion phase.

**2603 General Poster Session (Board #66), Sun, 8:00 AM-11:45 AM**

**A phase I study to assess the safety, tolerability, and PK of dovitinib (D) in combination with gemcitabine (G) and capecitabine (C) in patients with advanced solid tumors.** *Presenting Author: Gerald J. Fetterly, Roswell Park Cancer Institute, Buffalo, NY*

**Background:** Fibroblast growth factor receptor (FGFR) signaling is implicated in many cancer types. D is a potent multikinase inhibitor of FGFRs, VEGFRs and PDGFR. D's preclinical anti-cancer effect was most pronounced in pancreatic cancer (PC) with enhanced FGFR signaling. The trial aimed to determine the MTD, toxicity and PK profile of D plus G/C. **Methods:** Patients (pts) with advanced solid tumors in whom G/C was appropriate and ECOG PS 0-1 were eligible. Dose escalation was conducted per a 3+3 design (Part A) with an expansion cohort (Part B; n=20) at the MTD with advanced PC and biliary cancers. Dose levels were D 300/400/500 mg oral daily on a '5-days-on/2-days-off' schedule with G 1000 mg/m$^2$ i.v. weekly x 2 and C 650 mg/m$^2$twice-daily x 14 days (1 cycle = 21 days). Adverse events (AEs) were graded using CTCAE 4.0 while tumor response by RECIST 1.1. Plasma samples were collected up to 48 hr post-dose. D, G, and C concentrations were determined using LC/MS/MS, and PK analysis was performed. **Results:** 18 pts were enrolled in total. 6 of 9 pts enrolled to Part A were evaluable for DLT. One of 6 pts treated at D 300 mg level experienced dose-limiting Gr3 colitis; 2 pts experienced non dose-limiting Gr2 neuropathy (reversible) after multiple cycles requiring D dose reduction. Dose escalation was halted and D 300 mg level used for Part B, which enrolled 9 pts so far. D 300 mg level was tolerable when dosed over multiple cycles. Preliminary efficacy included PFS > 12 months in 2 PC pts (1$^{st}$ line and post-FOLFIRINOX respectively). Common (>15%) ≥Gr 2 AEs included asthenia, elevated LFTs, N/V, hypertension, neutropenia and thrombocytopenia. Median $C_{max}$ and $AUC_{24}$ for D were similar after 3 weeks of dosing; 181 (Day 1) vs. 221 ng/ml (Day 19) and 3419 vs. 3854 ng*hr/mL, indicating no presence of autoinduction of D metabolism. Median $T_{1/2}$ of D was 13.1 hr. G and C PK were similar to literature. **Conclusions:** D 300 mg level was determined to be the recommended phase II dose and tolerable when dosed over multiple cycles. The PK analysis showed no drug-drug interaction. A clinical trial of D/G/nab-paclitaxel in PC is currently underway. Full toxicity and PK profile will be presented at the conference. Clinical trial information: NCT01497392.

**2604 General Poster Session (Board #67), Sun, 8:00 AM-11:45 AM**

**Risk of serious infection with mTOR inhibitors everolimus and temsirolimus in the treatment of cancer: A meta-analysis of randomized controlled trials.** *Presenting Author: Christine Ann Garcia, Stony Brook University Hospital, Stony Brook, NY*

**Background:** Everolimus and temsirolimus are inhibitors of mammalian target of rapamycin (mTOR), and utilized in the treatment of a variety of cancers. The use of mTOR inhibitors is associated with serious infections. This meta-analysis of randomized controlled trials (RCTs) was conducted to determine the overall risk of infection with mTOR inhibitors in cancer patients. **Methods:** Databases from PubMed and abstracts presented at the American Society of Clinical Oncology annual meetings up to October 2013 were searched for relevant studies. Eligible studies included randomized controlled clinical trials in which everolimus or temsirolimus was compared to controls in cancer patients. Data on all-grade and high-grade (grade 3 and 4) infections were extracted from the safety profiles of each clinical trial. Incidence and relative risk (RR) were calculated using random- or fixed-effects models. **Results:** A total of 10 RCTs with 3,535 patients (mTOR 1,911, controls 1,624) of various tumors were included in the analysis. The incidence of all-grade and high-grade infections were 21.0% (95% CI 15.0-28.9%) and 4.0% (95% CI: 2.2-7.0%), respectively. In comparison with controls, mTOR inhibitors significantly increased the risk for developing all-grade (RR: 1.82, 95% CI: 1.08-3.08, P=0.03), and high-grade infections (RR: 2.86, 95% CI: P<0.001). The increased risk of high-grade infection was observed for both everolimus (RR: 3.91, 95% CI: 1.67- 9.13, P=0.002) and temsirolimus (RR: 2.42, 95% CI: 1.30-4.50, P=0.005). However, the increased risk did not vary significantly with different mTOR inhibitors (everolimus vs temsirolimus: P=0.37) and among different tumor types (P=0.47). There was also no significant difference between mTOR inhibitors alone and their combination with other agents (P=0.68). **Conclusions:** The mTOR inhibitors everolimus and temsirolimus are associated with a significantly increased risk of high-grade infections in cancer patients. Further studies are needed to identify the risk factors for high-grade infection.

**2605 General Poster Session (Board #68), Sun, 8:00 AM-11:45 AM**

**Phase I trial of daily PI3K$\alpha$ inhibitor BYL719 plus letrozole (L) or exemestane (E) for patients (pts) with hormone receptor-positive (HR+) metastatic breast cancer (MBC).** *Presenting Author: Payal Deepak Shah, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Hyperactivation of phosphatidylinositol 3-kinase (PI3K) signaling is implicated in endocrine therapy resistance. Addition of an $\alpha$-selective PI3K inhibitor to hormonal therapy may be tolerable and beneficial in hormone resistant HR+ MBC. **Methods:** This 3+3 dose-escalation trial studied daily oral PI3K inhibitor (BYL719) added to standard dose aromatase inhibitor L (Arm A) or E (Arm B). Pts with HR+ MBC, any/no *PIK3CA* mutation, and on L/E were eligible. A cycle (C) was 28 days. Endpoints were dose-limiting toxicity (DLT), tolerability (CTCAE 4.0), and efficacy (RECIST v1.1). Paired tumor biopsies were performed for genomic and proteomic correlatives. **Results:** 14 pts (median (M) age: 55 (30-69) yrs), 7 per arm, received a M of 2 (<1-7) cycles. All were evaluable for toxicity. *PIK3CA* status was mutant/wild-type/unknown in 8/5/1 pts. M number of prior MBC therapies was 2 (1-12) in Arm A and 6 (2-14) in Arm B. BYL719 was given at 2 dose levels (DL0, 300mg; DL-1, 250mg). Both arms had similar toxicities. DLTs were maculopapular rash (N=2), hyperglycemia (N=2), and abdominal pain (N=1). Toxicity required dose de-escalation (4pts) and study discontinuation (2 pts). Treatment-related events included: G2 mucositis (21%), hyperglycemia (14%), dyspepsia (14%), fatigue (14%); G3 maculopapular rash (50%; 6/7 cases occurred on days 10-14 of C1; skin biopsies showed non-specific inflammation), hyperglycemia (7%) and abdominal pain (7%). There were no G≥4 treatment-related events. Of 9 pts evaluated for efficacy, 8 week best response was SD in 5 pts (included 1 pt with -29%, 1 with -19%) and PR in 1 pt with heavily pre-treated (including prior L) *PIK3CA*-mutated MBC to liver (C5+ on Arm A after initial DLT). **Conclusions:** Continuously dosed BYL719 with L or E shows promising antitumor activity in this hormone-refractory population. Early onset maculopapular rash results in frequent dose de-escalations. We are now exploring the addition of supportive dermatologic measures and non-continuous BYL719 dosing schedules. Examination of pharmacodynamic markers of PI3K inhibition and tumor genotype is ongoing. Further safety and efficacy data will be presented. Clinical trial information: NCT01870505.

**2606 General Poster Session (Board #69), Sun, 8:00 AM-11:45 AM**

**PI3K/AKT/mTOR genomic alterations in 94 patients with metastatic breast cancer in the phase I clinic at MD Anderson: Prevalence and association with response.** *Presenting Author: Jennifer J. Wheler, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Activation of the PI3K/AKT/mTOR pathway has a key role in breast cancer development and therapeutic resistance. Next generation sequencing (NGS) has expanded our understanding of this pathway. **Methods:** Genomic libraries were selected for all exons of 236 (or 182) cancer-related genes sequenced to average depth of >500× in a CLIA laboratory (Foundation Medicine, Cambridge, MA, USA) and analyzed for all classes of genomic alterations. **Results:** We report NGS profiles on 94 patients with metastatic breast cancer (MBC), median age 50 (range 23-69), including 41 (44%) with hormone receptor (HR)+/HER2- tumors; 4 (4%) that were HR+/HER2+; 2 (2%) that were HR-/HER2+; and 47 (50%) with HR-/HER2- (a disproportionate number of HR-/HER2- patients were seen in clinic). 46 patients (49%) had tumors with at least one molecular alteration (6 patients > 1) in the PI3K/AKT/mTOR pathway including: *PIK3CA* mutations (28 patients) and amplifications (2); *PIK3R1* mutations (4); *PTEN* mutations (4) and deletions (8); *AKT1* mutation (1) and amplification (1); and *AKT3* amplifications (4). Frequency of alterations was similar for HR+ and HR- tumors. 74 of 94 patients received treatment and are evaluable for response. The remaining 20 patients had not yet been treated in the phase I clinic. 31 of 74 evaluable patients had alterations in the PI3K/AKT/mTOR pathway *and* received therapy directly matched to that alteration ('matched'). 15 of 74 patients with a molecular alteration in this pathway did not receive matched therapy ('unmatched'). 28 of the 74 patients did not have an alteration in the pathway and were excluded from response analysis. Of patients on 'matched' therapy, 15 of 31 (48%) achieved partial response (PR) or stable disease (SD) ≥6 months compared to 2 of 15 (13%) patients who were 'unmatched' (*P*=0.02). **Conclusions:** Almost half of these patients with MBC cancer referred for Phase I trials had at least one molecular alteration in the PI3K/AKT/mTOR pathway. Patients treated with 'matched' therapies had significantly better outcomes than patients treated with 'unmatched' therapies. Prospective studies of NGS profiling are ongoing to validate this preliminary data.

**2607 General Poster Session (Board #70), Sun, 8:00 AM-11:45 AM**

**TAX-TORC: A phase I trial of the combination of AZD2014 (dual mTORC1/mTORC2 inhibitor) and weekly paclitaxel in patients with solid tumors.** *Presenting Author: Desamparados Roda, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, United Kingdom*

**Background:** AZD2014 (A) is a dual mTORC1/mTORC2 inhibitor and a previous phase I study determined the maximal tolerated dose (MTD) of A to be 50 mg BD 7/7. We have shown high p-P70S6K levels in cancer cells derived from ascites is associated with resistance to subsequent chemotherapy in ovarian cancer. Additive apoptosis was seen when A was added to paclitaxel (P) in preclinical models. We thus set up a multicentre phase I trial to evaluate this combination. **Methods:** The aims of the study were to determine the MTD, profile safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and antitumor activity of the combination of A+P. Dose escalation was performed using a 3+3 design. Patients (pts) with advanced cancers received 6 doses of weekly P (80 mg/m$^2$) and escalating doses of A, BD 3/7, starting on the same day as P in 49-day cycles. **Results:** 12 pts have been evaluated so far at a fixed dose of P (80 mg/m$^2$) and escalating doses of A; 25 mg (n=3), 50 mg (n=6) and 75 mg (n=3). Two pts had dose-limiting toxicities at 75 mg BD of A (grade 3 fatigue and grade 3 mucositis). The most frequently observed adverse events were fatigue (8/12), diarrhea (6/12), anemia (6/12), mucositis (5/12) and anorexia (4/12). However, of these, only fatigue (2/12) and mucositis (1/12) were grade 3 toxicities and occurred above the MTD. At the dose level of 50 mg BD, the AUC and $C_{max}$of A was 926.8 ng/mL and 2821.6 ng.hr/mL, respectively. Updated PD data will be presented. Currently, 3/5 pts with taxane pre-treated ovarian cancer have had a GCIG CA125 partial response (PR) (2 of these pts had a RECIST PR). 2/2 pts with squamous non small cell lung cancer (both previously pre-treated with docetaxel) had significant central necrosis of their tumors and one of these pts achieved a RECIST PR. **Conclusions:** The maximal tolerated dose of P is 80 mg/m$^2$q weekly and for A is 50 mg BD 3/7. This dose/schedule is well tolerated and has shown potentially promising clinical activity. A further intermittent schedule is being tested following which dose expansions in ovarian and lung cancer are planned. This study was supported by AstraZeneca, Cancer Research UK, Experimental Cancer Medicine Centre and Biomedical Research Centre initiatives. Clinical trial information: EudraCT number: 2012-003896-20.

**2608 General Poster Session (Board #71), Sun, 8:00 AM-11:45 AM**

**A study of risk of infection with drugs targeting the PI3 kinase (PI3K), AKT, and mTOR pathway.** *Presenting Author: Saeed Rafii, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, United Kingdom*

**Background:** Infection is a recognised side effect of chemotherapy, however its incidence varies across non-myelotoxic targeted agents. We studied the incidence of infection across phase I studies of the PI3K-AKT-mTOR inhibitors (PAMi) and compared them to other targeted therapies. **Methods:** This is a retrospective case-control study of electronic records of patients who were treated at the Royal Marsden Hospital, UK between 06/2008 and 05/2013. **Results:** A total of 366 pts treated in 12 phase I (Ph1) clinical trials with single agent PAMi were compared with a control group of 92 randomly selected patients from 10 other non-PAMi Ph1 trials. Median age was 56.3 and 54.6 years for the cases and controls (p:0.1). ECOG PS, tumour types and characteristics were balanced between the cases and controls. There were 99/366 (27%) infective events requiring antibiotics (Abx) in cases versus 8/92 (8.6%) in the controls (OR: 3.89, 95% CI: 1.8-8.3, $p<0.0005$). Grade 3/4 infective events requiring hospital admission and IV Abx were 30 (8.1%) in cases and 2 (2.17%) in the controls (OR: 4.0, 95% CI: 0.9- 17.1, $p=0.06$). The incidence of infection was similar between PI3K, AKT or mTOR inhibitors (Anova, $p = 0.76$). In addition to the 366 cases of single agent PAMi, we also collected data from 42 patients on 2 trials of PAMi combined with MEK inhibitors (MEKi) and 24 patients on 3 trials combined with chemotherapy. The all grade infective events were 26/42(62%) and 15/29 (62.5%), while G3/4 infective events were 3/42 (7.1%) and 4/29 (16.6%) in MEKi and chemotherapy combination trials respectively. **Conclusions:** This study shows for the first time that the overall risk of infection is significantly increased in patients treated with PAMi compared with other non-myelotoxic targeted agents. The incidence of G3/4 infective events was higher in the PAMi treated patients compared to the control group, although it was not statistically significant. In the cohort studied, there was no difference in the risk of infection between PI3K, AKT or mTOR inhibitors. With the increased use of PAMi in clinical practice, the risk of infection with these drugs either as single agents or in combinations should be taken into consideration when designing and conducting clinical trials.

**2609 General Poster Session (Board #72), Sun, 8:00 AM-11:45 AM**

**Correlation of intratumoral metabolic changes measured with 18F-FDG PET parametric response maps with concentrations of CC-223, a TORC 1/2 kinase inhibitor, in human glioblastoma.** *Presenting Author: Benjamin M. Ellingson, Department of Radiological Sciences, Biomedical Physics, and Bioengineering; University of California, Los Angeles, Los Angeles, CA*

**Background:** CC-223 is a potent selective inhibitor of mTOR kinase. Through inhibition of TORC1, TOR kinase inhibitors may result in down regulation of genes involved in glucose metabolism. A decrement in 18F-FDG PET uptake might represent early response of mTOR kinase inhibition. PET parametric response maps (PRMs) are a new technique involving voxel-by-voxel quantification of changes in PET uptake before and after therapy. This study explored relationships between intratumoral metabolic changes with PET PRMs, intratumoral and plasma drug concentration in a Phase I, surgical dose-expansion study in GBM. **Methods:** Eight evaluable patients with recurrent GBM received CC-223 daily for $15\pm7$days before planned salvage tumor resection. Tumor and plasma samples were obtained at surgery. MRI and $^{18}$F-FDG PET scans were obtained prior and after CC-223treatment. MRI and FDG standard uptake value (SUV) maps were aligned to baseline images. Voxel-wise percentage change and volume of changing FDG uptake in enhancing tumor was correlated with intratumoral and plasma measures of CC-223. **Results:** A positive linear correlation was found between tumor volume with decreasing FDG SUV and CC-223 concentration within resected tumor ($R^2=0.63$, $P=0.02$), suggesting a higher penetration of CC-223 results in a larger decrease in FDG metabolism within tumor. The volume of tumor with increasing FDG SUV correlated with maximum CC-223 plasma concentration ($R^2=0.52$, $P=0.04$), suggesting that lower plasma CC-223 concentration may result in a higher volume of growing tumor. There was a negative trend between the proportion of enhancing tumor with increasing FDG SUV and maximum CC-223 concentration in tumor ($R^2=0.39$, $P=0.1$), suggesting more drug penetration results in a lower proportion of tumor with increasing metabolic activity. Results are preliminary based on a sparse sample size. **Conclusions:** The volume and proportion of tumor with changing FDG uptake may correlate with plasma and intratumoral CC-223 concentration, suggesting FDG PET PRMs may provide non-invasive insight into CC-223 brain penetration and changes in intratumoral metabolic activity.

**2610 General Poster Session (Board #73), Sun, 8:00 AM-11:45 AM**

**Phase 1 dose escalation study of copanlisib (BAY 80-6946) in combination with gemcitabine or gemcitabine-cisplatin in advanced cancer patients.** *Presenting Author: Richard D. Kim, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

**Background:** Copanlisib (BAY 80−6946) is a potent and reversible pan-class I PI3K inhibitor with significant activity against PI3K-$\delta$ and PI3K-$\alpha$ isoforms. We report the results of an open-label, Phase 1 study of copanlisib in combination with gemcitabine alone and with gemcitabine plus cisplatin in advanced cancer patients. **Methods:** On Treatment A, patients received gemcitabine at 1000 mg/m$^2$ IV and 2 dose levels of copanlisib 0.6 mg /kg or 0.8 mg/kg IV on days 1, 8 and 15 of a 28-day cycle to determine whether the single agent maximum tolerated dose (MTD) of copanlisib (0.8mg/kg) was tolerable with the chemotherapy. On Treatment B, patients received cisplatin at 25 mg/m$^2$ IV, gemcitabine 1000 mg/m$^2$ IV and copanlisib IV on days 1 and 8 of a 21-day cycle at the MTD determined in Treatment A. The primary objective was to determine the safety, tolerability, and MTD of copanlisib in combination with gemcitabine and gemcitabine-cisplatin. **Results:** A total of 29 patients were treated with copanlisib. In Treatment A, 8 patients received copanlisib at 0.6 mg/kg and 8 at 0.8 mg/kg in combination with gemcitabine. There were no reported dose-limiting toxicities (DLTs) and the 0.8 mg/kg dose was the maximum tested dose. In Treatment B, 13 patients received copanlisib at 0.8 mg/kg with gemcitabine-cisplatin and no DLTs were observed. The most frequently observed drug-related adverse events reported in >20% of the patients were hyperglycemia, nausea, diarrhea, anemia, and fatigue. There were no treatment-related deaths. Pharmacokinetic evaluations showed comparable results across treatment groups indicating the absence of relevant PK interactions. Of the 2 patients enrolled in treatment schedule B with biliary tract cancer (BTC), one achieved a complete response (CR) and one a partial response (PR) according to RECIST criteria. An expansion cohort in patients with BTC with treatment schedule B is now ongoing, and one PR has been observed to date. **Conclusions:** The combination of copanlisib with gemcitabine alone or with gemcitabine plus cisplatin is generally well tolerated, with an early efficacy signal seen in patients with BTC. Clinical trial information: NCT01460537.

**2611 General Poster Session (Board #74), Sun, 8:00 AM-11:45 AM**

**Analysis of inactivation of PI3K/AKT/mTOR signaling pathway using neoadjuvant BKM120 in PI3KCA mutated early breast cancer.** *Presenting Author: Estevez G Laura, Centro Integral Oncológico Clara Campal, Madrid, Spain*

**Background:** The PI3K/AKT/mTOR signaling pathway plays a key role for the growth and survival of breast cancer cells and aberrations such as phosphatidylinositol-3-kinase (*PIK3CA*) mutations are common. BKM120 is an oral pan-class I *PIK3CA* inhibitor. The aim of this study was to evaluate neoadjuvant BKM120 in *PIK3CA* mutated early breast cancer in order to assess the effect in PI3K/Akt/mTOR signalling pathway. **Methods:** Patients (pts) with previously untreated invasive, non-metastatic histologically confirmed breast cancer, with a tumor size ≥ 1,5cm and non-urgent surgical treatment were enrolled. Only women with ER+ / HER2- and *PIK3CA* gene mutated were eligible. *PIK3CA* as well as *KRAS* mutation were evaluated at the diagnosis core biopsy .Patients received treatment with BKM120 (100mg/day; administered orally) during 4 weeks. Subsequently, surgery was performed. Inmunohistochemical analysis of p*Akt* and pRS6 (the H-score intensity x %) were evaluated on tumor tissue at surgery. H score < 150 was related with inactivation of PI3K signalling pathway. **Results:** To date 54 patients has been included (median age, 52,5 years; range 38-69 years;). 20 out of 54 (37%) had *PIK3CA* mutated and 19 have completed BKM120 treatment. *PIK3CA* mutation: Exon 20, 9 pts; exon 9, 7 pts; exon 4, 2 pts, exon 7, 1 pts and exon 1, 1 pts. None of the tumors had mutations in *KRAS* at the core biopsy. One patient discontinued treatment due to adverse event (nausea grade 2). The most relevant adverse events included transitory increase of transaminases. No serious or grade 4 adverse events were observed. Preliminary results of 19 pts showed inactivation of pRS6 (H score < 150) in 14 pts (74%) with no change in the reminder 5 pts. Inactivation of pAkt was only observed in 4 out of 11 tumors. **Conclusions:** Four weeks of neoadjuvant BKM120 produced a noticeable decrease level of the downstream effector pRPS6 in 74% of the tumors. However, decrease level of p*Akt* was only observed in 4 out of 11 tumors. In our experience, measurement of p*Akt* in tissue required very stringent conditions for sampling and handling. Thus, assessment of pRS6 seems more reliable and a more appropriate target. Final p*Akt* analysis will be presented along with updated results. Clinical trial information: CBKM120XES01T.

**2612 General Poster Session (Board #75), Sun, 8:00 AM-11:45 AM**

**Complications of hyperglycemia in phase 1 trials targeting the PI3K-akt-mTOR (PAM) pathway.** *Presenting Author: Elena Geuna, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, United Kingdom*

**Background:** PAM inhibitors (PAMi) are targeted agents increasingly being used as single agents or in combinations to treat metastatic cancer. Hyperglycemia has often been reported as an on-target toxicity of agents inhibiting this pathway and will become increasingly important with their use in larger number of patients (pts). We aimed to compare the incidence and degree of hyperglycemia across a range of PAMi phase I clinical trials. **Methods:** Retrospective case-control study of 510 pts with advanced solid tumours treated on 28 different phase 1 clinical trials at the Royal Marsden Hospital, UK, between June 2008 and May 2013. Data were collected on pt treatment and tumor characteristics, baseline and highest blood sugar levels during the trial. **Results:** 400 pts were treated in 18 trials with PAMi (82 pts with PI3Ki, 139 with mTORi, 150 with AKTi and 29 with PI3K/mTORi). A control group of 110 pts treated in 10 trials of targeted agents not targeting the PAM pathway were randomly selected. Baseline characteristics were well balanced between both study groups. There was no difference in the incidence of all grade hyperglycemia in the PAMi and control group, 347/400 (86.7%) and 89/110 (80.9%), OR 1,55 (95% CI 0.89-2,69 p=0.124). Importantly there was increased grade 3-4 hyperglycemia in pts in PAMi versus controls respectively, (28/400 vs 0/110, p = 0.005). Within the PAMi treated group the incidence of grade 3-4 hyperglycemia was 1.2%/11.3%/ 2.9%/20% in PI3K, AKT, m-TOR and PI3K/mTOR inhibitors, respectively and these differences were statistically significant (p = 0.001). In the PAMi group the study drug was stopped in 9 pts (2.3%) due to hyperglycemia. Only 27 pts (7%) required treatment for hyperglycemia; n=23 (6%) metformin and n=4 (1%) insulin. No pts developed severe metabolic complications, e.g. diabetic ketoacidosis or hyperosmolar hyperglycemic state. **Conclusions:** PAMi are associated with a significantly increased risk of high-grade hyperglycemia, compared with controls but high-grade hyperglycemia was not found to be associated with severe metabolic complications. These data confirm that hyperglycemia is a common, predictable and manageable toxicity which should not impair the development of these agents.

**2613 General Poster Session (Board #76), Sun, 8:00 AM-11:45 AM**

**Presurgical evaluation of the AKT inhibitor MK-2206 in patients with operable invasive breast cancer.** *Presenting Author: Kevin Kalinsky, Columbia University Medical Center, New York, NY*

**Background:** The PI3K/Akt signaling pathway is an important signaling pathway in breast cancer (BC). MK-2206 is the first allosteric Akt inhibitor in clinical development. The purpose of this pre-surgical study is to determine the biologic effects of MK-2206 on tumor and blood markers in newly diagnosed operable BC. **Methods:** In this trial, 2 doses of weekly MK-2206 were administered in pts with stage I-III invasive BC (at least T1c): first dose at day -9 and second at day -2 from surgery (goal n=30). The primary endpoint was reduction of $pAkt^{Ser473}$. Secondary endpoints included change in downstream proteomic changes, tumor proliferation (ki-67), and blood based-markers [phospho-markers in peripheral blood mononuclear cells (PBMCs)]. To maintain tumor quality, samples were processed rapidly by a standardized protocol. Paired t-tests were used to compare biomarker changes before and after MK-2206. **Results:** From 8/11-3/13, 12 pts were enrolled. The mean age was 53.1 years (SD: 11.2). At diagnosis, the mean tumor size was 2.5 cm (SD: 1.1). Eight pts had HR+/HER2- BCs, 1 HR+/HER2+ BC, and 3 triple negative BCs. At 200 mg (n=4), 2 pts experienced grade III rash and/or pruritus (Table), requiring 1 pt delay to surgery for 11 days. The dose was lowered to 135 mg (n=3), with 1 pt experiencing grade III rash/pruritus. Upon dose reduction to 90 mg (n=5), 1 pt had grade III rash. In PBMCs for 2 pts treated at 200 mg, reduction was seen in pS6 [mean fluorescence intensity (pre- vs. post-MK-2206); 5034 vs. 1749] and pAKT (5595 vs. 4165), with an increase in IGFR1 (6740 vs. 8653). Biomarker assessment is ongoing. **Conclusions:** We observed a high rate of toxicity that resulted in study suspension despite 2 dose reductions. Preliminary biomarker analysis demonstrates MK-2206 interacts with the proposed target *in vivo*, with up-regulation of upstream tyrosine kinase levels. If confirmed, this may identify mechanisms in which anti-tumor activity is attenuated. Clinical trial information: NCT01319539.

**Toxicities.**

| Dose level | # of Pts | Grade I (# of pts) | Grade II | Grade III |
|---|---|---|---|---|
| **200 mg** | 4 | Mucositis (1)<br>Hyperglycemia (1) | Mucositis (2)<br>Rash (1)<br>Fever (1)<br>Hyperglycemia (1) | Rash (1)<br>Pruritus (2) |
| **135 mg** | 3 | Pruritus (1) | Rash (1) | Rash (1)<br>Pruritus (1) |
| **90 mg** | 5 | Mucositis (1)<br>Dry Skin (2) | Mucositis (1) | Rash (1) |

**2614 General Poster Session (Board #77), Sun, 8:00 AM-11:45 AM**

**Phase 1 study of combination carboplatin, paclitaxel, and ridaforolimus in patients with solid, endometrial, and ovarian cancers.** *Presenting Author: Hye Sook Chon, Department of Gynecologic Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

**Background:** Ridaforolimus (RIDA) is a mTOR inhibitor that has demonstrated tolerability as intravenous (IV) and oral formulations. PI3K/AKT/mTOR signaling is associated with taxane resistance. In cancer cells, inhibition of mTOR signaling counteracts AKT-mediated resistance to drugs inhibiting tubulin. Paclitaxel and carboplatin (PC) have broad anti-cancer activity, and mTOR inhibition with PC has synergistic and additive effects in solid tumors. This 3+ 3 phase I study was to determine the maximal tolerated dose and R2PD of oral RIDA with PC during the first cycle of treatment. **Methods:** Solid cancer patients (pts) with measureable disease and <4 prior therapies received P (175mg/m2 IV) and C (AUC 5 to 6 mg/ml/min IV) on day (D)1 of each 3-week (wk) cycle. RIDA in escalating cohorts of 10-40 mg is administered orally daily for 5 days per wk (D1-5, D 8-12, D 15-19) in phase IA cohorts. Samples were collected for pharmacokinetics of RIDA and P and pharmacodynamics. > 1 DLT of thrombocytopenia or neutropenia in latter cycle shifted RIDA to alternate schedule (D1-5, D 8-12). **Results:** 22 pts have been enrolled; 9 ovarian/fallopian/peritoneal, 5 endometrial, 3 cervical, 2 esophageal, 1 urethral, 1 vaginal, 1 mesothelial. Median age was 63 (ranged 30-72). There were two Grade 4 neutropenias as DLT in dose level 1, thus a switch to predefined alternate dosing schedule (D1-5, D8-12). Dose escalation continued to PC(AUC5) + 40 mg RIDA with 1 of 4 DLTs. Total 166 cycles (ranged 1-12) were administered. Sixteen of 22 pts were evaluable for response: PR (32%), SD (27%), and PD (14%). One non-related to drug death was reported (non-related to drug). Grade 3/4 toxicities were observed in 21 of 22 pts (118 cycles of treatment) and were predominately myelosuppression. **Conclusions:** Treatment with RIDA combined with PC has no new unanticipated toxicities with activity in pretreated cancers. The RP2D is PC(AUC5) + RIDA 30mg D1-5, D8-10 q 3wk. Clinical trial information: NCT01256268.

**2615 General Poster Session (Board #78), Sun, 8:00 AM-11:45 AM**

**First-in-human (FIH) phase I study of a selective VEGFR/FGFR dual inhibitor sulfatinib with milled formulation in patients with advanced solid tumors.** *Presenting Author: Jian-Ming Xu, Cancer Center, 307 Hospital, Academy of Military Medical Science, Beijing, China*

**Background:** Sulfatinib is a highly selective oral small molecule tyrosine dual inhibitor of vascular endothelial growth factor receptors (VEGFR) and fibroblast growth factor receptors (FGFR). The FIH phase I data of the original formulation was reported in ASCO 2013(abs#3040). A milled formulation was subsequently developed to improve the PK property of this compound. **Methods:** This phase I dose-escalation study was to determine the maximum tolerated dose (MTD), dose-limiting toxicities (DLTs), pharmacokinetic (PK) profiles, and preliminary antitumor activity of sulfantinib when given orally in continuous cycles of 28 days, until disease progression or unacceptable toxicity. **Results:** Totally 60 pts have been enrolled (43 were treated with original formulation and 17 with milled formulation). For the 17 pts treated with milled sulfatinib at doses of 200mg, 300mg and 350mg once daily, the median age was 57 (23-69) yrs, with 82% male. Common adverse events included hypertension, nausea, diarrhea and elevated AST/ALT, mostly grade1/2. No DLT was observed. MTD has not been reached. PK analyses showed that drug exposures in terms of Cmax and AUC was increased while the inter- and intra-individual variability was reduced with milled formulation comparing to original formulation, indicating improved oral absorption. A reasonable 2-fold accumulation was observed at steady-state with $t_{1/2}$ of 20.2±4.75 h and 15.4±3.66 h at 200 and 300 mg, respectively. Among 13 evaluable pts, partial response (PR) was observed in 4 pts (ORR 30%) including 1 HCC in 200mg QD cohort, 1 liver neuroendocrine tumor (NET) and 1 NET with unknown primary site in 300mg cohort, and 1 lymph node NET in 350mg cohort. 7 (54%) pts had stable disease. **Conclusions:** Sulfatinib in milled formulation was well tolerated at doses up to 350 mg daily and demonstrated improved oral absorption and reduced exposure variability. Encouraging preliminary clinical efficacy including PR in pts with HCC and NET was observed. Further clinical development with sulfatinib milled formulation is warranted. Clinical trial information: CTR20131070.

**2616 General Poster Session (Board #79), Sun, 8:00 AM-11:45 AM**

**A phase I, open-label, nonrandomized trial of OPB-31121, a STAT3 inhibitor, in patients with advanced hepatocellular carcinoma (HCC).** *Presenting Author: Masafumi Ikeda, Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

**Background:** OPB-31121 is an orally administered novel STAT3 inhibitor. STAT3 is found to be activated in the majority of HCC with poor prognosis. Following phase I studies for solid tumors, this multicenter phase I study was performed to evaluate the safety, recommended dose (RD), pharmacokinetics, and antitumor activity of OPB-31121 in patients (pts) with advanced HCC. **Methods:** HCC pts with Child-Pugh A or B who progressed on or were intolerant to sorafenib were eligible. A standard 3 + 3 dose-escalation design was used with a 28-day cycle. The tested dose levels were 50, 100, 200, and 400 mg/day. Tumor response was assessed by modified RECIST. **Results:** Twenty-three pts were enrolled. All pts had previously received median 2 different regimens (range, 1-5) of chemotherapy. Median age was 65 (range, 45-79) and 20 pts were male. ECOG PS 0/1=15/8, HBV/HCV=8/7, Child-Pugh A/B =22/1. The most common toxicities of all grades were nausea (87%), vomiting (83%), diarrhea (70%), fatigue/malaise (57%), and peripheral sensory neuropathy (26%). These toxicities were predominantly grade 1 or grade 2. The dose-limiting toxicities were persisting grade 2 nausea which needed a drug withdrawal at 200 mg and grade 3 nausea, diarrhea, peripheral sensory neuropathy and gait disturbances at 400 mg. The RD for OPB-31121 in advanced HCC pts was determined to be 200 mg. PK analysis showed that T1/2 was approximately 30 h and Tmax was around 8 h at 200 mg. Both Cmax and AUC exhibited dose proportionality. The mean Cmax value at 200 mg was 2-3 times higher than IC50 values for inhibitory effect against cell proliferation and phosphorylated STAT3 in human HCC cell lines in vitro. In 200 mg, 3 pts (44%) had stable disease among 7 pts. **Conclusions:** A 200mg/day of OPB-31121 was well-tolerated in pts with advanced HCC and toxicities were manageable. Further clinical development of OPB-31121 will be considered after getting results from an ongoing phase I study of another novel, chemically related compound with similar pharmacologic activities. Clinical trial information: NCT01406574.

**2617 General Poster Session (Board #80), Sun, 8:00 AM-11:45 AM**

**A phase I dose escalation study of weekly BI 836845, a fully human, affinity-optimized, insulin-like growth factor (IGF) ligand neutralizing antibody, in patients with advanced solid cancers.** *Presenting Author: Chia-Chi Lin, Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan*

**Background:** The IGF signaling pathway has an important role in neoplasia and is associated with cancer progression, prognosis, and resistance to anti-cancer treatment. IGF-1 and IGF-2 are up-regulated in many tumors and exert multiple cellular activities through endocrine, autocrine, and/or paracrine manner. BI 836845 binds to and neutralizes the function of IGF-1 and IGF-2. The ligand-targeting approach differs from receptor-targeting by additional inhibition of IGF-2 signaling through IR-A. Objectives of this first-in-human trial were to assess the MTD or relevant biological dose (RBD), safety, PK, pharmacodynamics, and anti-tumor activity of weekly BI 836845 in cancer patients. **Methods:** In a 3+3 design, sequential cohorts of 3 to 6 patients (pts) with advanced or metastatic solid cancers refractory or not amenable to standard therapy received a weekly 1-hour intravenous infusion of BI 836845 following an AE-guided dose escalation. Treatment was continued in the absence of progressive disease and undue AE. The primary endpoints were DLT, MTD and/or RBD. **Results:** 48 pts, median age 57.5 (19-76) years were treated with BI 836845 at 14 dose levels (range: 10 to 1800 mg). Only one DLT, potentially drug-related grade 3 pulmonary hemorrhage originating from a tumor-adjacent vessel, was observed at 450 mg. The other of the two reported grade 3 drug-related AEs was lymphocyte decrease. No drug-related grade 4 or 5 AE was reported. Infusion-related reaction or drug-related hyperglycemia was not reported. MTD was not reached. BI 836845 showed a dose-proportional PK with a terminal half-life of about 6 days, a volume of distribution of 5.8 L, and a total plasma clearance of 0.5 mL/min. A RBD for further clinical development was selected at 1000 mg weekly. There were two confirmed PRs (nasopharyngeal carcinoma, at 800 mg; peripheral primitive neuroectodermal tumor, at 1050 mg) and 12 pts (25%) with confirmed SD. **Conclusions:** Weekly infusion of BI 836845 is well tolerated in cancer patients in the dose range tested without determination of a MTD. Preliminary anti-tumor activity has been observed. Clinical trial information: NCT01403974.

**2618 General Poster Session (Board #81), Sun, 8:00 AM-11:45 AM**

**Heregulin expression level as a predictive biomarker for patritumab efficacy.** *Presenting Author: Matthias Schneider, U3 Pharma GmbH, Martinsried, Germany*

**Background:** Activation of the receptor tyrosine kinase HER3 and its oncogenic downstream signaling pathways are thought to be critically involved in the development of various cancer types, including non-small cell lung cancer (NSCLC). HER3 serves as a scaffold for PI3K/AKT signaling via heterodimeric interaction with other HER family members, which can be mediated by binding of heregulin (HRG), the natural high affinity ligand for HER3. Patritumab (P) is an internalizing, fully human anti-HER3 monoclonal antibody that competes with HRG for receptor binding. We examined whether HRG expression correlates with P efficacy in vitro and in vivo. **Methods:** Protein and phosphoprotein levels in tumor cell lines were determined by western blot. Endogenous HRG mRNA expression was analyzed by RT-PCR. To examine signaling in vitro, tumor cells were treated with 10 $\mu$g/ml of P. Cells then remained untreated or were stimulated with recombinant HRG for 1 hour prior to lysis. Cell lysates were analyzed for HER3/pHER3- and AKT/pAKT-levels. To determine the efficacy of P in vivo, mice bearing ~200 $mm^3$ tumor xenografts were treated with P twice weekly, and tumor volumes were assessed. **Results:** Cell lines endogenously expressing HRG showed decreased HER3- and AKT-phosphorylation following treatment with 10 $\mu$g/ml of P, whereas no inhibitory effects of P were observed in HRG-negative cell lines. Remarkably, while HCC1569 cells are normally insensitive to P, the addition of exogenous HRG conveyed sensitivity to these cells. In line with these in vitro observations, HRG expression was found to correlate with P single-agent efficacy in 13/15 in vivo tumor models, from a range of tissue types. In contrast, neither levels of HER3 expression nor levels of HER3 phosphorylation were found to consistently correlate with P single-agent efficacy. **Conclusions:** Unlike HER3 expression or activation, HRG expression reliably correlated with P-mediated inhibition of signaling in vitro and tumor growth inhibition in vivo. Based on these data, HRG expression levels were nominated as the primary predictive biomarker for P efficacy and were clinically evaluated in the HERALD phase 1b/2 trial in patients with NSCLC (Mendell-Harary et al., von Pawel et al. ASCO 2014).

**2619 General Poster Session (Board #82), Sun, 8:00 AM-11:45 AM**

**Pharmacokinetics and pharmacodynamics of the dual syk/jak inhibitor PRT062070 (cerdulatinib) in patients with advanced B-cell malignancies.** *Presenting Author: Ian Flinn, Sarah Cannon Research Institute, Nashville, TN*

**Background:** Syk and Jak appear to have independent but cooperative roles in promoting the survival of certain B cell malignancies. Syk is upstream of BTK and PI3K on the B cell antigen receptor (BCR) signaling pathway, and Jak mediated survival signals have been observed in leukemia and lymphoma. Combined knockdown of Syk and Jak results in greater cell kill in B cell lymphoma cell lines relative to knock down of either alone (Ma, et al, 2013), suggesting dual pharmacological targeting of these pathways may be an effective treatment strategy. PRT062070 is a potent and selective inhibitor of Syk, JAK1, JAK3, and Tyk2. Here we present PK and PD data from a dose escalation study with PRT062070 in patients with NHL, CLL, and SLL. **Methods:** Patients were enrolled in a 3+3 dose escalation study beginning at 15 mg orally daily. PK/PD relationships were determined using a variety of whole blood assays measuring Syk (BCR-mediated) and Jak (IL2-, IL4-, and IL6-mediated) kinase activity. Specificity controls included GM-CSF (JAK2 mediated) and phorbol 12-myristate 13-acetate (PKC-mediated) stimulations. Plasma concentrations were assessed on Days 1, 8, 15, and 22 of the first treatment cycle with standard LC/MS/MS methods. **Results:** The average elimination $T_{1/2}$ at steady state (SS) is ~12 hours and $T_{max}$ ~2 hours. The SS peak-to-trough ratio is 3:1. The mean $C_{maxss}$ value was 80% higher than the Day 1$C_{max}$. Increases in $C_{max}$ and exposure were dose proportional from the 15 to 30 mg dose. Relative to pre-dose, assays measuring Syk (BCR) and Jak (IL2, IL4, IL6) activity at SS were inhibited by 25-50% at the 15 mg dose level, and 50-70% at the 30 mg dose level. No corresponding inhibition of JAK2 or PKC-mediated signaling was observed. The PK/PD relationship is consistent with pre-clinical in vitro experiments. **Conclusions:** PRT062070 demonstrates a favorable PK profile, supporting once daily dosing. The PD data demonstrate selective target inhibition with $IC_{50}$'s consistent with that observed pre-clinically. Data to date suggest that high levels of Syk and Jak inhibition in peripheral blood can be safely achieved following oral dosing. Clinical trial information: NCT01994382.

**2620 General Poster Session (Board #83), Sun, 8:00 AM-11:45 AM**

**A phase 1 expansion cohort of the fibroblast growth factor receptor (FGFR) inhibitor AZD4547 in patients (pts) with advanced gastric (GC) and gastroesophageal (GOJ) cancer.** *Presenting Author: Hendrik-Tobias Arkenau, Sarah Cannon Research Institute UK, London, United Kingdom*

**Background:** AZD4547 is a potent selective inhibitor of FGFR 1, 2, and 3 tyrosine kinases. Pre-clinically, gastric cancer cell lines and patient-derived xenograft models with *FGFR2* gene amplification were sensitive to AZD4547, resulting in reduced cell proliferation and tumor regression. **Methods:** A multicentre phase-1 study assessed the safety, pharmacokinetics, pharmacodynamics (PD) and antitumor activity of AZD4547 (80 mg bd) in an expansion cohort of pts with advanced/metastatic GC/GOJ cancer (NCT00979134) who were prospectively selected for *FGFR1/2* amplification using fluorescent in situ hybridization (FISH) analysis of archival or fresh tumors. **Results:** 238 GC/GOJ pts were pre-screened, of which 38 pts (16%) had the pre-specified *FGFR1/2* amplification (*FGFR*:Centromeric ratio ≥2). 13 pts were treated (9 m: 4 f, mean age 57yrs). 6 had high *FGFR* amplification (*FGFR*:Centromeric ratio ≥ 2.8), 3 had low amplification (FGFR:Centromeric ratio >2 to < 2.8), and 4 were of a cluster type (FGFR gene amplification clusters in > 10% cells). A total of 136 treatment-emergent adverse events (CTC-AE all grades) were reported including vomiting (8 pts; 61.5%), decreased appetite and diarrhoea (7 pts each; 53.9%), fatigue and nausea (6 pts each; 46.2%), hyperphosphatemia, constipation and dry eye (4 pts each, 30.7%). 8 pts (61.5%) reported epithelial and mucosal dryness, 5 pts (38.5%) stomatitis, and 4 pts (30.8%) retinal pigment epithelial detachment. Preliminary exploratory analysis revealed an increase in serum phosphate following dosing. 1 PR was observed in a patient with a tumor that had clusters of FGFR gene amplification and 4 pts had stable disease (3 with high FGFR amplification and 1 with clusters). **Conclusions:** AZD4547 was well-tolerated in pts with *FGFR1* amplified advanced/metastatic GC/GOJ cancer but did not meet its pre-specified efficacy endpoint, in terms of overall response rate, for continuation. The increase in plasma phosphate concentration observed in this study, provides evidence that AZD4547 at this dose and schedule causes pharmacologic target inhibition. Clinical trial information: NCT00979134.

**2621 General Poster Session (Board #84), Sun, 8:00 AM-11:45 AM**

**Identifying actionable targets in advanced cancer patients: Preliminary results from the Profiler program.** *Presenting Author: Philippe Cassier, Centre Léon Bérard, Lyon, France*

**Background:** The ProfiLER study was designed to characterize tumor genomic alterations (GAs) in a panel of selected genes in patients (pts) with advanced malignancies. Whether the presence of GAs may guide treatment (trt) decision regardless of histological subtype remains unclear. **Methods:** Pts with advanced solid and hematologic cancers were offered a genetic profiling of their tumor. DNA extracted from archival or freshly collected tumor samples was analyzed by sequencing of 59 cancer-related genes (NGS, Ion Torrent PGM system) and whole genome CGH array (Agilent platform). A multidisciplinary panel of clinicians and scientists reviewed results to determine the relevance of GAs and recommended molecular targeted therapies (MTT) when relevant. **Results:** From March to October 2013, 431 pts from a single center were consented and 283 (66%) had their tumor analyzed, either by NGS+CGH (186 pts, 66%), NGS alone (86, 30%) or CGH alone (11, 4%). 137 (48%) had at least one actionable target (AT) with a recommended MTT: 20% were breast cancers, 17% head and neck, 15% lung, 9% sarcoma, 8% colon and 31% other tumor types. NGS was conclusive for 132 pts, identifying actionable mutations (hot spot or described in COSMIC database) mainly in *PIK3CA* (15% of pts), *EGFR* (9%), *MET* (4%), *MTOR* (4%), *ALK* (4%), *PTEN* (4%), *ERBB2* (3%), *BRAF* (2%) (median nb of mutations/pt: 1 [range: 0-11]). Main ATs identified with CGH (n=105 pts) were amplifications of *CCND1* (17%), *FGFR1* (11%), *MDM2* (7%), *EGFR* (5%), *ERBB2* (5%), *CDK4* (4%), *CDK6* (3%), homozygous deletion of *CDKN2A* (21%) and *PTEN* (5%) (median nb of copy number variations/pt: 1 [0-6]). 19/137 pts (14%) have so far received an MTT, mainly mTOR inhibitors (7 pts, 37%), ALK/MET inhibitors, anti-HER2, FGFR inhibitors or anti-VEGF (2 pts each, 10%). Best responses were PR (2/19, 10%), SD (6/19, 32 %), PD (9/19, 47%) and not evaluable in 2 pts. Median trt duration was 2.2 months [0.8–7.5] (Data, censored on December 1st2013, will be updated). **Conclusions:** Systematic tumor profiling is feasible in routine practice, highly attractive for pts with advanced malignancies and identifies ATs in nearly 50% of the pts. Clinical trial information: NCT01774409.

**2622 General Poster Session (Board #85), Sun, 8:00 AM-11:45 AM**

**Phase I dose escalation study of 3-weekly BI 836845, a fully human, affinity optimized, insulin-like growth factor (IGF) ligand neutralizing antibody, in patients with advanced solid tumors.** *Presenting Author: Karim Rihawi, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, United Kingdom*

**Background:** Insulin-like growth factor signaling is reported to play a role in the pathogenesis of several tumours. BI 836845 is a HumAb of the IgG1 isotype against the human insulin-like growth factors IGF-1 and IGF-2, which are up-regulated in many tumors. This ligand-targeting approach is broader than specific IGF-1 receptor blockade. This first in man Phase I trial of 3-weekly i.v. BI 836845 was pursued to evaluate safety, tolerability, MTD and relevant biological dose (RBD). Secondary objectives included assessment of tumor response, PK and PD. **Methods:** Patients (pts) with advanced solid tumours, ECOG PS 0-2, and adequate organ function were recruited in a 3+3 dose escalation design. BI 836845 was administered at escalating doses in 3-weekly (21 day) cycles until progression or unacceptable toxicity. A past history of diabetes was an exclusion criterion. **Results:** 33 pts across 11 cohorts were enrolled and treated, median age 59.0 (23 – 79) years. Tumor types were colorectal (6), adrenal (4), NSCLC (2), head and neck (2), pancreas (2), prostate (2), ovary (2) and others (13). No DLT was observed in any of the 11 dose levels explored (range 10 to 3600 mg); MTD was not reached. The most common (> 5% of pts) related AEs were abdominal pain, constipation, decreased appetite, fatigue, lethargy and nausea all being ≤ Grade 2. 2 pts had Grade 3 related AEs (hyponatremia and diarrhea). 0 had Grade 4 related AEs. No drug-related hyperglycemia was observed. BI 836845 plasma exposure ($AUC_{0-\infty}$ and $C_{max}$) increased dose-proportionally with steady state volume of distribution ($V_{ss}$) of about 5.8 L and a total plasma clearance (Cl) of 0.5 mL/min. The terminal half-life was about 6 days. There were no objective responses but confirmed SD was achieved in 4 pts. RBD of 1000 mg weekly was selected based on integration of preclinical and clinical data from this study and a study investigating weekly dosing. **Conclusions:** BI 836845 is well tolerated in patients with advanced solid tumours. An RBD of 1000 mg weekly was identified. An expansion phase is ongoing and recruiting patients with Ewing sarcoma or all tumor types with biopsiable disease. Clinical trial information: NCT01317420.

**2623 General Poster Session (Board #86), Sun, 8:00 AM-11:45 AM**

**Phase I trial of bortezomib daily dose: Safety, pharmacokinetic profile, biological effects, and early clinical evaluation in patients with advanced solid tumors.** *Presenting Author: Rastislav Bahleda, Drug Development Department (DITEP), Gustave Roussy Institute, Villejuif, France*

**Background:** Bortezomib (BTZ) is proteasome inhibitor with activity in multiple myeloma used as a weekly or twice-weekly subcutaneous regimen. BTZ showed modest activity in solid tumors, potentially related to sub-optimal tumor penetration. **Methods:** This is a dose escalation study to define the MTD of daily low dose schedule of BTZ given SC on days 1-5, 8-12, 15-19 of 28 day cycle based on 3+3 design. Primary objective: to establish the MTD. Secondary objectives: safety, efficacy, PK and PD. Patients ≥ 18 years with advanced solid tumors, ECOG ≤ 1, adequate organ functions, without pre-existent neuropathy were included. Biomarkers for proteasome inhibition, pre- and post-treatment tumor biopsies, circulating proteins were evaluated. **Results:** As of Sep 2013, 18 pts have been treated (8 M/10 F), median age 57.5 years (range 41-76). BTZ dose cohorts were (no. pts): 0.5 mg/m$^2$ (3), 0.6 mg/m$^2$ (11), 0.7 mg/m$^2$(4). 11 pts received 1 cycle; 4, 2 and 1 pts received 2, 5 and 6 cycles, respectively (total 35 cycles, 13 with full doses). Three DLTs were observed in 3 pts: Sweet's syndrome (at 0.6 mg/m$^2$), G3 anorexia with asthenia (2 pts at 0.7 mg/m$^2$). The most common study drug-related AEs (all grades) were fatigue (56%), thrombocytopenia (56%), rash (39%), anorexia (39%) and neuropathy (39%). 4 additional pts were enrolled at 0.6 mg/m$^2$ considered as RP2D. Dose-normalized mean systemic exposure to BTZ was time-independent, with similar BTZ PK on day 5 and day 19. Maximum proteasome inhibition was observed at day 19 in blood, and subsequently recovered until last time point measured at day 26. Proteasome inhibition was compared in tumor/blood (n = 3) and % inhibition on day 5 varied between 0.95 – 2.01 , indicating a good correlation between tumor and blood. One PR has been observed in pt with heavily pre-treated GIST and 2 minor responses (-20%) in pt with melanoma and mesothelioma. **Conclusions:** Daily BTZ administration showed an acceptable safety profile, dose dependent plasma exposure, evidence of target inhibition, and preliminary signs of clinical activity. RP2D of daily above-mentioned regimen of BTZ is 0.6 mg/m$^2$. Additional clinical, PK and PD data will be presented. Clinical trial information: eudraCT 2009-014354-15.

**2624^ General Poster Session (Board #87), Sun, 8:00 AM-11:45 AM**

**Safety, activity, and pharmacokinetics of an oral anaplastic lymphoma kinase (ALK) inhibitor, ASP3026, observed in a "fast follower" phase 1 trial design.** *Presenting Author: Michael L. Maitland, University of Chicago Medicine, Chicago, IL*

**Background:** The efficient early development of agents intended for selected patient populations is challenging. ASP3026 is a selective, ATP-competitive, kinase inhibitor with in vitro $IC_{50}$for ALK of 3.5 nM. **Methods:** Advancedsolid tumor patients (pts) received oral ASP3026 under fasting conditions without interruption in 3+3 dose escalation cohorts from 25 to 800 mg once daily (QD). The primary endpoint was to identify the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of ASP3026. To identify rapidly evidence of therapeutic activity a previously cleared cohort could enroll up to an additional 3 pts with advanced *ALK*driven solid malignancies(ALK+) . A planned phase Ib expansion cohort was opened at the R2PD. RECIST 1.1 was used to determine response. **Results:** The dose escalation phase enrolled 33 pts, including 3 ALK+ pts , and the expansion cohort enrolled another 13 ALK+ pts [total pts N = 46; 48% men; median (range) age = 61 (19-77) years]. Three dose-limiting toxicities (DLTs) were observed: grade 2 nausea and vomiting leading to dose reduction at 525 mg QD; grade 3 rash at 800 mg QD leading to dose reduction and grade 3 ALT/AST elevation leading to study withdrawal at 800 mg QD, making 525 mg daily the MTD and RP2D. The most common adverse events of the entire cohort were: fatigue (44%), vomiting (39%), nausea (37%), and constipation (24%). Of 15 pts with ALK+ non-small cell lung cancer (NSCLC) who progressed on prior crizotinib 7 (44%) had a partial response (PR) and 8 (50%) had stable disease as the best response. The median progression free survival in the ALK+ pts was 5.9 (95% CI: 3.8-9.4) months. Eight pts were still receiving treatment at data cut off. There was no correlation between response and plasma ASP3026 concentrations (AUC and Cmax) in the ALK+ pts. ASP3026 demonstrated dose-proportionality for AUC and Cmax with a terminal half-life compatible with QD dosing. **Conclusions:** The "fast follower" design enabled enrollment of ALK+ pts who had partial responses before the MTD of 525mg QD was determined. ASP3026 had clinical activity in ALK+ NSCLC pts who progressed on crizotinib. Clinical trial information: NCT01401504.

**2625 General Poster Session (Board #88), Sun, 8:00 AM-11:45 AM**

**MAPK/ERK as a biomarker for cisplatin resistance in squamous cell carcinoma (SCC).** *Presenting Author: Li Ren Kong, Cancer Science Institute, Singapore, Singapore*

**Background:** Significant progress in therapy of non SCC of the lung has been made through genomic profiling and subtyping according to oncogenic drivers. In SCC, cisplatin-based therapy remains the mainstay, and resistance to treatment is common. We sought to understand the molecular underpinnings of cisplatin resistance in SCC. **Methods:** SCC of patients were characterized by Next-Generation Sequencing. *In vitro* drug sensitivity in lung SCC cell lines (n= 3) was determined by MTS assay, transcriptomic analysis was performed with microarray and signalling regulation was investigated with phospho-kinase array. Cisplatin-mediated cellular signalling identified by transcription and phospho-kinase array was validated in SCC cell lines by Western blotting (n= 3). Expression of p-Erk in SCC specimens was detected with IHC staining. **Results:** We verified the paucity of oncogenic driver mutations in 45 lung SCC specimens. H596, H1869, H226 and ChaGo-k-1 cell lines were deemed sensitive while Calu-1, H2170, SW900 and H2066 resistant to cisplatin. MAPK/Erk pathway proteins were up-regulated in resistant compared to sensitive cell lines by gene expression and phospho-kinase arrays. p-Erk1/2 was activated in cisplatin-resistant cell lines in increasing cisplatin doses, while gene silencing (siRNAs) and pharmacological inhibition (MEK inhibitors) of Erk1/2 reversed cisplatin resistance and enhanced cisplatin sensitivity in lung SCC cells. High p-Erk1/2 expression in HNSCC tumours was found correlated with shorter progression-free survival of SCC patients treated with cisplatin. **Conclusions:** Our data suggest that 1) therapeutic targeting of MAPK/Erk signalling is potentially effective in abrogating cisplatin resistance in SCC, and 2) p-Erk1/2 is a predictive biomarker for cisplatin treatment in SCC tumours.

**2626 General Poster Session (Board #89), Sun, 8:00 AM-11:45 AM**

**Concomitant blockade of EGFR and MEK overcomes acquired resistance to anti-EGFR therapy in colorectal cancer cells and patients' avatars.** *Presenting Author: Alberto Bardelli, IRCC Institute for Cancer Research and Treatment, University of Torino, Medical School, Candiolo, Candiolo, Italy*

**Background:** The anti-EGFR antibodies cetuximab and panitumumab are approved for the treatment of RAS wild-type colorectal cancer (CRC) patients. The clinical efficacy of EGFR targeted antibodies is limited by the development of acquired (secondary) resistance. Here we investigated the molecular bases of relapse to anti-EGFR blockade in CRC cells and patients' samples and use xenotransplants to define a clinically applicable strategy to overcome acquired resistance. **Methods:** Molecular profiling of circulating tumor DNA was used to identify the emergence of mutations in plasma samples of patients who relapsed after anti EGFR therapies. Xenografted tumors (avatars) from patients who relapsed after EGFR blockade were established and exploited to assess the efficacy of drugs aimed at bypassing acquired resistance. **Results:** Emergence of concomitant mutations in KRAS and NRAS was detected in samples from 5 CRC patients who developed resistance to anti-EGFR antibodies. Acquired resistance to cetuximab and panitumumab was modeled in 4 CRC cell models. Resistant cells were a mixture of clones bearing alterations in KRAS, NRAS and BRAF thus closely recapitulating the patients' findings. Pathway analyses revealed that, although genetically polyclonal, resistant cells consistently displayed MEK and ERK activation but, surprisingly, were refractory to MEK inhibition. However, the resistant derivatives were sensitive to the concomitant inhibition of MEK and EGFR independently from their genetic status. Mouse xeno-transplants of lung and liver biopsies from two CRC patients who responded and subsequently relapsed upon EGFR therapy showed exquisite sensitivity to combinatorial treatment with the MEK inhibitor pimasertib and EGFR blockade with cetuximab. **Conclusions:** These observations provide a rational strategy to overcome the clonal heterogeneity that emerges when CRCs are treated with anti EGFR antibodies. We propose that MEK inhibitors, in combination with cetuximab or panitumumab, should be evaluated in CRC patients who become refractory to anti-EGFR therapies. A clinical trial (ARES) has been initiated to test this hypothesis.

**2627 General Poster Session (Board #90), Sun, 8:00 AM-11:45 AM**

**A phase 1 study of the c-Met inhibitor tivantinib (ARQ 197, IND#112603) in children with relapsed or refractory solid tumors: A Children's Oncology Group study.** *Presenting Author: James I. Geller, Cincinnati Children's Hospital Medical Center, Cincinnati, OH*

**Background:** Tivantinib is an oral small molecule that inhibits the c-Met receptor tyrosine kinase (RTK), which is dysregulated in many pediatric cancers. A phase I and pharmacokinetic (PK) trial evaluating tivantinib was conducted in children with refractory solid and CNS tumors. **Methods:** Oral tivantib capsules were administered bid, continuously in 28-day cycles. Three dose levels (170, 200 or 240mg/$m^2$/dose) were evaluated using a rolling 6 design (Part A). In Part B, patients received tivantinib powder sprinkled on food at the RP2D from Part A. Serial PK (day 1) and trough samples (day 28) were obtained in Cycle 1. CYP450 genotyping was performed in all participants. **Results:** Thirty-six patients were enrolled (24 male, median age 12.1 years (range, 3.8-21): 20 in Part A, 6 to a PK expansion cohort, and 10 to Part B. Fifteen patients had primary CNS tumors and 21 had solid tumors. Twenty-six patients were evaluable for toxicity assessment and 32 for response. In Part A there were 0/5, 0/6 and 0/5 pts with DLT at dose levels 1-3. There was 1 grade (GR) 4 intracranial hemorrhage in a patient with a progressive brain tumor in the expanded PK cohort (240 mg/$m^2$). Non dose-limiting toxicities at least possibly attributable to tivantinib included grade 3 or 4 myelosuppression [lymphopenia (3), neutropenia (2), anemia (2), and thrombocytopenia (1)]; Gr 1 or 2 toxicities occurring in $>$ 10% of evaluable patients included fatigue (9), leukopenia (7), vomiting (5), nausea (5), anemia (12), neutropenia (5), lymphopenia (3), hypoalbuminemia (4), and thrombocytopenia (3). PK analysis showed marked inter-patient variability (20-fold) in the $C_{max}$ and $AUC_{last}$ across all dose levels. Sprinkling tivantinib powder over food did not appear to alter exposure. The average terminal elimination $t_{1/2}$ was 2.5 hours. **Conclusions:** The RP2D of tivantinib given with food is 240 mg/$m^2$/dose. PK of tivantinib in children demonstrated high variability. Clinical trial information: NCT01725191.

**TPS2628 General Poster Session (Board #91A), Sun, 8:00 AM-11:45 AM**

**A phase I trial of dabrafenib (BRAF inhibitor) and pazopanib in *BRAF*-mutated advanced malignancies.** *Presenting Author: Sigurdis Haraldsdottir, The Ohio State University Comprehensive Cancer Center - Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH*

**Background:** BRAF inhibitor therapy is associated with an impressive albeit short-lived response rate in the treatment of malignant melanoma. Mechanisms of resistance include upregulation of the MAPK pathway through mutations in *NRAS*, *MEK* and *BRAF* alternate splicing; furthermore upregulation of PDGFR-$\beta$ can cause resistance. Some malignancies, such as thyroid malignancies, have upregulation of VEGF pathways and also carry a *BRAF* mutation. Combination of therapies targeting VEGF and MAPK pathways could enhance the effects of both agents as well as target potential pathways of resistance. We are conducting a NCCN-sponsored phase I trial combining both agents in the treatment of advanced *BRAF* mutated malignancies. **Methods:** This is a phase I dose-escalation trial with a conventional 3+3 approach. Dose escalation of pazopanib preceeds escalation of dabrafenib doses as dabrafenib is a CYP3A4 inducer and might therefore cause more rapid metabolism of pazopanib, a CYP3A4 substrate. Inclusion criteria include any advanced malignant tumor carrying a mutation in the *BRAF* gene. Prior use of dabrafenib or pazopanib is not allowed and only 3 prior tyrosine kinase inhibitor regimens are allowed. Patients with a history of *BRAF* mutated malignancies within 5 years of study enrollment are allowed on the study. Starting doses on dose level 1 are 50 mg bid for dabrafenib and 400 mg qd for pazopanib, escalating to 150 mg bid for dabrafenib and 800 mg qd for pazopanib on dose level 5. Both agents are given continuously on a 28 day schedule. Cohorts 1 and 2 have been completed without dose-limiting toxicities. Enrollment to cohort 3 began in November 2013. Correlative studies include quantification of the copy number of the *BRAF V600E* mutant allele in circulating plasma. Clinical trial information: NCT01713972.

**TPS2629^ General Poster Session (Board #91B), Sun, 8:00 AM-11:45 AM**

**First-in-human phase I "basket" study of Debio1347 (CH5183284), a novel FGFR inhibitor, in patients with FGFR genomically activated advanced solid tumors.** *Presenting Author: Martin Henner Voss, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Deregulated fibroblast growth factor receptor (FGFR) signalling is associated with tumorigenesis. Debio 1347 is an orally-available ATP competitive inhibitor of FGFR 1, 2 and 3 with preclinical data showing high target-specificity and antitumor activity across models of FGFR amplified, mutated or translocated tumors for various human malignancies. **Methods:** This first-in-human, phase I dose-escalation multiple tumor type "basket" study enrols patients with advanced solid malignancies harbouring defined activating alterations of FGFR 1, 2, or 3. These include amplifications and translocation events with known activating effect as well as somatic mutations previously reported as activating or located in genomic regions of relevance for kinase activity. The dose-escalation part of the trial enrols patients with advanced solid tumour malignancies and presence of any such alteration. Genetic screening is performed independently at each site with post-hoc centralised confirmation of molecular status by Next Generation Sequencing (NGS). The primary endpoint is determination of maximum tolerated dose (MTD). Patients receive Debio 1347 orally once daily and are assessed for dose-limiting toxicities (DLT) during the first 4 weeks. With a starting dose-level of 10 mg the study follows a 3+3 algorithm with dose-escalation on a modified Fibonacci sequence. The MTD is defined as the level where $\geq$ 2/6 patients suffer a DLT. All the patients receive dietary phosphate restriction.The secondary objective is exploration of antitumor effect in the various tumor types enrolled on trial. Pharmacokinetics is evaluated after single and repeated administration. Pharmacodynamics biomarkers including phosphate and FGF23 are explored in plasma samples. Pre- and post-treatment skin and tumor biopsies are used for pharmacodynamics analyses. Recruitment started in September 2013. Cohort 1 has been completed. Cohort 2 began in January 2014. Subsequent dose expansion is planned at the final recommended dose across pre-defined disease-specific baskets to evaluate safety and efficacy in the setting of specific FGFR alterations of relevance to each disease. Clinical trial information: NCT01948297.

**TPS2630 General Poster Session (Board #92A), Sun, 8:00 AM-11:45 AM**

**A phase 1 dose-escalation study of EC1456, a folic acid-tubulysin small-molecule drug conjugate, in adult patients (pts) with advanced solid tumors.** *Presenting Author: Wael A. Harb, Horizon Oncology Center, Lafayette, IN*

**Background:** The folate receptor (FR) is expressed in alarge number of epithelial tumors and is a valid anticancer target. EC1456 is a potent folic acid-tubulysin B hydrazide (TubBH) small-molecule drug conjugate that exerts its antitumor effects by inhibiting the polymerization of tubulin into microtubules and arresting cells in metaphase. EC1456 acts as a cell-specific cytotoxic agent and preferentially targets TubBH to cancer cells that express FR. **Methods:** This is a phase 1, multicenter, open-label, nonrandomized dose-escalation study (NCT01999738) to evaluate the maximum tolerated dose (MTD) of biweekly (BIW) EC1456 treatment in pts with solid tumors (part A) and assess preliminary efficacy in pts with FR-expressing tumors treated at the MTD (part B). Key eligibility criteria include: age $\geq$18 years; histologically confirmed metastatic or locally advanced solid tumor; Eastern Cooperative Oncology Group (ECOG) performance status 0–1. At baseline all pts undergo a $^{99m}$Tc-etarfolatide scan to determine FR status. For part B, only FR(100%) pts, in whom all target lesions (Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria) express FR, are included. EC1456 is given intravenously BIW on weeks 1 and 2 (days 1, 4, 8, and 11) of a 4-week cycle. The dose-escalation scheme is shown in the Table. Cohorts will consist of 3–6 pts/dose level, and EC1456 escalation is via the standard 3+3 schema. All pts in a cohort must complete cycle 1 dose-limiting toxicity (DLT) evaluation before dosing is initiated at the next higher level. DLTs observed in cycle 1 will determine whether additional pts should be enrolled at the same dose, or a lower/higher dose level. The primary objective is to determine the MTD and recommended phase 2 dose of EC1456 in pts with advanced tumors. The secondary objectives include safety and pharmacokinetic analysis of EC1456 in pts with solid tumors, and preliminary efficacy evaluation in selected pts at MTD (part B). Enrollment to cohort 1 began in November 2013. Clinical trial information: NCT01999738.

| Level | Dose (mg/m$^2$) |
|---|---|
| **1** | 0.5 |
| **2** | 1 |
| **3** | 1.5 |
| **4** | 2 |
| **5** | 2.5 |
| **6** | 3.5 |
| **7** | 4.5 |
| **8** | 6 |

**TPS2631^ General Poster Session (Board #92B), Sun, 8:00 AM-11:45 AM**

**Phase I, dose-escalation study of the investigational drug D07001-F4, an oral formulation of gemcitabine HCl, in patients (pts) with advanced solid tumors.** *Presenting Author: Chia-Chi Lin, Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan*

**Background:** Gemcitabine HCl is a nucleoside analogue that exhibits antitumor activity and is approved for IV use in the world. Oral dosing of gemcitabine HCl would simplify administration and extend the systemic exposure time after a dose relative to an intravenous exposure profile, which has been correlated with increased activity of gemcitabine in both preclinical and clinical studies. Nonetheless, in a reported clinical study, the systemic exposure to oral gemcitabine was low due to extensive first-pass metabolism to dFdU. D07001-F4 is a unique oral formulation of gemcitabine HCl that is expected to enhance the systemic exposure to difluorodeoxycytidine (dFdC) and ultimately dFdCTP, intracellularly. **Methods:** D07001-F4 is being evaluated of in an open-label, dose escalation study in patients with advanced solid tumors or lymphoma. Eligibility: pts with evaluable tumors, age $^3$a 20 yrs, PS 0–2 and with adequate oral therapy absorption. Primary objects includes determination of maximum tolerated dose, dose-limiting toxicity(ies) and the recommended phase 2 dose of D07001-F4. Secondary objectives include characterization of pharmacokinetic (PK) and assessment of safety, tolerability and anti-tumor activity. Sequential cohorts of 3 to 6 patients receive doses ranging from 2 mg to 80 mg oral D07001-F4 on Days 1, 3, 5, 8, 10, and 12 of a 21-day cycle. MTD is determined based on DLTs in cycle 1. Tumor response is determined according to RECIST or Cheson criteria. Plasma and peripheral blood samples were obtained for PK analysis in cycle 1. Accrual has completed in Cohorts 1 (2 mg) to 4 (20mg). Accrual is underway for Cohort 5 (30 mg). Clinical trial information: NCT01800630.

**TPS2632^ General Poster Session (Board #93A), Sun, 8:00 AM-11:45 AM**

**The HALO study: A phase I-II of the oral HSP90 inhibitor Debio0932 in combination with SOC in first- and second-line therapy of advanced NSCLC.** *Presenting Author: Jesus Corral, University Hospital Virgen del Rocío, Seville, Spain*

**Background:** Debio0932 is an oral second-generation Heat Shock Protein 90 (HSP90) inhibitor, structurally unrelated to geldanamycin. In multiple pre-clinical models Debio0932 has demonstrated anti-tumor activity both as monotherapy and in combination with conventional anticancer agents. Debio0932 monotherapy was well tolerated in cancer patients up to 1000 mg daily (QD) and showed signs of activity in patients with Non-Small Cell Lung Cancer (NSCLC). **Methods:** The HALO (HSP90 inhibition And Lung cancer Outcomes) study is recruiting patients with Stage IIIb or IV NSCLC (EGFR wild type or unknown mutation) and consists of three parts. Part A is an open-label dose escalation of Debio0932 administered QD in 21-day treatment cycles in combination with standard of care (SOC) for first and second line treatment of advanced NSCLC. Cisplatin + gemcitabine (SCC) or cisplatin + pemetrexed (Non SCC NSCLC) are used as first-line SOC whereas docetaxel is used for later lines of therapy. The starting dose is 100 mg and will be escalated up to 1000 mg. Part B is a double-blind, placebo-controlled study in which 138 untreated advanced NSCLC patients will be randomized to receive placebo or Debio0932 at the dose recommended in part A in combination with first-line SOC. The primary endpoint of Part B is 6-month progression free survival (PFS); secondary endpoints include best overall response rate (ORR), duration of objective response, change in tumor size from baseline until 6 months and overall survival (OS). Patients who subsequently develop progressive disease are newly randomized to double-blind treatment with docetaxel +/- Debio0932 (Part C). Approximately 100 patients are expected to enter part C. The primary endpoint of part C is the change from baseline tumour size at month 6; secondary endpoints include best ORR, duration of objective response, 6-month PFS, and OS. Extensive PK, PD and pharmacogenomic assessments are included. As of January 2014 58 patients have been enrolled in the study Part A at all dose levels (Debio0932 100 mg to 1000 mg QD). MTD was not reached yet. One DLT occurred in the cisplatin + gemcitabine arm at Debio0932 250 mg dose and one in the docetaxel arm at Debio0932 1000 mg dose. Clinical trial information: NCT01714037.

**TPS2633 General Poster Session (Board #93B), Sun, 8:00 AM-11:45 AM**

**Transforming the clinical trial process: The I-SPY 2 trial as a model for improving the efficiency of clinical trials and accelerating the drug-screening process.** *Presenting Author: Meredith B. Buxton, University of California San Francisco, San Francisco, CA*

**Background:** The I-SPY 2 TRIAL is a standing, phase 2 trial that screens novel, targeted chemotherapeutic regimens in the neoadjuvant setting for women with stage II/III breast cancer. I-SPY 2 compares the efficacy of novel agents in combination with standard chemotherapy versus standard therapy alone, using pathologic complete response as the primary endpoint. Using an adaptive design, the goal is to identify/graduate regimens that have ≥85% Bayesian predictive probability of success (statistical significance) in a 300-patient biomarker-linked Phase 3 neoadjuvant trial defined by hormone-receptor (HR), HER2 status and MammaPrint. **Methods:** I-SPY 2 opened to accrual in March 2010, and is currently enrolling at 18 sites in the US, with 2 additional sites opening in 2014 (one in Canada and one in the US). As of January 2014, I-SPY 2 has screened 961 patients, enrolled 541 patients, and 326 patients have completed surgery. Seven novel regimens have entered the trial from 5 different pharmaceutical companies. In 2013, the trial announced the graduation of 2 regimens for two different biomarker signatures – veliparib+carboplatin (HR-/HER2-) and neratinib (HR-/HER2+). The I-SPY 2 TRIAL incorporates many innovative procedures and tools to increase the efficiency of the clinical trial process including: developing a standing trial consortium of academic, industry, governmental and nonprofit partners; involving key stakeholders from the development to implementation to ongoing management phases; democratizing data access; and driving organization efficiencies including testing drugs by class, developing a "Master" IND and protocol to accommodate testing multiple agents, sharing a control arm across multiple treatment arms, focusing on the collection of critical data elements, and utilizing previously and newly developed informatics tools to create an IT bundle to support next generation trials. The I-SPY Program includes a series of linked standing trials (I-SPY 2 and I-SPY 3, a confirmatory phase 3 trial) that may allow for a more efficient process for new chemotherapeutic agents to obtain both accelerated and full FDA approval. Clinical trial information: NCT01042379.

**TPS2634 General Poster Session (Board #94A), Sun, 8:00 AM-11:45 AM**

**Patient preference trial comparing capecitabine and S-1 in metastatic breast cancer patients.** *Presenting Author: Daigo Yamamoto, Department of Surgery, Kansai Medical University, Moriguchi, Japan*

**Background:** Capecitabine and S-1 are an orally administered fluorinated pyrimidine with high activity in metastatic breast carcinoma (MBC). We reported the activity and safety of two oral fluoropyrimidines, capecitabine or S-1, in breast cancer patients (ASCO, 2013). While capecitabine was as efficacious as S-1 for the treatment of MBC, there were differences between the two drugs with respect to their toxicity profiles. **Methods:** This study is an open-label, multicentre, phase II patient preference trial with two treatment arms, comparing capecitabine and S-1 in patients with MBC. Patients are required to be between 25 and 75 years of age, with ECOG performance status <3. Patients are centralized by Japan Breast Cancer Research Network. Oral capecitabine is administered at a dose of 1,657 mg/m2 twice daily on days 1–21 every 4 weeks. S-1 is 40–60mg two times daily according to body surface area on days 1–28 every 6 weeks. In this cross-over study, patients receive either two cycles of S-1 followed by three cycles of capecitabine, or three cycles of capecitabine followed by two cycles of S-1 and then patients are asked about their preference. After 12 weeks patients are asked to choose which of the two regimens they preferred. Therapy is given unless there is any sign of progression or severe toxicity or the patient wants to discontinue the therapy. Patients with stable disease (SD) or partial response (PR) after two treatment cycles, could continue on their regimen of choice thereafter. Tumor response is assessed according to the RECIST criteria. The primary end point is to investigate patient preference. The secondary end point is PFS, OS, address quality of life (EORTC-30), and anxiety and depression (HADS). NCI-CTCAE, ver. 4.0 and PRO-CTCAE are used to assess toxicity. We estimate that 70% of the patients in S-1 treatment group and 30% in the capecitabine group would like to continue the same treatment after three months after the treatment initiation. About 30 patients in each group are needed to detect the difference of the preference proportion with two-sided significance level 0.05 and 80% power. Chi-squared test will be used to test the null hypothesis for the primary analysis. Clinical trial information: UMIN000013045.

**TPS2635 General Poster Session (Board #94B), Sun, 8:00 AM-11:45 AM**

**Phase I study of IGF-methotrexate conjugate in the treatment of refractory malignancies expressing IGF-1R.** *Presenting Author: Rozina A. Chowdhery, University of Illinois at Chicago, Chicago, IL*

**Background:** The insulin-like growth factor 1 receptor (IGF-1R) is overexpressed in multiple malignancies, including breast, prostate, lung, colorectal, CLL, T-ALL, and mantle cell lymphoma. Activation of IGF-1R through binding of IGF-1 and IGF-2 induces activation of the MAPK and PIRK/ATK/mTOR pathways, resulting in inhibition of cell differentiation, resistance to apoptosis, chemotherapy resistance, and metastasis. Serum IGF binding proteins (IGFBP1-6) regulate IGF-1 and IGF-2 bioavailability. IGF-IR down-regulation leads to massive apoptosis; in vitro and in vivo IGF-IR inhibition leads to anti-proliferative effects and appears synergistic with chemotherapy. IGF-Methotrexate (IGF-MTX) is a novel conjugate of methotrexate (MTX) and 765IGF, a variant of IGF-1 with high affinity for IGF-1R and reduced affinity for IGFBP; in vivo studies confirmed tumor control at lower doses than free MTX. Targeting IGF-MTX towards malignancies overexpressing IGF-1R is a novel therapeutic strategy. **Methods:** This is a single center Phase I dose escalation study with a modified toxicity probability interval design to determine the MTD of 765IGF-MTX in patients with previously treated advanced malignancy expressing IGF-1R. Primary objectives: establish the MTD, safety and toxicity. Secondary objectives: pharmacokinetics (PK) / pharmacodynamics (PD) /biomarker profiles, and preliminary antitumor activity in patients with refractory malignancies expressing IGF-1R. Inclusion **criteria:** IGF-1R expression > 10% on tumor tissue via IHC or IGF-1R density > 0.1% on flow cytometry, ECOG PS 0-2, good organ function and a rest period of 2-6 weeks from their last treatment (duration based on previous therapy). Exclusion criteria: previous MTX use, or uncontrolled chronic illness. Administration and design: 765IGF-MTX is given IV over 1 hour on days 1, 8 and 15 of a 28 day cycle. This study has two components: first, an initial dose finding component with up to 7 cohort dose levels (0.05, 0.10, 0.20, 0.40, 0.80, 1.6, 2.5 μeq/kg), and second, an expansion cohort of 9 patients at MTD, with PK/PD/biomarker profile. The study is currently enrolling patients. Clinical trial information: NCT02045368.

**TPS2636 General Poster Session (Board #95A), Sun, 8:00 AM-11:45 AM**

**A phase 1 study of a novel inhibitor of protein phosphatase 2A alone and with docetaxel.** *Presenting Author: Vincent M. Chung, City of Hope, Duarte, CA*

**Background**: Protein phosphatase 2A (PP2A) is a target of several viral oncoproteins suggesting that it contributes to tumor suppression. Several human cancers have decreased PP2A function by mutations or by increased cellular PP2A inhibitors, CIP2A and SET, including about 40% of NSCLC and 60% of prostate cancers. Tumors with decreased PP2A activity may be particularly vulnerable to further PP2A inhibition. Recently, several groups have shown that inhibition of PP2A activity with a novel small molecule, LB-100, enhances the effectiveness of anticancer agents (temozolomide, docetaxel, doxorubicin, cisplatin) and radiation against different human cancer cell types in vivo without significantly enhancing toxicity. LB-100 inhibition of PP2A appears to potentiate cytotoxic therapy by altering regulation of cell cycle with enhanced S-phase entry and delayed mitotic exit and inhibition of DNA-damage-response including suppression of p53 induction and homologous recombination repair (HRR). Impaired HRR in PP2A deficient cells increases their sensitivity to PARP inhibition (PARPi), leading to the suggestion that PP2A status may indicate cancer cell vulnerability to PARPi. Based on these data, we sought to determine the maximum tolerated dose of LB-100 as a single agent, and in combination with docetaxel. **Methods**: The aims of this two-part phase I study are to determine the MTD of LB-100 alone given intravenously over 15 minutes daily for 3 days every 3 weeks, and the MTD when given with docetaxel on day 2. In part 2, the dose of LB-100 will start two levels lower than its MTD as a single agent with docetaxel given at 60mg/m$^2$. LB-100 will then be escalated to its MTD, if tolerated, and docetaxel will be escalated to 75mg/m$^2$. Eligible patients are >=18 y with progressive or metastatic tumors who have failed available standard treatment. In part 2, docetaxel naïve patients will be entered who have failed standard treatment. All patients must have an ECOG performance status of 0 or 1, have recovered from acute adverse effects of prior therapies, and have adequate bone marrow, renal, and hepatic function. Clinical trial information: NCT01837667.

**TPS2637 General Poster Session (Board #95B), Sun, 8:00 AM-11:45 AM**

**Phase I/IB trial of eribulin and everolimus in patients with triple-negative metastatic breast cancer.** *Presenting Author: Thehang H. Luu, City of Hope Cancer Center/Beckman Research Institute, Duarte, CA*

**Background:** Eribulin mesylate is a synthetic analog of halichondrin B via tubulin-based anti-mitotic mechanism, leads to G2/M cell cycle arrest, disruption of mitotic spindles, apoptotic cell death and inhibits the phosphorylation of AKT in TNBC cells. Everolimus inhibits mTOR pathway. With mTOR inhibition, pAKT is enhanced, seen at 24 hours with everolimus alone in TNBC cell lines Ser473 and SKBR3. Combination of eribulin and everolimus suppressed both pAKT and pS6K1 at 24 hours. Based on our preclinical findings, we hypothesize that everolimus and eribulin will have a synergistic effect with inproved clinical activity in metastatic TNBC. **Objectives:** phase I/IB trial of everolimus plus eribulin in metastatic TNBC. Phase I determines the safety & tolerability and the recommended Phase II dose (RP2D), while the Phase IB will evaluate event free survival rate at RP2D. **Methods:** Eligibility: Metastatic TNBC who progressed on anthracyclines/taxanes, and previous chemotherapy for metastatic disease (up to 3 prior lines). Dose schedule: eribulin 1.4 mg/m2 on days 1,8 every 21 days. Everolimus will be started at 5mg oral daily day 1 to 21 and escalated to maximum of 10mg. Study Design: Phase I use toxicity equivalence range design with dose-limiting toxicities is 0.20-0.35, levels of ≥0.51 will be too toxic. Patients enter in cohorts of three. Phase I will end when 12 patients at a single dose level with toxicity level <0.51. Phase IB will use Simon's Optimal two-stage design which will enroll up to 15 patients to evaluate event-free survival (EFS) rate at RP2D. Based on the EMBRACE trial, the 4-month EFS is 45% for eribulin and we target a 4-month EFS rate of ≥70% (25% improvement) for the combination. The secondary endpoints include response rate using RECIST, overall survival, toxicity, and pharmacokinetics since both drugs are substrates for the membrane transporter P-glycoprotein. Further secondary objective is proteomic analysis of PI3K pathway. Blood and skin punch biopsy from normal skin will be performed. Analysis performed by Luminex and mass spectrometry, and western blotting for pAKT (Ser473), and AKT, p4E-BP1 (ser65/Thr70) and 4E-BP1, pS6K1 (Thr389) and S6K1, and pS6 (Ser235/236) and S6. Clinical trial information: na.

**TPS2638 General Poster Session (Board #96A), Sun, 8:00 AM-11:45 AM**

**A phase II study of sirolimus and erlotinib in recurrent/refractory germ cell tumors.** *Presenting Author: Theodore Willis Laetsch, The University of Texas Southwestern Medical Center, Dallas, TX*

**Background:** Germ cell tumors (GCTs) affect children and young adults, with testicular germ cell tumor the most common cancer in young men. While platinum-based treatment has been successful for many GCTs, patients whose tumors are platinum-refractory have a poor prognosis. We have previously shown that non-seminomatous germ cell tumor cell lines are dependent on EGFR and mTOR signaling for survival and that the combined inhibition of these two targets in the same pathway results in >1000-fold sensitization to drug in vitro (Rakheja, AACR Peds Cancer 2013). The combination of the EGFR inhibitor erlotinib and the mTOR inhibitor sirolimus has been studied in other tumors, but never in germ cell tumors. Previous studies have not included assessment of pharmacodynamic inhibition of the targets in patients. Recently, flow cytometry based methods for detection of intracellular phosphorylated forms of S6 (downstream of mTOR), and ERK and AKT (downstream of EFGR) in peripheral blood mononuclear cells (PBMC) have been developed. This is the first pediatric trial to determine target inhibition in patients treated with the combination of EGFR and mTOR inhibitors. **Methods:** Eligible patients are those aged 1-50 years with relapsed or refractory germ cell tumors who have failed at least two prior platinum containing regimens. Patients with CNS disease are excluded. Patients receive daily sirolimus adjusted to a trough of 10-15 ng/mL and daily erlotinib at a starting dose of 120 mg/m$^2$. As the development of rash may be a biomarker of response to erlotinib, patients who don't develop grade II or worse rash during cycle 1 receive 150mg/m$^2$ for subsequent cycles. Pharmacokinetics and target inhibition in PBMCs using phospho-flow cytometry are measured during cycles 1 and 2 and correlated with response. The primary endpoint is progression free response (PFR) after 16 weeks of therapy. Using a Simon 2-stage design, 11 patients will be enrolled in the first cohort and an additional 16 patients in the second if 2 or more of the initial 11 patients have PFR. This regimen will be considered beneficial if greater than or equal to 6 of the 27 evaluable patients have PFR (response rate of 20%). This study began enrollment in January 2014 and no results are yet available. Clinical trial information: NCT01962896.

**TPS2639 General Poster Session (Board #96B), Sun, 8:00 AM-11:45 AM**

**A phase 1 trial of vandetanib (multikinase inhibitor of EGFR, VEGFR, and RET) in combination with everolimus (mTOR inhibitor) in patients with advanced malignancies.** *Presenting Author: Manojkumar Bupathi, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Preclinical models have shown that concurrent inhibition of the mammalian target of rapamycin (mTOR) pathway signaling cooperates with epidermal growth factor (EGFR)/vascular endothelial growth factor (VEGFR) and RET inhibitors to overcome primary and / or acquired resistance to tumors sensitive and resistant to anti-EGFR/VEGFR/RET inhibitors. EGFR, VEGF, RET and mTOR are validated targets in numerous malignancies. Tumor responses induced by these single agents are transient and patients can develop secondary resistance. The predominant mechanism underlying resistance to these agents is unknown but likely due to activation of several concomitant pathways. Therefore, multi-kinase targeting of EGFR, VEGFR and mTOR may improve results compared to either agent alone. Based on this hypothesis, we are conducting an investigator initiated phase I trial combining vandetanib and everolimus for patients with advanced malignancies. **Methods:** This is a phase I dose escalation and expansion trial with a conventional "3+3" design. During the escalation phase, vandetanib and everolimus were given at the following respective doses: level 0 (100 mg, 2.5 mg), level 1 (200mg, 2.5mg), level 2 (200mg, 5mg), level 3 (300 mg, 5mg), and level 4 (300mg, 10mg). The inclusion criterion includes any patient with advanced cancer which is refractory to standard therapy, relapsed after standard therapy, or those who have no standard therapy options. Both study drugs are given continuously on a 28 day schedule. Dose adjustments for everolimus were done if patients were on CYP3A4 inducers or inhibitors so that appropriate serum concentration is reached. At this time all dose levels have been completed and the study is in a dose expansion phase. Dose expansion is being done in patients with genomic alternations in *RET, EGFR, VEGFR, KDR, or P13K,PIK3R1, TSC1/2 and AKT* aberrations and patients with tumor types for which vandetanib or everolimus is individually FDA approved. Clinical trial information: NCT01582191.

**TPS2640 General Poster Session (Board #97A), Sun, 8:00 AM-11:45 AM**

**A phase I trial of MK-2206 and hydroxychloroquine(HCQ) in solid tumors, melanoma, renal, and prostate cancer to examine the role of autophagy in tumorigenesis.** *Presenting Author: Amanda D. Kaveney, Cancer Insti of New Jersey-Robert Wood Johnson Hospital, New Brunswick, NJ*

**Background:** AKT is a frequently hyperactivated oncogenic kinase in human cancers (Degenhardt 2006). Inhibition of AKT activates autophagy, promoting tumor survival, and hence AKT inhibitors may limit their own efficacy. HCQ inhibits autophagy and may prevent this survival mechanism. Treating renal cell carcinoma lines with temsirolimus, an mTOR inhibitor, promoted autophagy-mediated stress tolerance and the concomitant inhibition of autophagic degradation with chloroquine, enhanced tumor cell death (Bray 2012, Xie 2013). A similar phenomenon was reported with AKT inhibition (Degtyarev 2008, Cheny 2011) We hypothesize that Akt inhibition by the allosteric inhibitor MK-2206 will induce autophagy which may be inhibited by the addition of HCQ, potentially enhancing cell death and improving therapeutic outcomes. The purpose of this study is to define the maximum tolerated dose of MK-2206 and HCQ when used in combination, to determine the pharmacokinetic (PK) profile of the combination and to assess surrogate markers of autophagy modulation in blood and tumor samples from these patients. **Methods:** We designed an open-label Phase I trial using a 3+3 design to enroll patients with advanced solid tumors who were refractory to or declined standard therapy with the primary objective of determining the MTD of the combination. Treatment cycles were 3 weeks in length. Patients received MK-2206 alone in Cycle (C) 1 with HCQ beginning on C2, Day 1. Dose level (DL1) enrolled patients at a dose of MK-2206 135 mg weekly, with HCQ given at 200 mg twice a day (BID). Dose escalation is planned to a maximum dose of 200mg weekly and a maximum dose of 600mg BID for MK-2206 and HCQ respectively. We will assess changes in PK parameters of MK-2206 and HCQ co-administration. We will examine expression of Beclin1 and LC3, known to accumulate with autophagy inhibition. Surrogate markers will be used to assess the activation of the AKT pathway. Correlations between steady-state plasma concentration of HCQ and the degree of autophagy inhibition will be assessed. To date, twenty-seven patients have been enrolled and enrollment continues with HCQ 600mg BID and MK-2206 135mg/day. Clinical trial information: NCT01480154.

**TPS2641 General Poster Session (Board #97B), Sun, 8:00 AM-11:45 AM**

**A phase Ib study of BKM120 combined with abiraterone acetate for castrate-resistant, metastatic prostate cancer.** *Presenting Author: Akash Patnaik, Beth Israel Deaconess Medical Center/Dana Farber Harvard Cancer Center, Boston, MA*

**Background:** There is significant cross-talk between PI3-kinase (PI3K) pathway and androgen receptor (AR) signaling pathways, respectively, which are both critical for cell survival in castrate-resistant prostate cancer (CRPC). The primary study objective is to determine the safety profile and maximum tolerated dose (MTD) of BKM120 (pan-PI3K inhibitor) in combination with abiraterone/prednisone (A/P) in CRPC patients. The secondary study objectives are to assess the impact of PTEN status on duration of response/time to progression in the expansion cohort, and to evaluate the impact of BKM120 on a PI3-kinase activation fingerprint in metastatic bone or lymph node tissue samples. An exploratory objective of the study is to assess the effect of BKM120 on transcription of a set of AR-regulated genes in metastatic bone biopsy samples. **Methods:** The trial design involves a 14 day lead-in phase with BKM120 alone, to assess single-agent toxicity and perform correlative studies. A/P is combined with BKM120 at the end of 14 days using the standard 3+3 dose-escalation design with 3 dose levels of BKM120 (80 mg, 100 mg, 120 mg, respectively), and participants are assessed for safety and MTD on the combination therapy. The MTD dose will be used in the expansion cohort to assess safety of the combination. To determine pharmacodynamic impact of single agent BKM120 on the PI3K activation signature at a metastatic site, a mandatory CT-guided bone or lymph node biopsy is performed prior to BKM120 initiation and at the end of 2 weeks on BKM120 single-agent therapy. Immunohistochemical (IHC) stains for four markers (p-AKT, p-S6, PTEN and stathmin) are used to obtain a PI3K activation score, based on the quartile levels of continuous staining scores of each marker. Clinical trial information: NCT01741753.

**TPS2642 General Poster Session (Board #98A), Sun, 8:00 AM-11:45 AM**

**NCI mpact: National Cancer Institute molecular profiling-based assignment of cancer therapy.** *Presenting Author: Shivaani Kummar, Division of Cancer Treatment and Diagnosis and Center for Cancer Research, National Cancer Institute, Bethesda, MD*

**Background:** There is growing interest in matching targeted agents to genetic aberrations found in tumors of patients in early phase trials. MPACT is a randomized trial designed to assess whether response rate (CR+PR) and progression-free survival (PFS) are improved following treatment with agents chosen based on the presence of specific mutations in patient tumors compared to treatment regimens assigned from the complementary set not prospectively identified to target one of their mutations. **Methods:** Eligible adult patients have refractory solid tumors that had progressed following at least one line of standard therapy (std) and/or for which no std has been shown to improve survival. Patients are required to undergo tumor biopsy, which will be sequenced in a CLIA-certified lab for the presence of specific actionable mutations of interest (aMOIs) in 20 genes belonging to 3 pathways: DNA repair, PI3K, and RAS/RAF (total of 391 aMOIs). Patients in whom an aMOI is detected will be randomized 2:1 into Arms A or B using a rules-based, locked algorithm: Arm A will receive an agent prospectively identified to target that mutation/pathway; Arm B will receive an agent from the complementary set (not prospectively identified to target one of their mutations). Patients in Arm B will be allowed to cross over at time of disease progression to a treatment regimen based on their mutational analysis. Targeted drugs are administered at recommended Phase 2 doses and schedules: ABT-888 (PARP inhibitor) with temozolomide, or MK-1775 (Wee1 inhibitor) plus carboplatin for defects in the DNA repair pathway; everolimus (mTOR inhibitor) for mutations in the PI3K pathway; trametinib DMSO (MEK inhibitor) for mutations in the RAS pathway. A total of 180 evaluable patients will be randomized; the comparison of response rates will have 88% power to detect an overall difference of 20% vs. 5% objective response, conducted at the 1-sided, 0.04 significance level. The comparison of PFS will have 90% power to detect an increase of 80% in median PFS, conducted at the 1-sided, 0.01 significance level. The trial is currently open and accruing at the NIH Clinical Center in Bethesda, Maryland. Clinical trial information: NCT01827384.

**TPS2643 General Poster Session (Board #98B), Sun, 8:00 AM-11:45 AM**

**A randomized, parallel-dose phase 1 study of onapristone (ONA) in patients (pts) with progesterone receptor (PR)-expressing cancers.** *Presenting Author: Paul H. Cottu, Institut Curie, Paris, France*

**Background:** ONA is a type I PR antagonist, which prevents PR-induced DNA transcription. Presence of transcriptionally activated PR (APR), could indicate potential for ONA anticancer activity and could be used as a predictive biomarker. Development of an IHC companion diagnostic which identifies distinct subnuclear PR distribution patterns is ongoing, and could help select patients with PR-positive cancers most likely to respond to ONA, including endometrial and breast cancers. ONA anti-cancer activity has been documented in multiple preclinical models. Prior ONA clinical studies led to objective responses in pts with hormone therapy-naïve or tamoxifen-resistant breast cancer. ONA appeared well tolerated with the exception of LFT abnormalities, which would not preclude development in oncology. An extended-release (ER) tablet formulation of ONA was designed to address the LFT elevations seen with immediate-release (IR) ONA, by reducing the $C_{max}$. **Methods:** This is a multi-center, open-label, randomized, parallel-group, 2-stage phase 1 study with an expansion component (total n~60). Female pts ≥18 years with tumors expressing PR are eligible. Tumor tissue is required to determine PR (both A and B isotypes) and APR status. The primary endpoint is determination of the recommended phase 2 dose (RP2D) of ER ONA, with a 57-day period for observation of dose-limiting toxicity (DLT). Secondary endpoints include safety/tolerability, efficacy, and real-time PK. Tissue specimens will be used to determine relationship of APR to preliminary efficacy. Six pts per cohort are receiving ONA ER tablets 10, 20, 30, 40 or 50 mg BID, or ONA IR tablets 100 mg QD until progressive disease or intolerable safety Stage 1: Six dose cohorts are randomized in parallel. A data review committee (DRC) monitors/reviews safety signals and all DLTs. Stage 2: when sufficient pts have been treated for 8 weeks, the DRC will review all safety, PK and efficacy data to determine the RP2D. The RP2D dose cohort will be expanded by enrolling 24 additional pts to confirm the safety profile and provide a preliminary assessment of anti-tumor activity. Stage 1 is open for accrual. Clinical trial information: NCT02052128.

**TPS2644 General Poster Session (Board #99A), Sun, 8:00 AM-11:45 AM**

**Phase I study combining MLN8237 with nab-paclitaxel in patients with advanced solid malignancies.** *Presenting Author: Kian-Huat Lim, Division of Oncology, Washington University School of Medicine, St. Louis, MO*

**Background:** MLN8237 is a small molecule inhibitor against Aurora A kinase, a key serine/threonine kinase that is commonly overexpressed in human cancers, particularly in pancreatic cancer. Abraxane is an albumin-bound paclitaxel (nab-paclitaxel) that effectively disrupts mitosis and is approved by the FDA for treatment of pancreatic, breast and non-small cell lung cancers. Several preclinical studies showed that suppression of Aurora A kinase by RNA interference or MNL8237 effectively blocks mitosis and key oncogenic signaling. Blocking Aurora A kinase has been shown to reverse resistance to paclitaxel in preclinical studies, therefore investigation of MLN8237 combined with nab-paclitaxel in patients with solid tumors is warranted. **Methods:** This phase I study employs the standard 3+3 design with the primary objective of defining the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT). The starting dose for MLN8237 is 20 mg twice daily, day 1-3 of each week for 3 weeks out of a 4-week cycle, while nab-paclitaxel is 100 mg/m$^2$ weekly for 3 weeks out of a 4-week cycle. The secondary objective is to observe early signals of anti-tumor activity in an expanded cohort (N=15) of patients with advanced pancreatic cancer. Other exploratory objectives include assessment of pharmacodynamic markers such as mitotic catastrophe, apoptotic index, phosphorylation of Aurora A at threonine 288, and phosphorylation of Histone H3 at serine 28 (pHisH3 Ser28) from skin punch biopsies before and after administration of MLN8237. Additionally, we plan to investigate the impact of Aurora A genotypic polymorphisms such as 91A>T and 169G>A, on MLN8237 metabolism. To date, this trial is ongoing without any safety concerns. Clinical trial information: NCT01677559.

**TPS2645^ General Poster Session (Board #99B), Sun, 8:00 AM-11:45 AM**

**BARIS: A phase I trial to evaluate the safety and tolerability of combined BIBF 1120 and RAD001 in solid tumors and to determine the maximum tolerated dose (MTD) of the combination.** *Presenting Author: Matthias Scheffler, Lung Cancer Group Cologne, Department I of Internal Medicine and Center for Integrated Oncology, University Hospital Cologne, Cologne, Germany*

**Background:** Simultaneous inhibition of several signalling pathways involved in angiogenesis as well as in tumor cell growth regulation by kinase inhibitor combination therapy may increase therapeutic efficacy. Here we evaluate the combination of the mTOR-inhibitor RAD001 (everolimus) and the triple kinase (FGFR, VEGFR, PDGFR) inhibitor BIBF 1120 in a phase I trial in advanced solid tumors. In addition we use DCE-MRI for early identification of patients with benefit from BIBF 1120 **Methods:** Patients in arm A receive 5 mg of RAD001 and 2 x 150 mg BIBF 1120, in arm B 10 mg RAD001 and 2 x 150 mg BIBF 1120 will be administered, whereas in arm C, 10 mg of RAD001 and 2 x 200 mg BIBF 1120 will be given. Eligible are all patients with relapsed or refractory advanced/metastatic solid tumors and an ECOG performance state of 0-1 for whom no further standard therapies are available. All patients will start with a 2-week run-in phase of 2 x 200 mg BIBF 1120. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) scans will be performed at baseline staging, on day 3 and day 14. On day 14, there will also be 12 hours-pharmacokinetic (PK) assessment. Combination therapy starts on day 15. On day 29, a DCE-MRI scan and 12-hours PK will be performed. Restaging is performed on day 57. Patients who experience clinical benefit (i. e., response or stable disease) on day 57 with adequate tolerability of the combination will further receive the medication, as long as the benefit lasts. **Results:** 15 patients have been enrolled so far in arm A and B, and one patient started in arm C. Of the enrolled patients, the majority (9 patients) had non-small cell lung cancer (NSCLC) as the underlying tumor. Two patients turned out to be screening failures in arm B. The trial procedures proved to be feasible. **Discussion:** So far, the combination of BIBF 1120 and RAD001 has reached its predefined third dosage step. We expect the termination of the trial by summer 2014. In case of efficacy in a molecular defined subset of patients, an expansion phase (phase II) is planned. Clinical trial information: NCT01349296.

**TPS2646^ General Poster Session (Board #100A), Sun, 8:00 AM-11:45 AM**

**The signature program, a series of tissue-agnostic, mutation-specific signal finding trials.** *Presenting Author: Eric Daniel Slosberg, Novartis Oncology, East Hanover, NJ*

**Background:** Here we are introducing a novel signal-finding clinical trial protocol series, termed the Novartis "Signature" program. These are tissue-agnostic, mutation specific protocols that do not include pre-identified clinical trial sites. In part these are responsive to the increased frequency of molecular profiling in the oncology community, and the incidence of patients whose tumors are identified with actionable mutations yet without access to drugs targeting those alterations. As these patients are identified via routine physician-directed profiling, we bring the 'Protocol to the Patient', utilizing a rapid study start-up process, such that a de novo site can have one of these trials opened within weeks of the originating patient being identified. **Methods:** The core of this rapid start-up process includes mandating the use of a non-negotiable standard contract, budget and informed consent, and the use of central IRB. We allow any research experienced site in the US accepting our study model and with a pre-identified patient to participate. The primary endpoints of these trials are to assess clinical benefit associated with study compound. A novel statistical design is incorporated to adaptively cluster patients of like indications into cohorts for independent analysis for futility or efficacy, with subsequent consideration of the initiation of confirmatory trials. Currently the 5 open protocols include buparlisib (PI3Ki), dovitinib (multi-kinase inhibitor), binimetinib (MEK162, MEKi), encorafenib (LGX818, RAFi) and sonidegib (LDE225; SMOi) [NCT01833169, NCT01831726, NCT01885195, NCT01981187 and NCT02002689]. 5 additional single agent and novel-novel protocols are planned to open in 2014. At the time of this submission, 73 patients have been consented at 46 network, academic, and community sites. The average time from a new site approaching Novartis with a potential patient, through site start-up activities, to patient consent and screening, was 4 weeks. This program should enable the enrollment of molecularly profiled patient populations with mutations linked to targeted agents, with expedited timelines, and the evaluation of clinical activity in these (potentially rare) populations. Clinical trial information: NCT01833169, NCT01831726, NCT01885195, NCT01981187 and NCT02002689.

**TPS2647 General Poster Session (Board #100B), Sun, 8:00 AM-11:45 AM**

**Biomarker-driven access to crizotinib in ALK-, MET-, or ROS1-positive malignancies in adults and children: Feasibility of the French National Acsé Program.** *Presenting Author: Gilles Vassal, SFCE, Gustave Roussy, Cancer Campus, Villejuif, France*

**Background:** Crizotinib (czb) is registered only for the treatment of patients (pts) with ALK+ lung cancer. Czb targets (ALK, MET, ROS1) are also altered (translocation, amplification, mutation) in a wide range of malignancies in adults and children. To avoid off label use and allow for a nationwide safe and controlled access to czb for pts with an ALK, MET or ROS1 positive tumor, the French National Cancer Institute (INCa) launched the AcSé program: access to tumor molecular diagnosis in the 28 INCa molecular genetic centers along with an exploratory phase II trial. **Methods:** Biomarker identification is proposed to pts ≥ 1 year with an advanced disease among more than 15 malignancies (such as colon, gastric, liver, thyroid, renal and breast cancers, cholangiocarcinoma, lymphoma, neuroblastoma, sarcomas, and ROS1 or MET lung cancer) (such as colon, gastric, liver, thyroid, renal and breast cancers, cholangiocarcinoma, lymphoma, neuroblastoma, sarcomas, and ROS1 lung cancer) known from literature to harbor a genomic alteration in a czb target. If not eligible for any other academic or industry trial targeting the same alteration, a patient with an ALK, MET or ROS1 positive tumor may enter one of the 22 specified cohorts defined as a disease and a type of target alteration, and receives czb (adult: 250 mg x 2; child: 280 mg/m2 x 2). Pts with an altered czb target as evidenced through a pangenomic tumor profiling program are also eligible. Tumor response is evaluated every 2 months using RECIST criteria. Three statistical 2-stage designs are considered for cohorts to anticipate 3 situations in terms of expected response rate and incidence. Accrual stops if 0 response / N1 pts; else N2 additional pts are recruited. 10,000 to 15,000 molecular tests and 490 pts treated in 150 centers are planned over 3 years. From Aug. 2013 to Jan. 2014, 22 pts have been accrued. The AcSé program is currently being expanded to other targeted drugs. Clinical trial information: NCT02034981.

| | P0 | P1 | $\alpha$ | $\beta$ | N1 | N2 |
|---|---|---|---|---|---|---|
| **Common case** | 10% | 30% | 10% | 10% | 11 | 14 |
| **Very rare disease, eg neuroblastoma** | 10% | 30% | 15% | 15% | 8 | 12 |
| **Optimistic case, eg ROS1+ lung cancer** | 20% | 40% | 10% | 10% | 7 | 30 |

**3000 Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**Randomized comparison of two doses of the anti-PD-1 monoclonal antibody MK-3475 for ipilimumab-refractory (IPI-R) and IPI-naive (IPI-N) melanoma (MEL).** *Presenting Author: Omid Hamid, The Angeles Clinic and Research Institute, Los Angeles, CA*

**Background:** MK-3475 has shown durable antitumor activity in MEL across multiple doses and schedules. We compared the efficacy and safety of 2 MK-3475 doses in MEL patients (pts). **Methods:** In separate cohorts, IPI-N and IPI-R pts were randomized 1:1 to MK-3475 2 or 10 mg/kg every 3 wk (2 Q3W or 10 Q3W). IPI-N pts received ≤2 prior systemic therapies. IPI-R pts had any number of prior therapies and unequivocal or confirmed PD per immune-related response criteria (irRC) after ≥2 IPI doses; all *BRAF*-mutant pts were previously treated with BRAF inhibitors. Primary endpoint was ORR assessed by RECIST 1.1 every 12 wk by independent central review. Investigator-assessed response by irRC was also obtained. **Results:** A total of 276 pts were randomized (103 IPI-N [2 Q3W, n = 51; 10 Q3W, n = 52] and 173 IPI-R [2 Q3W, n = 89; 10 Q3W, n = 84]. In both cohorts, treatment arms were well balanced for known prognostic factors. As of the 10/18/2013 cutoff, all IPI-N and 47% of IPI-T pts had ≥9 mo of follow-up. Among evaluable pts, no significant differences in ORR by RECIST were observed between doses in IPI-N (33% vs 40%) or IPI-R (26% vs 26%) pts. By RECIST, response duration ranged from 6+ wk to 39+ wk in both cohorts (median not reached), with ~90% of responses ongoing. PFS by RECIST was similar between doses. The safety profile was generally similar between pts treated with 2 Q3W and 10 Q3W. There were no drug-related deaths. **Conclusions:** MK-3475 2 mg/kg Q3W and 10 mg/kg Q3W provided similar efficacy and safety in both IPI-N pts and IPI-R pts. Treatment was well tolerated with acceptable toxicity profile. The high ORR provided by MK-3475 comes with long durability in both IPI-N and IPI-R MEL. Clinical trial information: NCT01295827.

| | RECIST 1.1 | | | irRC | | |
|---|---|---|---|---|---|---|
| | 2 Q3W | 10 Q3W | 2-sided *P* | 2 Q3W | 10 Q3W | 2-sided *P* |
| **IPI-N** | | | | | | |
| **ORR, % (95% CI)** | 33 (20-49) | 40 (26-56) | .4835 | 39 (26-54) | 40 (27-55) | .9040 |
| **Response duration, wk, range** | 7+ – 36+ | 6+ – 39+ | — | 12+ – 42+ | 10+ – 39+ | — |
| **Median PFS, wk(95% CI)** | 27 (12-NR) | 23 (12-48) | — | 36 (13-NR) | 26 (12-NR) | — |
| **24-wk PFS, %** | 51 | 48 | — | 60 | 50 | — |
| **IPI-R** | | | | | | |
| **ORR, % (95% CI)** | 26 (17-37) | 26 (17-38) | .9558 | 27 (18-37) | 32 (22-43) | .4568 |
| **Response duration, wk, range** | 6+ – 37+ | 8+ – 37+ | — | 12+ – 42+ | 4+ – 37+ | — |
| **Median PFS, wk (95% CI)** | 22 (12-36) | 14 (12-24) | — | 31 (22-48) | 35 (24-NR) | — |
| **24-wk PFS, %** | 45 | 37 | — | 57 | 57 | — |

**3001^ Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**A phase 1 study of MEDI4736, an anti–PD-L1 antibody, in patients with advanced solid tumors.** *Presenting Author: Jose Lutzky, Mount Sinai Comprehensive Cancer Center, Miami Beach, FL*

**Background**: Immune-suppressing molecules such as PD-L1 can be co-opted by cancer cells to suppress the natural immune response to cancer. Upregulation of PD-L1 and inhibition of antitumor T-cell activation is observed in several tumor types. MEDI4736 is a human IgG1 antibody which binds specifically to PD-L1, preventing binding to PD-1 and CD80. **Methods:** An ongoing phase 1 multicenter, open-label study (NCT01693562) is evaluating safety, pharmacokinetics (PK), and antitumor activity of MEDI4736 given IV every 2 (q2w) or 3 wks (q3w) in a 3+3 dose escalation with a 28-day (q2w) or 42-day (q3w) dose-limiting toxicity (DLT) window, followed by expansion in 8 solid tumors. Response was assessed by immune-related response criteria in escalation. **Results:** As of Jan 17, 2014, 26 patients (pts) (13 NSCLC, 8 melanoma, 5 other) in dose escalation (median age 59 yrs; 35-77), all PS 0-1, with a median of 4 prior treatments, received a median of 5 (1-25) q2w and 4.5 (1-7) q3w doses of MEDI4736 across 6 cohorts (0.1 – 10 mg/kg q2w; 15 mg/kg q3w). MEDI4736 showed dose-dependent PK. Evidence of ADA impacted PK exposure in only 1 patient. No DLTs or maximum tolerated dose were identified for q2w or q3w dosing. Treatment-related AEs occurred in 34% of pts, all Grade 1-2; none led to discontinuation of study drug. The most frequent treatment-related AEs were diarrhea, fatigue, rash, and vomiting (12% each). No pneumonitis, colitis, or hyperglycemia occurred. Of 26 pts, 4 PRs (3 NSCLC, 1 melanoma) and 5 additional pts with tumor shrinkage not meeting PR were observed. Disease control rate (PR + SD ≥ 12 wks) was 46%. Tumor shrinkage, as early as 6 wks, was seen at all dose levels, and benefit was durable; 11 pts remain on study as of the data cutoff (2+ to 14.9+ mos). Expansion cohorts opened Sep 2013 using a 10 mg/kg q2w dose; 151 pts have been dosed, with the opportunity to enroll > 600 pts. Preliminary clinical activity has been observed with acceptable safety across a range of tumors including SCCHN, pancreatic, gastric, NSCLC, and melanoma. **Conclusions:** MEDI4736 has demonstrated an acceptable safety profile and durable clinical activity in this dose-escalation study. Expansion in multiple cancers and development of MEDI4736 as monotherapy and in combination is ongoing. Clinical trial information: NCT01693562.

**3002^ Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**Preliminary data from a multi-arm expansion study of MEDI4736, an anti-PD-L1 antibody.** *Presenting Author: Neil Howard Segal, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Checkpoint blockade of the PD-1/PD-L1 and CTLA-4 pathways has shown to be active in multiple tumor types. MEDI4736 is a human IgG1 monoclonal antibody which binds specifically to PD-L1, preventing binding to PD-1 and CD80. In phase I, MEDI4736 showed acceptable safety (no maximal tolerated dose identified). With evidence of clinical activity in phase I, an expansion study was initiated in multiple cancer types including NSCLC, melanoma (cutaneous and ocular), gastroesophageal, hepatocellular carcinoma, pancreatic, SCCHN and triple negative breast cancer. **Methods:** 10 - 20 pts were initially enrolled per tumor type, with expansion allowed upon observation of clinical activity. MEDI4736 was administered as 10 mg/kg IV every 2 weeks for 12 months. Retreatment was permitted for progression after 12 months of therapy. Response was assessed by RECIST v1.1. **Results:** The expansion cohorts were initiated in Sep 2013. As of Jan 17, 2014, 151 pts had received ≥1 dose of MEDI4736. Safety data are available for 105 pts (median age 60y; 36-84), 59% male, ECOG 0/1 (27%/71%), with a median of 3 (1-8) prior treatments, who received a median of 3 (1-8) doses. The safety profile was consistent with previous reports. Treatment-related AEs occurred in 33% of pts, with related ≥ Grade 3 AEs in 7%; none led to discontinuation of study drug. The most frequently observed treatment-related AEs were fatigue (13%), nausea (8%), rash (6%), vomiting (5%), and pyrexia (5%). One pt developed Grade 2 pneumonitis which resolved with drug interruption and steroids. There were no reports of colitis or hyperglycemia of any grade. With a median follow-up of 6 weeks, tumor shrinkage is already detectable in multiple tumor types including pts with melanoma, pancreatic, head and neck, and gastroesophageal cancer. The study continues to enroll pts and generate more mature follow-up data. **Conclusions:** Preliminary data in expansion suggest the safety of MEDI4736 is acceptable, even in heavily pre-treated pts. Early evidence of clinical activity was reported in multiple tumor types. Further evaluation of MEDI4736 as monotherapy and in combination with a variety of immunomodulators and targeted agents is ongoing. Clinical trial information: NCT01693562.

**3003 Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**The neoantigen landscape underlying clinical response to ipilimumab.** *Presenting Author: Alexandra Snyder Charen, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Ipilimumab, an antibody against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), prolongs overall survival and can produce durable tumor regression in patients with advanced melanoma. Ipilimumab activates cytotoxic T-lymphocytes and enables them to destroy tumor cells. However, the molecular determinants of response to ipilimumab are unknown. **Methods:** Fresh frozen tumor DNA (and matching blood) from 25 melanoma patients treated with ipilimumab was subjected to whole exome sequencing. Exon capture was performed using the SureSelect Human All Exon 50MB kit (Agilent). Enriched exome libraries were sequenced on the HiSeq 2000 platform (Illumina) to a mean coverage of 103X. Somatic mutations and candidate somatic neoantigens generated from these mutations were identified and characterized. **Results:** Our cohort included complete responders (CR) and nonresponders (NR). Mutational burden ranged from 1-1121 mutations per tumor. Mutational load was significantly associated with clinical response (p=0.028, CR vs. NR, Fisher's Exact Test), but alone was not sufficient to predict response. Using genome-wide somatic neoepitope analysis, we defined candidate tumor neoantigens and identified a neoantigen landscape that is specifically present in tumors with complete responses to ipilimumab. These somatic neoepitopes share consensus sequences with experimentally validated antigens from a variety of pathogens. Furthermore, in four of six CR patients, a mutation led to the generation of a consensus amino acid sequence previously identified as necessary for T-cell recognition of melanoma antigen recognized by T-cells (MART-1). **Conclusions:** Somatic mutations and concomitant generation of neoepitopes in melanoma tumors confers enhanced antigenicity and response to the immune checkpoint modulator ipilimumab. Our study defines the neoantigen landscape in responders to ipilimumab, provides a rationale for examining the exomes of patients for whom ipilimumab is being considered, and builds a foundation for understanding the molecular determinants of response to cancer immunotherapy.

**3004 Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**Germline genetic determinants of immunotherapy response in metastatic melanoma.** *Presenting Author: Christina Adaniel, New York University Medical Center, New York, NY*

**Background:** Ipilimumab-based immunotherapy has substantially increased survival for patients with advanced melanoma, however, the benefit is observed only in a small portion of treated patients. It is highly plausible, yet completely unexplored, that germline genetic factors modulate immunotherapy outcome. In this study we performed whole-exome sequencing (WES) to discover novel germline determinants of response to ipilimumab. **Methods:** Blood samples were collected from >60 metastatic melanoma patients treated by ipilimumab at the New York University Langone Medical Center. WES was performed on objective responders (OR) and non-responders (NR), defined by immune-related response criteria, using the Nextera platform (Illumina) at average 30x coverage. We have implemented a novel modified method for testing the association between OR and NR by variant, gene and enrichment of molecular networks. Gene-Set Enrichment Analysis and Pathway Studio were used to test the pathway associations. **Results:** The preliminary data comparing an initial subset of 30 ORs and 30 NRs identified significant associations with ipilimumab response for several loci including RPS6KB1 (p=0.001) and LNX2 (0.001). In addition, the pathway analysis showed significant associations for SMAD 3 (p=0.04) and interleukin 1 (p=0.04) related pathways. **Conclusions:** Preliminary findings provide promising evidence supporting the presence of germline genetic factors associated with response to ipilimumab therapy and pointing to immune-related pathways associated with outcomes. As the study is still in progress, the anticipated accrual of a larger sample collection is underway. This will further increase the analytical power of the discovery phase, but will also allow expanded validation of the current findings, suggesting for the first time that germline genetic factors modulate immunotherapy response.

**3005^ Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**Clinical efficacy and correlation with tumor PD-L1 expression in patients (pts) with melanoma (MEL) treated with the anti-PD-1 monoclonal antibody MK-3475.** *Presenting Author: Richard Kefford, Westmead Hospital and Melanoma Institute Australia, University of Sydney, Westmead, Australia*

**Background:** MK-3475 demonstrated antitumor activity and acceptable safety in a phase I MEL cohort. We provide updated efficacy data and correlation with tumor PD-L1 expression. **Methods:** 135 pts received MK-3475 10 mg/kg Q2W (n = 57), 10 mg/kg Q3W (n = 56), or 2 mg/kg Q3W (n = 22). Response was assessed every 12 wk by RECIST 1.1 by independent central review and by immune-related response criteria (irRC) by investigator. Biopsy was required in the 60 d before MK-3475. Tumor PD-L1 expression was assessed by IHC. A preliminary cutoff of 1% of stained tumor cells defined PD-L1 positivity. **Results:** As of 10/18/2013, all pts had ≥13 mo follow-up. Median time on treatment was 23 wk (range, 1 dose to 97 wk). In pts with measurable disease, ORR was 41% by RECIST (Table). Objective responses were observed as late as 64 wk, with some conversions to CR seen as late as 72 wk. Median response duration was not reached; responses were ongoing for 87% of responders. Median PFS was 31 wk. Median OS was not reached, and OS rate at 1 y was 81%. Tumor PD-L1 expression was evaluable in 71 pts with measurable disease and ≥1 tumor evaluation (77% PD-L1$^+$). Of these pts, PD-L1 expression was associated with improved ORR by RECIST (51% vs 6%, $P$ = .0012 [Fisher's exact]) and PFS (median 12 vs 3 mo, HR 0.31, 95% CI 0.16-0.61, $P$ = .0004 [log-rank]). 1-y OS rate was 84% in PD-L1$^+$ and 69% in PD-L1$^-$ pts ($P$ = .2146 [log-rank]). There were no treatment-related deaths; 14% of pts experienced drug-related grade 3/4 AEs. **Conclusions:** MK-3475 induces durable responses and favorable 1-y OS with acceptable safety in MEL. Although tumor PD-L1 positivity was associated with improved ORR and PFS, antitumor activity was also observed in pts with low baseline PD-L1 expression. These preliminary data require confirmation. Clinical trial information: NCT01295827.

| | RECIST 1.1 | | | | irRC | | | |
|---|---|---|---|---|---|---|---|---|
| | 2 Q3W | 10 Q3W | 10 Q2W | Total | 2 Q3W | 10 Q3W | 10 Q2W | Total |
| ORR, % (95% CI) | 45 (23-69) | 31 (18-47) | 49 (35-63) | 41 (32-51) | 32 (14-55) | 32 (20-46) | 58 (44-71) | 43 (35-52) |
| Median response duration, wk (range) | NR (9+ – 60+) | NR (11 – 72+) | NR (8+ – 76+) | NR (8+ – 76+) | NR (9 – 60+) | NR (11 – 65+) | NR (12 – 93+) | NR (9 – 93+) |
| Median PFS, wk (95% CI) | 72 (12-NR) | 24 (12-36) | 50 (24-NR) | 31 (19-50) | 72 (12-NR) | 30 (15-NR) | 84 (24-NR) | 54 (24-NR) |
| 24-wk PFS, % | 56 | 44 | 60 | 53 | 51 | 54 | 64 | 58 |

**3006^ Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**Evaluation of immune-related response criteria (irRC) in patients (pts) with advanced melanoma (MEL) treated with the anti-PD-1 monoclonal antibody MK-3475.** *Presenting Author: F. Stephen Hodi, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Unique response patterns have been observed with immunotherapies, and both objective response and prolonged disease stabilization can occur after an initial increase in tumor size. irRC were developed to better characterize response to immunotherapy, but it is unclear how irRC perform in pts treated with PD-1 blockade. Here, we describe unique patterns of response to MK-3475 in MEL pts and evaluate irRC as an alternative criterion for comprehensive response assessment. **Methods:** Source population was pts from 3 MEL cohorts treated with MK-3475 2 mg/kg every 3 wk (Q3W), 10 mg/kg Q3W, or 10 mg/kg Q2W in a phase I trial. Tumor imaging was performed every 12 wk. Response was assessed by irRC and RECIST 1.1 by central review; irRC was used for pt management. Tumor flare and atypical delayed response were identified by using centrally assessed irRC data among pts on MK-3475 for ≥28 wk. Tumor flare was defined as unconfirmed PD at assessment 1 (ie, wk 12) and non-PD at assessment 2. Atypical delayed response was defined as PD at any time point followed by non-PD and then response. Survival data were analyzed in pts who had PD by RECIST but CR/PR/SD by irRC. **Results:** Among the 411 pts enrolled across the 3 MEL cohorts, 192 were on MK-3475 for ≥28 wk as of the analysis cut-off of 10/18/2013. Tumor flare was seen in 7 (3.6%) pts. In these pts, best overall response per irRC was CR (n = 1), PR (n = 4), and SD (n = 2). Atypical delayed response was seen in 6 (3.1%) pts. The 51 pts with PD by RECIST but CR/PR/SD by irRC had favorable OS compared with the 145 pts with PD by both criteria (Table). **Conclusions:** MEL pts treated with MK-3475 may experience unique patterns of response and should be managed accordingly. Similar to what has been observed with ipilimumab, conventional criteria such as RECIST may underestimate the benefit of MK-3475 in approximately 10% of treated pts. An updated version of response criteria that incorporate new data on PD-1 inhibitors may be appropriate for future consideration. Clinical trial information: NCT01295827.

| | OS Rate | | |
|---|---|---|---|
| | 3 mo | 6 mo | 12 mo |
| Pts with CR/PR/SD by RECIST and irRC (n = 215) | 100% | 98% | 92% |
| Pts with PD by RECIST but CR/PR/SD by irRC (n = 51) | 100% | 94% | 67% |
| Pts with PD by RECIST and irRC (n = 145) | 79% | 53% | 34% |

**3007 Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**A phase 1 study of PF-05082566 (anti-4-1BB) in patients with advanced cancer.** *Presenting Author: Neil Howard Segal, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** 4-1BB agonists markedly enhance cytotoxic T-cell responses, resulting in anti-tumor activity in several models. PF-05082566 is a fully humanized IgG2 agonist monoclonal antibody targeting 4-1BB.This portion of the first-in-human phase I study assessed the safety, pharmacokinetics (PK), pharmacodynamics (PD) and antitumor activity of PF-0508256 monotherapy in patients with advanced cancer. **Methods:** An open-label, dose escalation study was conducted in patients with advanced malignancies for which no curative therapy was available. Cohorts of 3-6 patients were enrolled initially using a 3+3 design (0.006 to 0.3 mg/kg), then a Time-To-Event CRM design for higher doses (0.6 to 5 mg/kg). Patients received PF-05082566 via intravenous infusion every 4 weeks (one cycle) with an 8 week period for assessment of dose-limiting toxicity (DLT). Radiographic assessments were conducted every 8 weeks, using RECIST 1.1. **Results:** 27 patients have been treated with PF-05082566 up to the 0.3 mg/kg dose level, including colorectal cancer (n=11), Merkel cell carcinoma (n=6), pancreatic adenocarcinoma (n=2), and one each of nasopharyngeal cancer, ampullary cancer, squamous cell lung cancer, carcinoma of unknown primary, melanoma, sarcoma, follicular lymphoma, and lymphocytic lymphoma (SLL). 25 patients completed the DLT assessment period and 7 patients remain on therapy. All discontinuations from treatment were due to disease progression. Median number of cycles ranged from 2 (at 0.006 mg/kg) to 7 (at 0.24 mg/kg). There was no apparent relationship between increasing doses and the frequency or severity of treatment emergent adverse events, which were mostly Grade 1. One patient treated at 0.06 mg/kg had Grade 3 elevation in alkaline phosphatase. No additional significant elevations in liver enzymes and no DLTs have occurred to date. Preliminary PK data suggests a linear increase in drug exposure with increasing dose, and a half life of ~10 days. A best overall response of stable disease was observed in 22% (6/27) patients. **Conclusions:** PF-05082566 was well tolerated, with evidence of disease stabilization in multiple patients. Enrollment continues at higher dose levels to obtain additional safety, PK, PD, and efficacy data. Clinical trial information: NCT01307267.

**LBA3008 Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**HPV-targeted tumor-infiltrating lymphocytes for cervical cancer.** *Presenting Author: Christian S. Hinrichs, National Cancer Institute, Bethesda, MD*

**The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Monday, June 2, 2014, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2014, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.**

**3009 Poster Highlights Session (Board #1), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Updated survival, toxicity, and biomarkers of nivolumab with/without peptide vaccine in patients naive to, or progressed on, ipilimumab (IPI).** *Presenting Author: Jeffrey S. Weber, Moffitt Cancer Center, Comprehensive Melanoma Research Center, Tampa, FL*

**Background:** PD-1 antibodyNivolumab was administered with/without a multi-peptide vaccine to 105 patients (pts) with unresectable melanoma that failed at least one regimen and were IPI naïve, or progressed after IPI, to assess its toxicity especially in those with prior dose limiting immune related adverse events (irAEs) to IPI, and to update survival data, characterize T cell gene expression and immune cell subsets. **Methods:** HLA A0201 IPI-naïve pts received nivolumab at 1, 3 or 10 mg/kg (34 pts); additional pts that failed prior IPI received nivolumab at 3 mg/kg: two cohorts of pts were A*0201 positive and had either grade 2 or less IPI-related irAE (10 pts), or grade 3-4 dose limiting irAE (20 pts); 41 pts had grade 2 or less irAE, were not HLA restricted and received nivolumab alone. Pre- and 12 week post-treatment peripheral blood was analyzed. **Results:** Median follow-up for all pts was 15 months (mos);median progression-free survival (PFS) was 4.2 mos, and estimated median overall survival (OS) was 16.7 mos (95% CI: 14.4, not reached) with 1 year OS of 65%. Median OS was similar for IPI-naïve or IPI-relapsed pts (15.9 vs. 18 mos, $p=0.6$), older or younger than 62 ($p=0.44$) and by dose ($p=0.86$). ORR, median PFS and OS were longer in males than females (all $p<0.05$). Of 20 pts with prior IPI-induced grades 3-4 irAEs, only 1 had a subsequent grade 3-4 irAE with nivolumab and it was different than seen with prior IPI, but treatment emergent grades 1-2 rash and injection reactions were common. Biomarker studies showed that circulating HLA-DR lo/CD14+/CD11b+ myeloid-derived suppressor cells (MDSC, $p=0.028$), and FCRL2+ CD8 T cells ($p=0.009$) were associated with progression. Decreased regulatory molecules BTLA and LAG3 on CD8+ T cells were associated with response ($p=0.04$). Principal component analysis of genes expressed by flow sorted CD8 T cells showed clustering by response ($p = 6.01E-10$) **Conclusions:** Median OS of 16.7 mos and PFS of 4.2 mos with nivolumab was observed in previously treated melanoma patients naïve to or failing IPI. Prior irAEs to IPI were not replicated with nivolumab. Novel biomarkers of outcome were found on circulating blood cells, including MDSC and CD8 T cell FCRL2 pre-treatment. Clinical trial information: NCT01176461.

**3010 Poster Highlights Session (Board #2), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Preliminary results from a phase 1/2 study of INCB024360 combined with ipilimumab (ipi) in patients (pts) with melanoma.** *Presenting Author: Geoffrey Thomas Gibney, Moffitt Cancer Center, Comprehensive Melanoma Research Center, Tampa, FL*

**Background:** Indoleamine 2,3-dioxygenase 1 (IDO1) is a tryptophan-catabolizing enzyme that is overexpressed in cancers and induces immune tolerance by suppressing T-cell responses. INCB024360, a potent, selective IDO1 inhibitor, was generally well tolerated as monotherapy up to 700 mg BID. Preclinical data support anti-tumor synergy for INCB024360 when administered with antibody antagonists to checkpoint receptors. **Methods:** This is an ongoing dose-escalation study of INCB024360 combined with ipi (3 mg/kg IV q 3 wks x 4) in pts with metastatic melanoma. Enrollment in 2 cohorts (300 mg BID, 25 mg BID) is complete. Toxicity, ORR (irRC), Duration of Response (DoR), and OS were evaluated. The DLT evaluation period was 8 wks andassessments for response were every 9 wks. **Results:** Seven pts were enrolled at 300 mg BID. When 5 pts developed clinically significant ALT elevations after 30–76 days on treatment, enrollment was stopped. ALT elevations were reversible with corticosteroids and treatment discontinuation. Six of 7 pts had evaluable on-study scans prior to discontinuation and all showed irSD. Time to subsequent therapy was >90 days in all 7 pts and >180 days in 4 of 7 pts. Enrollment was restarted at 25 mg BID (n=8), where 1 pt with progression of prior extensive liver metastases had a DLT (G3 AST elevation). Immune-related AEs (irAEs) were generally G1/2 and manageable with continued dosing or temporary dose interruption; 1 pt each discontinued for G3 colitis and G3 salivary amylase elevation. Six of 8 pts had tumor reduction by the 1st evaluation. Confirmed disease control rate was 75% (6/8). Three pts had confirmed irPR (2 occurred by the 1st or 2nd scan); DoR was 179, 148, and >127 (ongoing) days. Three pts had irSD for 116, >173 (ongoing), and >187 (ongoing) days. Pharmacodynamic effects at 25 mg BID were similar to those that were sufficient in preclinical models to achieve maximal therapeutic effect. A 50 mg BID cohort is enrolling. **Conclusions:** INCB024360 25 mg BID with ipi was generally well tolerated and irAEs previously observed with ipi were reversible with appropriate management. Tumor response and duration data suggest the potential for enhanced melanoma patient outcomes compared to ipi monotherapy. Clinical trial information: NCT01604889.

**3011 Poster Highlights Session (Board #3), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Combinatorial TGF-$\beta$ signaling blockade and anti-CTLA-4 antibody immunotherapy in a murine $BRAF^{V600E}$-PTEN-/- transgenic model of melanoma.** *Presenting Author: Brent Allen Hanks, Duke University Medical Center, Durham, NC*

**Background:** T cell-targeted checkpoint inhibitor immunotherapy for melanoma and other solid tumor malignancies only benefits a subpopulation of patients. Our work has shown that melanoma-expressed factors including TGF-$\beta$ can generate an immune privileged site by suppressing the function of critical dendritic cell populations within the local immune microenvironment. We hypothesized that inhibiting TGF-$\beta$ signaling in the tumor microenvironment could augment the efficacy of anti-CTLA-4 antibody therapy in a murine transgenic model of melanoma. **Methods:** Upon primary melanoma development in *Tyr::CreER;*$Braf^{CA/+}$*;*$PTEN^{lox/lox}$mice, the LY2157299 type I TGF-$\beta$ receptor serine/threonine kinase inhibitor was administered daily by oral gavage accompanied by intra-peritoneal delivery of anti-CTLA-4 monoclonal antibody (mAb) every three days. Tumor development was monitored by caliper and photodocumentation/imaging analysis. After 14 days, tumor tissue, tumor-draining lymph node (TDLN) tissue, and lung tissue was resected for whole tissue Western blot analysis, T cell flow cytometry, immunohistochemistry, and indoleamine 2,3-dioxygenase (IDO) enzymatic activity assays. **Results:** While LY2157299 and anti-CTLA-4 mAb monotherapy failed to suppress melanoma progression, LY2152799-anti-CTLA-4 mAb combination therapy synergistically suppressed both primary melanoma tumor growth as well as melanoma metastasis in this physiologically-relevant transgenic melanoma model. These observations correlated with significant increases in the $CD8^+$ T cell/$CD4^+FoxP3^+$regulatory T (Treg) cell ratio in melanoma tissues. In addition, LY2152799 effectively suppressed TDLN-derived dendritic cell IDO enzyme activity and this was found to correlate with diminished levels of Tregs in both TDLN and primary melanoma tissues. **Conclusions:** TGF-$\beta$ signaling inhibition is a promising strategy for augmenting the anti-tumor efficacy of immune checkpoint blockade in melanoma. The pharmacological manipulation of the tumor microenvironment to reverse local immune evasion mechanisms and enhance anti-tumor immune responses represents an important avenue for future studies.

**3012 Poster Highlights Session (Board #4), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**A phase 1 study of MEDI3617, a selective angiopoietin-2 inhibitor, alone and in combination with carboplatin/paclitaxel, paclitaxel, or bevacizumab in patients with advanced solid tumors.** *Presenting Author: David Michael Hyman, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** MEDI3617 (M) is an investigational monoclonal antibody that inhibits angiogenesis by preventing the interaction of angiopoietin-2 (Ang2) ligands with the Tie2 receptor. **Methods:** This is a 3+3 dose-escalation (monotherapy [mTx] and combination) study in adults with advanced solid tumors with mTx expansion in platinum-resistant ovarian cancer (prOC) (NCT01248949). Patients (pts) with Karnofsky performance status ≥70, and adequate organ function were treated in 21 or 28 day cycles with M alone or in combination with carboplatin/paclitaxel (CT), paclitaxel (T), or bevacizumab (B). Objectives included safety, pharmacokinetics, pharmacodynamics, and antitumor activity. **Results:** As of 22 Jan 2014, 95 pts (median age 61; 54% female) were enrolled: 25 in M mTx dose-escalation, 7 in M mTx prOC dose-expansion, and 63 in combination arms. The maximum tolerated dose was not defined in either mTx or combination arms. In the mTx arms, 72% (n=32) of pts had treatment-related adverse events (trAEs): 63% grade ≤2, 6% grade 3, and 3% grade 4. Non-hematologic grade 3 trAEs in the mTx arms included increased weight (6.3%), peripheral edema (3.1%), lymphedema (3.1%) and pleural effusion (3.1%). The grade 3 peripheral edema and lymphedema that occurred in 2 pts in the prOC expansion arm persisted despite discontinuation of M. In the mTx arms, 3 pts (9.4%) discontinued treatment due to trAEs. Exposure of M approached a linear range beyond 100 mg Q3W or 60 mg Q2W. Circulating serum Ang2 levels were >95% saturated at doses ≥500 mg. Objective responses in the combination arms included 5 partial responses plus 1 unconfirmed in: prOC (1 each in M/B and M/T, 1 unconfirmed in M/CT), renal cell cancer (1 in M/B), cervical cancer (1 in M/B), and lung cancer (1 in M/T). In the mTx arms, 1 unconfirmed partial response in a prOC pt was observed and 7 pts had stable disease for >12 weeks. **Conclusions:** MEDI3617 alone and in combination had an acceptable safety profile. Combination therapy exhibited signs of antitumor activity across a variety of tumor types. Enrollment in the mTx prOC expansion cohort is ongoing. Clinical trial information: NCT01248949.

**3013 Poster Highlights Session (Board #5), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Magnitude and quality of tumor-infiltrating T-cell response upon poxvirus-based active immunotherapy alone and in combination with CTLA-4 immune checkpoint inhibition.** *Presenting Author: Susan P Foy, Bavarian Nordic Inc., Mountain View, CA*

**Background:** PROSTVAC PSA-targeted immunotherapy for metastatic castration-resistant prostate cancer is being tested in the PROSPECT Phase 3 trial. Another poxvirus-based immunotherapy product, MVA-BN-HER2, has been tested in early-phase clinical trials for breast cancer. The potential for synergistic benefit from combination active immunotherapy plus immune checkpoint inhibition is hypothesized. Survival benefit plus magnitude and quality of immune responses were evaluated in non-clinical studies following MVA-BN-HER2 dosing alone and in combination with CTLA-4 immune checkpoint inhibition. **Methods:** In a therapeutic CT26-HER2 lung metastasis model, mice were treated with MVA-BN-HER2 without and with anti-CTLA-4 antibody. Tumor infiltrating and peripheral antigen-specific CD4 and CD8 T cells were evaluated by FACS. **Results:** Combining MVA-BN-HER2 immunotherapy with CTLA-4 inhibition in therapeutic mouse tumor models demonstrated synergistic efficacy for median overall survival ($p<0.001$). Improved survival following MVA-BN-HER2 administration was accompanied by a 30 fold increase in tumor infiltrating antigen-specific CD8 T cells (CD8 TILs) compared to no treatment, which was augmented to 90 fold in combination with anti-CTLA-4. By contrast, single agent CTLA-4 inhibition provided a 10 fold increase in antigen-specific CD8 TILs over no treatment. The CD8 T cell response was characterized by an activated IFN$\gamma$+TNF$\alpha$+ signature following poxvirus active immunotherapy compared to an IFN$\gamma$+TNF$\alpha$- response with CTLA-4 inhibition alone. Infiltrating ICOS+ CD4 T cells were primarily FoxP3+ regulatory T cells in untreated and anti-CTLA-4 treated mice, but were FoxP3- effector T cells in mice treated with MVA-BN-HER2 alone or in combination with anti-CTLA-4. **Conclusions:** In non-clinical studies, poxvirus-based immunotherapy induces a robust, functional tumor-infiltrating T cell response for improved survival that is augmented significantly in combination with CTLA-4 immune checkpoint inhibition.

| Therapy | Median survival (days) |
|---|---|
| **Untreated** | 30 |
| **$\alpha$-CTLA-4** | 35 |
| **MVA-BN-HER2** | 49.5 |
| **MVA-BN-HER2 + $\alpha$-CTLA-4** | not reached by day 100 |

**3014 Poster Highlights Session (Board #6), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Phase II study of autologous mRNA electroporated dendritic cells (TriMixDC-MEL) in combination with ipilimumab in patients with pretreated advanced melanoma.** *Presenting Author: Bart Neyns, Universitair Ziekenhuis Brussels, Brussels, Belgium*

**Background:** Autologous monocyte-derived mRNA electroporated dendritic cells (TriMixDC-MEL) are immunogenic and have anti-tumor activity in patients (pts) with pretreated advanced melanoma (Wilgenhof S. et al. Ann Oncol 2013). Ipilimumab (ipi) is a monoclonal antibody directed against the CTLA-4 receptor that counteracts physiologic suppression of T-cell activation and improves the overall survival of pts with advanced melanoma. **Methods:** The activity and safety of TriMixDC-MEL ($4.10^6$ cells id and $20.10^6$ iv, q3wks x4) combined with ipi (10 mg/kg q3wks x4), followed by ipi maintenance therapy (10 mg/kg q12w, in pts who are progression-free at week 24) was investigated in pts with advanced pretreated melanoma according to a Simon two-stage phase II study design. The primary endpoint was the 6-mths disease control rate (DCR) by irRC. **Results:** 39 pts initiated study treatment (16F/23M; median age 46y [range 24-70]; AJCC stage IIIc/IV M1a/-M1b/-M1c: 1/6/4/28; prior therapy: BRAF- or MEK-inhibitor: 23 pts, chemotherapy: 18 pts). Following DC-administration, gr2 skin injection site reactions were observed in all pts, post-infusion chills (< gr2) in 15 (38%), and transient flu-like symptoms (< gr2) in 33 pts (85%). Most frequent grade 3/4 adverse events of special interest were: dermatitis (2 pts [5%]); diarrhea/colitis (2 pts [5%]), hypophysitis/hypopituitarism (7 pts [18%]), hepatitis (5 pts [13%]), and pneumonitis (3 pts [8%]). Systemic corticotherapy was used to treat irAE in 18 pts (46%). Best overall tumor response by irRC: 8 CR, and 7 PR (BORR 38%), 6 SD, and 18 PD. All CR, and 3 PR are ongoing after a median duration of 19 mths (range 3-29 mths). The 6-mths DCR by irRC is 50% (95% CI 34-66). Median PFS and OS are respectively 6.2 (95% CI 3-9), and 14.4 mths (95%CI 10-18). **Conclusions:** This phase II trial of autologous mRNA electroporated dendritic cells in combination with ipilimumab in patients with pretreated advanced melanoma achieved its primary endpoint and resulted in an encouraging rate of durable tumor responses. Further clinical investigation of autologous mRNA electroporated DC-therapy in combination with immune checkpoint modulators is warranted. Clinical trial information: NCT01302496.

**3015 Poster Highlights Session (Board #7), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Baseline tumor size as an independent prognostic factor for overall survival in patients with metastatic melanoma treated with the anti-PD-1 monoclonal antibody MK-3475.** *Presenting Author: Richard Wayne Joseph, Mayo Clinic, Jacksonville, FL*

**Background:** We explored baseline tumor size (BTS) as a prognostic factor in addition to standard prognostic variables for overall survival (OS) in pts with metastatic melanoma treated with MK-3475. **Methods:** In a phase I clinical trial, 411 pts received MK-3475 2 mg/kg Q3W, 10 mg/kg Q3W, or 10 mg/kg Q2W. Response was assessed every 12 wk by RECIST 1.1 by independent central review. BTS was quantified as the sum of the longest dimensions of all RECIST target lesions. Log-rank, Kaplan-Meier (KM), and Cox proportional hazards regressions were used to identify independent prognostic factors for OS. Cutpoints and combinations of prognostic factors were determined by binary tree analysis. **Results:** Of the 411 melanoma pts studied, 365 had measurable tumors at baseline and a median follow-up duration of 10 mo as of the 10/18/2013 cutoff date. Median OS was not reached, and 1-y OS was 71% in all 411 pts and 69% in the 365 pts included in this analysis. By univariate analysis, the following traditional factors were associated with OS: elevated LDH, ECOG performance status of 1, and M-stage 1c (Table). BTS (median 97.8 mm, range 10.4-895 mm) was significantly and strongly associated with OS using log-rank tests, Cox models, KM methods, and binary tree analysis. Binary tree analysis provided a cutpoint of 90 mm BTS as an independent factor. While tumor size >90 mm was associated with a worse prognosis, these pts did have a median OS of 14 mo in the combined data set, suggesting they derive benefit from MK-3475. **Conclusions:** Baseline tumor size is the strongest independent prognostic factor in pts with metastatic melanoma treated with MK3475. If further validated, baseline tumor size could serve as an additional factor when randomizing pts for future clinical trials using anti-PD1 therapies. Clinical trial information: NCT01295827.

| | N = 363 | | | |
|---|---|---|---|---|
| | n | % Alive at 1 Year [95% CI] | HR | *P* value |
| **LDH** | | | | |
| **Elevated** | 135 | 54.8 [37.8-71.9] | 2.33 | <0.001 |
| **Normal** | 225 | 77.2 [69.6-84.9] | | |
| **M-Stage** | | | | |
| **M1c** | 213 | 64.9 [54.2-75.6] | 1.56 | <0.05 |
| **Not M1c** | 152 | 75.4 [65.5-85.4] | | |
| **ECOG performance status** | | | | |
| **0** | 261 | 74.6 [66.8-82.3] | 2.23 | <0.001 |
| **1** | 104 | 55.5 [36.5-74.4] | | |
| **Baseline tumor size** | | | | |
| **>90** | 194 | 54.8 [40.4-69.2] | 3.51 | <0.001 |
| **≤90** | 171 | 84.3 [77.4-91.3] | | |

**3016 Poster Highlights Session (Board #8), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Association of maintenance of pre-existing memory T-cell responses following anti-CTLA-4 antibody treatment with improved overall survival.** *Presenting Author: Lawrence Fong, University of California, San Francisco, San Francisco, CA*

**Background:** While treatment with anti-CTLA-4 antibody can induce clinical responses in advanced cancer patients, the immunobiology and biomarkers associated with improved clinical outcomes is unknown. **Methods:** We used a next-generation sequencing to track changes in the T cell repertoire in 46 patients with metastatic castration resistant prostate cancer (CRPC) or metastatic melanoma (MM). Peripheral blood mononuclear cells were obtained from patients prior to and during treatment with anti-CTLA-4 antibody. mRNA was amplified with locus-specific primer sets for T cell receptor (TCR) beta, and the amplified products were sequenced. Sequence reads were used to quantitate absolute TCR frequencies using standardized clonotype determination algorithms with normalization by spiked reference TCR sequences. Following clonotype quantitation, the kinetics of specific T cell clonotypes were tracked with anti-CTLA-4 treatment. Naïveand memory T cells were also sorted and sequenced to define changes in these subsets. **Results:** CTLA-4 blockade resulted in both expansion and loss of T cell clonotypes, consistent with a global turnover of the T cell repertoire. While this treatment increased TCR diversity as reflected in the number of unique TCR clonotypes, the vast majority of change occurred in the memory T cell pool. Whereas the number of clonotypes that increased with treatment was not associated with clinical outcome, declines of the highest frequency clonotypes following treatment were associated with short overall survival. These declines were not evident in patients with longer overall survival. This association was seen in both CRPC ($p<0.05$) and MM patients ($P<0.01$, two-sided Mann Whitney). **Conclusions:** Together, these results indicate that CTLA-4 blockade induces T-cell repertoire evolution and diversification. However, improved clinical outcomes are associated with maintenance of pre-existing high frequency memory T cells during treatment. These clones may represent the presence of pre-existing T cells that may be relevant in the anti-tumor response. Detection of these high frequency T cell clones could help to identify patients that benefit from treatment.

**3017 Poster Highlights Session (Board #9), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Biomarker characterization using mass cytometry in a phase 1 trial of urelumab (BMS-663513) in subjects with advanced solid tumors and relapsed/refractory B-cell non-Hodgkin lymphoma.** *Presenting Author: Cariad Chester, Department of Medicine, Division of Oncology, Stanford University, Stanford, CA*

**Background:** Anti-CD137 antibody was shown in both murine cancer models and in a first-in-human, phase I trial (Sznol et al., 2008) to increase peripheral activated CD8 T cells and IFN-inducible genes, thereby facilitating a cytolytic, antitumor, Th1 response. A multiparametric immune pharmacodynamic assessment of the effects of anti-CD137 therapy has not been previously performed. **Methods:** We employed the novel technology of mass cytometry time of flight (CyTOF) to investigate the patient's global immune status prior to and during a phase 1 study (NCT01471210) of Urelumab, a fully human anti-CD137 antibody, administered once per 3-week cycle in patients with solid tumors and B-cell non-Hodgkin's lymphoma. Peripheral blood was obtained at 4 time points throughout treatment (baseline, 24-hrs after 1st dose of cycle 1, immediately before cycle 2, and post cycle 3 at response evaluation, C3R). PBMCs were isolated and stimulated for 4 hours with PMA/ionomycin. Immune cell characterization and function were analyzed in FlowJo and SPADE from mass cytometry results. **Results:** Preliminary findings from 4 patients show an increase in CD8 T cells up to 40.6% (SEM+/-13%) and NK cells up to 61.7% (SEM+/-20%) with a decrease in CD4 T cells up to 23.2% (SEM+/-6.5%) and regulatory CD4 T cells up to 17.8% (SEM+/-15%) comparing C3R to baseline. CyTOF cytokine analysis, revealed increases in GMCSF and IFN-gamma by C3R. CyTOF cytokine analysis, revealed increases in GMCSF and IFN-gamma by C3R. **Conclusions:** These preliminary data are consistent with anti-CD137 agonism and generate hypotheses of putative biomarkers of clinical activity now being investigated and to be reported from the ongoing clinical trial. Clinical trial information: NCT01471210.

**3018 Poster Highlights Session (Board #10), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Association of epithelial-mesenchymal transition status with PD1/PDL1 expression and a distinct immunophenotype in non-small cell lung cancer: Implications for immunotherapy biomarkers.** *Presenting Author: Yanyan Lou, MD Anderson Cancer Center, Houston, TX*

**Background:** Programmed cell death 1 (PD-1) and its ligand PD-L1 have emerged as a critical inhibitory pathway that maintains immune suppression in the tumor microenvironment. Patients with non-small-cell lung cancer (NSCLC) have responded to PD-1/PD-L1 blockade, indicating the crucial role of immune suppression in NSCLC. It is imperative to understand the immune features of NSCLC and identify biomarkers to select which patients may benefit from checkpoint blockade. Epithelial-mesenchymal transition (EMT) is a key process driving metastasis. Our previous study developed a robust EMT gene signature predicting resistance to EGFR and PI3K/Akt inhibitors, highlighting differential patterns of drug responsiveness for epithelial and mesenchymal cells. **Methods:** We used this EMT gene signature and gene expression profiles in adenocarcinoma from The Cancer Genome Atlas (TCGA) and the PROSPECT database at MD Anderson Cancer Center (tumors collected in 240 patients undergoing surgical resection with curative intent) to study the tumor microenvironment immune profile. Tumor samples were first classified by our validated EMT signature as epithelial (low EMT scores defined by EMT scores $\leq$ lowest 1/3) or mesenchymal (high EMT scores defined by EMT scores $\geq$ highest 1/3). Gene expression profiles of immune related genes in each tumor were then analyzed. **Results:** Mesenchymal NSCLC is highly associated with a distinct immune phenotype in the tumor microenvironment as compared to epithelial NSCLC. Overexpression of genes for immune inhibitory molecules including PD-L1 ($P = 1.6 \times 10^{-13}$), PD-1 ($P = 9.5 \times 10^{-5}$), CTLA-4, TIM3, BTLA, IL-10, IL-6, and TGF-b ($P<0.0001$ for all others) are associated with mesenchymal NSCLC in both the TCGA and PROSPECT databases. **Conclusions:** This study demonstrates mesenchymal NSCLC (high EMT scores) is associated with distinct immune phenotypes with increased expression of immune inhibitory molecules. This study provides a potential mechanism for EMT associated immunosuppression. It suggests EMT may be a biomarker for checkpoint inhibitors and potentially other immunotherapy agents.

**3019 Poster Highlights Session (Board #11), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Clinical outcome and CD4+ differentiation in anti-CTLA-4/radiation and anti-CTLA-4/steroid therapy.** *Presenting Author: Anuj Bapodra, New York University Langone Medical Center, Department of Pathology, New York, NY*

**Background:** Combination of anti-CTLA-4 and radiation therapy with or without steroids are common in the management of melanoma patients. However, their clinical results and effects on immunity have not been examined in depth. In this study we observe the clinical and immune response of melanoma patients treated with anti-CTLA-4/radiation therapy and anti-CTLA-4/steroids. **Methods:** We anlayzed a cohort of patients treated with anti-CTLA-4 antibody therapy at NYU Medical Center. We examined differences in overall survival using log-rank test in patients treated with 1) anti-CTLA-4 with radiation therapy; 2) anti-CTLA-4 with steroids. Corticosteroids were administered to control symptoms (n=26) and/or toxicity (n=24). T cells were purified from patients; each represented by a minimum of two individual samples (before and after anti-CTLA-4 treatment). CD4+ T-helper cell subset phenotypes were characterized by their cytokine profiles by bead-based cytokine assays after stimulation using CD3/CD28 activation beads. Subsequently, we determined the association between treatment type and concentrations of cytokine production. **Results:** Patients treated with anti-CTLA-4 and radiation therapy given before, concomittant or after anti-CTL4 treatment (n=53) had better overall suvival prognosis compared to patients treated with anti-CTLA-4 alone (N=83; $p=0.02$). Anti-CTLA-4 therapy with steroids (n=50) conferred better prognosis compared to anti-CTLA-4 alone ($p=0.037$). The combination of anti-CTLA-4 and radiation therapy induced T cells to produce more IL-2, IL-17a and TNFa over the 4 cycles of treatment compared to anti-CTLA-4 alone. Similarly, anti-CTLA-4 with steroid treatment increased the production of IL-2 and IL17a, but not TNFa, compared to anti-CTLA-4 alone. No trend differences in IFN-g, IL-4, IL-6 or IL-10 production were detected. **Conclusions:** Our data suggests the enhanced immune response may be explained by effects of radiation therapy and corticosteroids. Increased production of IL-17a and TNFa indicate skewing towards Th17 CD4+ subset since other cytokines showed no trend. The polarized Th17 has clinical sgnificance due to higher anti-tumor activity than unpolarized Th subsets.

**3020 Poster Highlights Session (Board #12), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Effects of ipilimumab on expanded tumor-infiltrating lymphocytes in patients with stage IV malignant melanoma.** *Presenting Author: Jon Bjoern, Center for Cancer Immune Therapy, Herlev, Denmark*

**Background:** Adoptive cell therapy (ACT) is currently one of the most effective treatments for stage IV malignant melanoma. Clinical studies have indicated a link between prior anti-CTLA-4 treatment (e.g. Ipilimumab), and a favorable response to subsequent ACT. **Methods:** We compared phenotype and functionality of T cells generated from melanoma biopsies harvested from Ipilimumab naïve patients with patients that had received treatment with Ipilimumab within six month prior to tumor removal. Tumor biopsies were obtained from 32 stage IV melanoma patients (16 treated with Ipilimumab and 16 ipilimumab naive). T cells were cultured and expanded according to the rapid expansion protocol. Cells were stained for intra- and extracellular markers and subjected to flow cytometric analysis. Additionally, combinatorial coding with MHC-I multimers and co-culture assays with autologous tumor cells were performed in order to assess tumor-specific responses. **Results:** Analysis for phenotypic markers revealed several significant differences related to prior treatment. Importantly, cultured cells from Ipilimumab treated patients showed a median ten-fold higher expression of CD27 in CD8+ T cells, compatible with a more naïve phenotype, and two-fold higher expression of intracellular CTLA-4 in both CD4+ and CD8+ positive T cells. Furthermore, both TIM-3 and LAG-3 were more abundantly expressed in CD8+ T cells from Ipilimumab treated patients. We detected no difference in reactivity towards autologous tumor cells. Combinatorial coding revealed frequent responses toward common tumor associated antigens in both groups of patients. **Conclusions:** Despite several weeks of culture, Ipilimumab appeared to have lasting impact on the phenotype of expanded tumor infiltrating T cells. We observed higher expression of CD27, which previously has been linked to a favorable outcome of ACT, and up regulation of markers associated with immune suppression, possibly due to homeostatic regulation of the T cells. Over all, results indicate that influx of T cells with a less exhausted phenotype may underlie the favorable effect of pretreatment with Ipilimumab and ACT in the setting of metastatic malignant melanoma.

**3021 Poster Highlights Session (Board #13), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**T-cell receptor (TCR) DNA deep sequencing to evaluate clonality of tumor-infiltrating lymphocytes (TILs) in early-stage breast cancer patients (pts) receiving preoperative cryoablation (cryo) and/or ipilimumab (ipi).** *Presenting Author: David B. Page, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** In mice, cryo combined with cytotoxic T lymphocyte antigen 4 (CTLA-4) blockade increases antigen-specific TILs, generating a synergistic rejection of secondary tumors. In humans, breast cancer antigens are shared across pts in low frequency and are incompletely characterized. Thus, to evaluate for antigen-specific TILs in pts receiving cryo and/or the anti-CTLA-4 antibody, ipi, we employed deep sequencing of TCR CDR3 region DNA, which provides a quantitative measurement of the frequency of individual T cell clones, each putatively reactive to a unique antigen. **Methods:** 19 pts were treated with cryo (7 pts), single-dose ipi at 10mg/kg (6 pts), or cryo+ipi (6 pts). Core biopsy (Bx) +/- cryo was performed 7-10 days prior to standard-of-care mastectomy and ipi was given 1-5 days before core Bx. From available specimens, DNA was sequenced using the immunoSEQ™ assay. Utilizing CDR3 sequence copy number, the frequency of each unique T cell clone was determined. Nonparametric analyses were conducted on derivative metrics including T cell %, clonal overlap, and clonality. **Results:** In core Bx's, T cell % (median 6.8%, 0.6-30.7%) and clonality (median 0.13, 0.09-0.4) varied across pts, with a higher T cell % in poorly differentiated lesions ($p=.03$). Cryo reduced T cell counts but induced a polyclonal infiltrate ($p=.02$) with low clonal overlap, indicating influx of new clones. For the 3 ipi alone pts for whom Bx and mastectomy tissue were available, clonal repertoire appeared closer to baseline, as measured by clonality and overlap. Combination cryo+ipi frequently expanded the proportion of the most dominant (top 5) clones (3/6 cases), an effect which was rarely observed with monotherapy (1/8 cases). **Conclusions:** Cryo-associated polyclonality and influx of new clones may be related to cryo-mediated cell death, antigen release, and T cell engagement. A cryo+ipi mediated surge of the most dominant clones may reflect synergistic activation of a clonal subset. These findings call for further characterization of therapy-induced dominant clones, and support repertoire analyses in breast cancer. Clinical trial information: NCT01502592.

**3022 Poster Highlights Session (Board #14), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Graded potency of chimeric antigen receptor (CAR)-engineered T cells for cancer immunotherapy.** *Presenting Author: Michel Sadelain, Memorial Sloan-Kettering Cancer Center, New York, NY*

**Background:** Second generation chimeric antigen receptors (CARs) are recombinant receptors for antigen that retarget and reprogram T cell function. We and others have recently demonstrated that CAR-modified, CD19-targeted T cells can induce complete remissions in patients with relapsed or refractory B cell malignancies, especially acute lymphoblastic leukemia. While CARs endowed with either CD28 or 4-1BB costimulatory endodomains have shown significant therapeutic potential, we previously reported that combined CD28 and 4-1BB signals direct even greater tumor eradication. We have now thoroughly compared these graded levels of therapeutic potency and examined their mechanism of action. **Methods:** Using a xenogeneic B-ALL leukemia model, we titrated CD19-targeted human T cells engineered to receive CD28 and/or 4-1BB signals and compared their therapeutic potency. Purified T cell subsets were analyzed by genome wide expression to correlate costimulatory patterns and therapeutic outcomes. **Results:** We show here that combining a second generation CD28-based CAR, in which CD28 signaling is provided through the CAR's cytoplasmic domain,with 4-1BBL, which auto-costimulates T cells through their endogenous 4-1BB receptor, generates very highly efficacious T cells. We rigorously quantified the tumor eradication potential of T cell populations provided with CD28, 4-1BB or CD28+4-1BB costimulation. The most potent T cell populations were found to evade regulation by endogenous CTLA-4 and induce expression of the type I response pathway, which directly impacted on T cell expansion and function. **Conclusions:** We show here that T cell populations with graded therapeutic potency can be engineered through different CAR designs and costimulatory combinations. Our study further unravels a novel synergy between CD28 and 4-1BB signaling that is distinct from enhanced T cell proliferation or persistence, and results in increased therapeutic potency through the activation of the type I interferon response pathway. These findings open new perspectives for T cell engineering strategies intended to modulate the tumor microenvironment and augment tumor eradication.

**3023 Poster Highlights Session (Board #15), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**A phase I, first-in-human study of ARGX-110, a monoclonal antibody targeting CD70, a receptor involved in immune escape and tumor growth in patients with solid and hematologic malignancies.** *Presenting Author: Ahmad Awada, Institut Jules Bordet – Université Libre de Bruxelles, Brussels, Belgium*

**Background:** Distribution of CD70, a TNF superfamily receptor involved in transient, rapid-onset immune response, is normally restricted to subsets of T-, B-, and dendritic cells. It is chronically over-expressed in patients with malignancies in whom it mediates tumor growth and immune escape. ARGX-110, a monoclonal IgG1 SIMPLE Antibody glyco-engineered for enhanced ADCC (POTELLIGENT), is undergoing Phase 1 testing (ClinicalTrials.gov Identifier: NCT01813539). **Methods:** As of December 2013, 19 patients (median age: 56 years; prior chemo: 82%; prior biologics/TKIs: 29%) with > 10% tumor cells staining positive for CD70 by immunohistochemistry were treated at 0.1, 1, 5, and 10 mg/kg IV q3 weeks; n = 6, 5, 3, and 5) and received a total of 82 cycles (median = 4; range 1-11). **Results:** The most common drug-related adverse events (AE) observed in 14 patients were: infusion-related reaction (26%), fatigue (21%) and diarrhea (16%). Drug-related Grade 3 AEs (hypoxia, anorexia, fatigue) were observed in 2 patients. No immune-related AE was observed. Pharmacokinetics were dose-linear (T 1/2 = 11 days). Saturated target-mediated clearance ($C_{target}$) was observed as of 1 mg/kg. ADCC and depletion of circulating CD70+ cells (qPCR) were demonstrated in all patients. Complement-derived cytotoxicity (CDC) was maximal at > 0.1 mg/kg. Circulating $T_{regs}$ were reduced by ≥ 50% in most patients treated at the highest doses. One CR (in blood) was confirmed in a patient with stage IVA (T2NxM0B2) Sézary syndrome. Five patients maintained SD for > 6 months (RCC, parotid, myoepithelial, platinum-resistant ovarian, mesothelioma). **Conclusions:** Based on the clinical and immunological parameters an intermediate dose level of 2 mg/kg is being studied. Full results will be presented. Clinical trial information: NCT01813539.

| Dose | 0.1 mg/kg | 1 mg/kg | 5 mg/kg | 10 mg/kg |
|---|---|---|---|---|
| PK ($C_{target}$) | Not saturated | Saturated | Saturated | Saturated |
| ADCC | Yes | Yes | Yes | Yes |
| CDC | Not saturated | Maximal | Maximal | Maximal |
| CD70 qPCR | 70% ↓ | 61% ↓ | 72% ↓ | NA |
| B-cell count | Stable | Stable | Stable | Stable |
| T-cell count | Stable | Stable | Stable | Stable |

**3024 Poster Highlights Session (Board #16), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Phase I evaluation of an agonist anti-CD27 human antibody (CDX-1127) in patients with advanced hematologic malignancies.** *Presenting Author: Stephen Maxted Ansell, Division of Hematology, Mayo Clinic, Rochester, MN*

**Background:** CD27, a member of the TNF receptor superfamily, is a co-stimulatory molecule that regulates T cell activation, survival, and memory responses through interaction with a tightly regulated ligand, CD70. CDX-1127 is an anti-CD27 human antibody shown to activate human T cells when combined with T cell receptor stimulation, and mediate anti-tumor activity in human CD27 transgenic mice challenged with syngeneic tumors. **Methods:** In a 3+3 dose-escalation (DE), patients (pts) with advanced B-cell lymphoma received CDX-1127 (0.1, 0.3, 1.0, 3.0 or 10 mg/kg IV) as a single dose with 28-day observation, followed by up to 5 treatment cycles (4 weekly doses / Day 85 restaging), until progression. **Results:** 19 pts (3 Hodgkin (HL), 5 follicular, 9 diffuse large B-cell, 2 unspecified non-Hodgkin) have received CDX-1127. DE has exceeded 3 mg/kg with no DLT; enrollment at 10 mg/kg is ongoing. Treatment-related toxicity, generally Grade 1-2, included fatigue, nausea, decreased appetite and anemia. A pt with Stage IV Hodgkin lymphoma who had previously failed chemotherapy, autologous stem cell transplant, and brentuximab vedotin experienced a complete response (CR) and remains in remission at 8.6+ months. IHC analysis of archived tumor for the 3 HL pts showed CD27-negative reed-sternberg cells and CD27-expressing infiltrating lymphocytes. The highest tumor CD27 expression was noted for the pt who had CR. Three additional pts had stable disease (4.5, 5.6 and 14.0 months), including a pt with follicular lymphoma who has completed 3 cycles of therapy and a pt with marginal zone lymphoma with 36% shrinkage in measurable disease. Response data are pending for the 10 mg/kg dose level. Immune correlates including serum cytokines, soluble CD27 levels, and changes in circulating lymphocyte populations are being investigated. **Conclusions:** Emerging results suggest that weekly dosing of CDX-1127 is well tolerated with promising biological and clinical activity in pts with B-cell lymphoma. A DE in pts with T cell malignancies is underway. Single agent safety and activity data support planned combination studies with both conventional and immune-based therapies. Clinical trial information: NCT01460134.

**3025^ Poster Highlights Session (Board #17), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Updated phase I data of AFM13: A bispecific tandem antibody (TandAb) in relapsed/refractory (R/R) Hodgkin lymphoma (HL).** *Presenting Author: Achim Rothe, Formerly of University Hospital of Cologne, Department of Internal Medicine I, Cologne, Germany*

**Background:** AFM13 is a bispecific anti-CD30, anti-CD16A antibody construct which recruits NK cells for targeted lysis of $CD30^+$ tumor cells. HL cells are characterized by CD30 positivity and represent a promising target for AFM13. 30-40% of HL patients (pts.) relapse after standard chemotherapy ± radiation. 2nd line therapies induce durable remission in only 50% of the patients. Hence, there is a high medical need in R/R HL. **Methods:** This was a dose escalation trial in heavily pre-treated R/R HL pts. AFM13 was infused weekly (0.01-7.0 mg/kg) or twice weekly (4.5 mg/kg) over 4 weeks. The primary objectives were safety and tolerability, secondary objectives were pharmacokinetics (PK), pharmacodynamics (PD), and efficacy measured using Cheson criteria. **Results:** 28 pts. were recruited, 26 were eligible for efficacy. 4 pts. were treated twice weekly. AFM13 was well tolerated with mainly mild to moderate adverse events (AEs). The maximum tolerated dose was not reached. Only one relevant, possibly treatment-related toxicity was observed in the 0.5 mg/kg cohort: hemolytic anemia CTCAE Grade 4. The most common AEs were pyrexia (53.6%) and chills (39.3%). 8 pts. (26.8%) experienced serious AEs. PK data revealed that a weekly dose regimen is suboptimal, the half-life was 10-22 hours. PD data showed a dose dependent activation of NK cells ($CD69^+$). Clinical activity was observed over all dose levels but was more pronounced at dose levels ≥1.5 mg/kg (n=13). In this cohort 3 PR (23%), 7 SD (54%), 3 PD (23%) were observed with a disease control rate of 77%. Pts. were not followed-up for duration of response. The time to next treatment (TTNT) was assessed retrospectively for pts. with PR and SD. Mean TTNT was 5.14 months (1.5 – 9.0). 6/7 patients refractory to most recent brentuximab vedotin (BV) therapy achieved SD under AFM13. Mean time between end of BV and start of AFM13 treatment was 1.86 months (1 – 3). **Conclusions:** AFM13 was well tolerated and demonstrated clinical activity also in pts. refractory to BV. The dose regimens investigated seem to have been suboptimal to demonstrate the full clinical potency of AFM13. A phase II study with a modified dose regimen is in preparation. Clinical trial information: NCT01221571.

**3026 Poster Highlights Session (Board #18), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Correlation of immune response with clinical outcomes in melanoma patients receiving adjuvant therapy of pegylated interferon alpha-2b combined with gp100 peptide vaccine.** *Presenting Author: Luis M Vence, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Vaccination using tumor-associated antigen peptides alone has shown limited clinical benefit. Preclinical studies have demonstrated interferon-alpha promotes vaccine-induced tumor-specific T-cell responses. Our randomized 3-arm study explored the optimal biological dosing (OBD) schedule of pegylated IFN-alpha-2b (PEG-IFN) when combined with gp100 vaccine in patients (pts) with resected melanoma, while demonstrating safety with acceptable toxicity. **Methods:** After definitive surgical resection, melanoma pts were randomized into 1 of 3 PEG-IFN arms [Induction Phase (6 mcg/kg/wk)/Maintenance Phase (3 mcg/kg/wk)]: (1) Arm 1: 4 wk/20 wk; (2) Arm 2: 8 wk/16 wk; (3) Arm 3:12 wk/12 wk. All pts were vaccinated with $gp100_{209\text{-}2M}$ every 3 wk x 8. Toxicity and gp100-specific T-cell responses were assessed every 3 wk. **Results:** 30 pts (8 stage II, 22 stage III) were enrolled and treated in 3 arms (11 Arm 1, 9 Arm 2, 10 Arm 3). All 3 dosing schedules were found to be safe and well tolerated. Despite PEG-IFN-induced lymphopenia [CD8+ T-cells decreased from average 326.5 to 169.7 cells/microL ($P<0.0001$)], gp100-specific CD8+ T-cell frequency increased from baseline 0 cells/ml to 15.5 cells/ml of blood at the end of 24-wk study ($p = 0.0007$). Arm 2 pts showed the highest median maximum gp100-specific T-cell response. Median time to reach maximum T-cell response was 16 wk for Arm 1, and 19 wk for Arms 2 and 3. At median follow-up of 3 years (range 21-54 mo), 11 pts developed recurrent disease, 4 of whom died of metastases. Although median RFS and OS were not reached, the proportion of pts alive and free of distant metastasis at 3 years was 85% among those with maximum gp100-specific T-cell response > 0.025% of CD8+ T-cells, compared to 50% among those with ≤ 0.025% T-cell response ($P=0.04$; HR=0.24). **Conclusions:** In our study, Arm 2 demonstrated the OBD schedule of PEG-IFN combined with gp100 vaccination. The increased T-cell response induced by PEG-IFN correlated with improved clinical outcomes. Clinical trial information: NCT00861406.

**3027 Poster Highlights Session (Board #19), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Immunologic activity of an activating anti-CD27 antibody (CDX-1127) in patients (pts) with solid tumors.** *Presenting Author: Jeffrey R. Infante, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN*

**Background:** CD27 is a co-stimulatory molecule that regulates T cell activation, survival, and memory responses through interaction with a tightly regulated ligand, CD70. CDX-1127 is an anti-CD27 antibody shown to activate T cells when combined with T cell receptor stimulation, and mediate anti-tumor activity in human CD27 transgenic mice challenged with syngeneic tumors. **Methods:** In a 3+3 dose-escalation (DE), 25 pts with advanced solid tumors received a single dose of CDX-1127 (0.1, 0.3, 1.0, 3.0 or 10 mg/kg IV) with 28-day observation, followed by up to 5 treatment cycles (4 weekly doses / Day 85 restaging), until progression. 16 melanoma and 11 renal cell carcinoma (RCC) pts have been enrolled in expansion (EX) cohorts (target n=15 each). Pharmacokinetic (PK) and immune parameters were assessed on serum and PBMC collected during study. **Results:** DE completed at 10 mg/kg with one dose-limiting toxicity, grade 3 transient asymptomatic hyponatremia, at 1.0 mg/kg. Treatment-related toxicity, generally grade 1-2, included fatigue, rash, nausea, decreased appetite and headache. 3 mg/kg was selected for EX based on DE immunological activity, PK and preclinical modeling. Stable disease has been seen in 4/25 DE pts (3.0, 3.8, 5.7 and 16.8+ months duration); 3/14 evaluable melanoma EX pts (2.6+, 3.1+, 5.7+ months); and 2/6 evaluable RCC EX pts (2.8+, 2.9+ months). In DE, sustained serum CDX-1127 levels were consistent with expected PK profile and correlated with binding to circulating lymphocytes; rapid and transient increases in serum IP-10 (mean [pg/ml]: Day 1 = 215, peak (6 hours post) = 731 [$p<0.0001$]); lesser increases in IL-6 and MCP-1; a significant reduction in regulatory T cells (mean [% of lymphocytes]: Day 1 = 1.66, Day 85 = 0.68 [$p = 0.01$]) and increase in NK cells. Ex vivo analysis demonstrated an increase in T cells responding to melanoma antigens in select melanoma pts. Gene expression analysis of RNA from PBMC is ongoing. **Conclusions:** In pts with solid tumors, CDX-1127 is well tolerated and induces immune activation consistent with CD27 co-stimulation. These results support combination studies with both conventional and immune-based therapies, which have shown synergistic activity in preclinical models. Clinical trial information: NCT01460134.

**3028 Poster Highlights Session (Board #20), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Phase 2 open-label study of MEDI-551 and bendamustine versus rituximab and bendamustine in adults with relapsed or refractory CLL.** *Presenting Author: Douglas Gladstone, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

**Background**: Patients (pts) with relapsed/refractory (RR) chronic lymphocytic leukemia (CLL) need therapies that induce prolonged disease control. MEDI-551, an affinity-optimized anti-CD19 antibody, destroys CLL cells by antibody-dependent cellular cytotoxicity. A phase 2 randomized, open-label study (NCT01466153) is evaluating the clinical activity and safety/tolerability of 2 doses of MEDI-551 + bendamustine compared to rituximab + bendamustine in RR CLL patients. **Methods:** Pts were initially randomized to receive bendamustine + MEDI-551 2 or 4 mg/kg or rituximab (R). Safety assessments include adverse events (AEs) and laboratory parameters. Disease response was determined using 2008 International Working Group criteria. **Results:** The safety population comprised 124 pts across all arms. Median age was 66y (range 41–81); with deletion (del) (17p): 9%, del (11q): 22%, del (13q): 31%, trisomy 12: 11%. Median number of treatment cycles: 4 (range 1–6). The most common (≥20%) treatment-related AEs with MEDI-551 were infusion-related reaction (IRR), fatigue and nausea; neutropenia and nausea were most common with R; most treatment-related AEs were grade 1/2; grade 3/4 treatment-related AEs are listed in Table 1. 20% of pts receiving MEDI-551and 18% patients receiving R discontinued treatment due to AEs. An interim analysis of the MEDI-551-treated pts (25 per arm) showed response rates of 48 vs. 64% in the 2 vs. 4 mg/kg arms. **Conclusions:** MEDI-551 in combination with bendamustine has a manageable toxicity profile that appears to be different compared to rituximab in RR CLL patients. MEDI-551 dosed at 4 mg/kg as compared to 2 mg/kg may have a greater efficacy without any increase in toxicity. Clinical trial information: NCT01466153.

**Treatment-related grade 3/4 AEs (≥5% of patients).**

| | MEDI-551 | | Rituximab |
|---|---|---|---|
| **n (%)** | **2 mg/kg (n=33)** | **4 mg/kg (n=44)** | **(n=47)** |
| **Pts reporting ≥1 event** | 18 (55) | 16 (36) | 21 (45) |
| **Neutropenia** | 6 (18) | 4 (9) | 11 (23) |
| **Febrile neutropenia** | 0 | 1 (2) | 5 (11) |
| **Thrombocytopenia** | 0 | 1 (2) | 5 (11) |
| **IRR** | 6 (18) | 4 (9) | 1 (2) |
| **Decreased neutrophils** | 1 (3) | 2 (5) | 3 (6) |
| **Cytokine release syndrome** | 2 (6) | 0 | 0 |
| **Tumor lysis syndrome** | 0 | 2 (5) | 0 |

**3029 Poster Highlights Session (Board #21), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Correlation of anti-calreticulin antibody titers with improved overall survival in a phase 2 clinical trial of algenpantucel-L immunotherapy for patients with resected pancreatic cancer.** *Presenting Author: Gabriela R. Rossi, NewLink Genetics, Ames, IA*

**Background:** Algenpantucel-L immunotherapy consists of allogeneic pancreatic cancer cells that have been genetically modified to express the carbohydrate α(1,3)Gal, to which humans have an inherent pre-existing immunity. It is αGal that is primarily responsible for the hyperacute rejection of foreign tissue via this potent immune defense mechanism in humans. Algenpantucel-L leverages this mechanism to educate the immune system towards components of the patients' own tumor cells. Calreticulin is a calcium-binding chaperone protein that functions in the immune response by folding major histocompatibility complex (MHC) class I molecules and influencing antigen presentation to cytotoxic T cells. In pre-clinical models, drugs that induce cell surface CALR confer enhanced tumor protection. Components of algenpantucel-L express cell surface CALR. **Methods:** An open-label, 71 patient multicenter phase II study evaluating algenpantucel-L plus standard of care gemcitabine with 5-FU-XRT for resected pancreatic cancer was conducted. Endpoints included DFS at 1 year, OS, and immunologic analysis. Evaluable patients (n=64) were tested for the induction of anti-CALR Ab by ELISA. Increased titers greater than 20% relative to baseline were considered significant ($p<0.001$). **Results:** The study reached its endpoint at 1 year with DFS of 62% and OS of 86%. Thirty-one of 64 patients (48%) had increased anti-CALR Ab. Patients responding with an increase in anti-CALR Ab had a median OS of 35.8 months compared to 19.2 months for patients without an increase. The positive correlation between increased anti-CALR Ab and improved median OS was statistically significant ($p=0.03$). **Conclusions:** This study of algenpantucel-L with SOC for resected pancreatic cancer compared favorably to historical controls. Induction of anti-CALR Ab after therapy correlates with improved survival. Immunological monitoring of algenpantucel-L immunotherapy with this biomarker is feasible and might predict patient response to therapy. Follow up studies are in progress in a multi-institutional, phase III study which recently completed enrollment. Clinical trial information: NCT00569387.

**3030 Poster Highlights Session (Board #22), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Matrix metalloproteinase-23 as a new immunotherapeutic checkpoint target in melanoma.** *Presenting Author: Duane Moogk, NYU School of Medicine, New York, NY*

**Background:** Matrix metalloproteinase-23 (MMP-23) can inhibit T cell activation by selectively blocking the voltage-gated potassium channel Kv1.3, and may also alter T cell activity and phenotype through cleavage of proteins affecting cytokine and chemokine signaling. We therefore tested the hypothesis that MMP-23 can negatively regulate the anti-tumor T cell response in human melanoma. **Methods:** We characterized MMP-23 expression in primary melanoma patients who received adjuvant immunotherapy. We examined the association of MMP-23 with the intrinsic anti-tumor immune response - as assessed by the prevalence of tumor-infiltrating lymphocytes and $Foxp3^+$ regulatory T-cells. Further, we examined the association between MMP-23 expression and response to immunotherapy. Considering also an *in trans* mechanism, we examined the association of melanoma MMP-23 and melanoma Kv1.3 expression. **Results:** Our data revealed an inverse association between primary melanoma MMP-23 expression and the anti-tumor T-cell response, as demonstrated by decreased tumor-infiltrating lymphocytes (TIL) ($P=0.05$), in particular brisk TILs ($P=0.04$), and a trend towards an increased proportion of immunosuppressive $Foxp3^+$ regulatory T-cells ($P=0.07$). High melanoma MMP-23 expression is also associated with recurrence in patients treated with immune biologics ($P=0.037$) but not in those treated with vaccines ($P=0.64$). Further, high melanoma MMP-23 expression is associated with shorter periods of progression-free survival for patients receiving immune biologics ($P=0.025$). On the other hand, there is no relationship between melanoma MMP-23 and melanoma Kv1.3 expression ($P=0.27$). **Conclusions:** Our data support a role for MMP-23 as a potential immune checkpoint blockade target in melanoma, as well as a possible biomarker for informing melanoma immunotherapies.

**3031 Poster Highlights Session (Board #23), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**CALM study: A phase II study of an intratumorally delivered oncolytic immunotherapeutic agent, coxsackievirus A21, in patients with stage IIIc and stage IV malignant melanoma.** *Presenting Author: Robert Hans Ingemar Andtbacka, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

**Background:** Coxsackievirus A21 is an oncolytic immunotherapy consisting of a bio-selected oncolytic strain of Coxsackievirus A21. Following intratumoral injection, preferential tumor infection causes cell lysis and enhancement of a systemic anti-tumor immune response. We present interim findings of the open-labeled, multicenter Phase II Coxsackievirus A21 in Late stage Melanoma (CALM) study. **Methods:** The CALM study investigated the efficacy and safety of intratumoral Coxsackievirus A21 in 57 patients with treated or untreated unresectable Stage IIIC-IVM1c melanoma. Patients received up to $3 \times 10^8$ $TCID_{50}$Coxsackievirus A21intratumorally on study days 1,3,5 and 8 and then every three weeks for a further 6 injections. Patients displaying immune-related progression-free survival (irPFS) or better at 6 months were eligible for 9 additional injections. Key eligibility criteria were ≥ 18 yrs old, ECOG 0-1, and at least 1 injectable cutaneous, subcutaneous, or nodal melanoma metastasis >1.0 cm. The primary endpoint was to achieve >9 of 54 evaluable patients with irPFS at 6 months. The irPFS was calculated as the proportion of patients demonstrating a Complete Response, Partial Response or Stable Disease by immune-related RECIST 1.1 (irRECIST 1.1) criteria 6 months after the initiation of treatment. Secondary endpoints included 1-year survival, irRECIST1.1 best overall response and safety. **Results:** The primary endpoint of the study was achieved with 14 of 40 (35%) evaluable patients displaying irPFS at 6 months. The number of patients surviving 1-year from the initial treatment is 13 of 21 (62%). Best overall response rate (irRECIST 1.1) is 24% (9 of 38 evaluable patients). Patients received on average 8.3 series of injections, with the most common side effects being Grade 1 fatigue, chills, local injection site reactions and fever. There were no Grade 3 or 4 product-related AE's. **Conclusions:** Intralesional Coxsackievirus A21 is a promising novel oncolytic immunotherapeutic agent in the treatment of unresectable Stage IIIC-IV M1c melanoma based on good patient tolerability, with both local and distant tumor responses. A randomized phase 2 clinical trial is planned. Clinical trial information: NCT01227551.

**3032 Poster Highlights Session (Board #24), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**IMMU-132, an SN-38 antibody-drug conjugate (ADC) targeting Trop-2, as a novel platform for the therapy of diverse metastatic solid cancers: Clinical results.** *Presenting Author: Alexander Starodub, Indiana University Health Goshen Center for Cancer Care, Goshen, IN*

**Background:** IMMU-132 is an ADC of the internalizing, humanized, anti-Trop-2 antibody, hRS7, conjugated by a pH-sensitive linker, to SN-38, the active metabolite of CPT-11 (mean drug-antibody ratio = 7.6). Trop-2 is a type I transmembrane, calcium-transducing, protein expressed at high density (~1 x 10*5), frequency, and specificity by many human carcinomas, with limited normal tissue expression. **Methods:** We report the initial Phase I trial of 25 patients (pts) who had failed multiple prior therapies (some including topoisomerase-I/II inhibiting drugs), and the ongoing Phase II extension that focused on pts with colorectal (CRC), small-cell lung (SCLC) and triple-negative breast (TNBC) cancers. **Results:** Trop-2 is not detected in serum, but was strongly expressed (≥2+) in most archived tumors. In a 3+3 trial design, IMMU-132 was given on days 1 and 8 in repeated 21-day cycles, starting at 8 mg/kg/dose, then 12 and 18 mg/kg before dose-limiting neutropenia. To optimize cumulative treatment with minimal delays, phase II is focusing on 8 and 10 mg/kg (n=22 and 14, respectively). Most common non-hematological toxicities were fatigue (17 ≤G2 ,4 G3), nausea (20 ≤G2), diarrhea (12 ≤G2, 3 G3), alopecia (14), and vomiting (10 ≤G2) ; 2 pts had a rash. Homozygous UGT1A1 *28/*28 was found in 5 pts, 2 of whom had more severe hematological and GI toxicities. Over 80% of 24 assessable pts in Phase I had stable disease or tumor shrinkage (17 SD; 3 PR [CRC, TNBC, SCLC]) as best CT response; median TTP = 18 weeks for all pts, except pancreatic cancer. Of the 36 pts in the Phase II, 14 had their first response assessment by CT: 6 PD, 7 SD; 1 PR (SCLC) by RECIST1.1. Tumor markers (CEA, CA19-9) correlated with responses. No anti-hRS7 or anti-SN-38 antibodies were detected despite dosing over months. The conjugate clears within 7 days, consistent with *in vivo* animal studies where 50% of the SN-38 is released daily. **Conclusions:** These results indicate that this novel SN-38-containing ADC is active in metastatic solid cancers, with manageable diarrhea and neutropenia. The Phase II continues, while also accruing in other epithelial tumors. Clinical trial information: NCT01631552.

**3033 Poster Highlights Session (Board #25), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**ELYPSE-7: A randomized, placebo-controlled, phase 2a study evaluating the impact of IL-7 on CD4 count, hematological toxicity, and tumor progressionin metastatic breast cancer (MBC) patients (pts).** *Presenting Author: Jean-Yves Blay, University Claude Bernard Lyon I, Centre Léon Bérard, Lyon, France*

**Background:** Lymphopenia is an independent predictive and prognostic factor for chemotherapy (CT)-induced death, febrile neutropenia, overall survival and progression in several cancers, including breast carcinoma. CYT107 is a glycosylated recombinant human IL-7 (CYTHERIS) able to increase lymphocyte pool in man. Whether IL-7 can correct lymphopenia in cancer pts receiving CT and improve patient outcome is not known. **Methods:** Using a 2x2 factorial design, 20 lymphopenic (<1000/$\mu$L) MBC pts, treated with capecitabine (2.5g/m2/d1-14, d1=21), were randomly allocated to 4 arms to receive 1) before the 1$^{st}$ cycle of CT : IL-7 (CYT107:10$\mu$g/kg, SC, weekly) or placebo (pbo), then 2) during the 3$^{rd}$cycle of CT: IL-7 weekly or pbo. The primary endpoint was CD4 count changes before (D0 to D21) and during CT (D57 to D78). Secondary endpoints were toxicity, safety and PFS. Quantitative and functional changes in immune cells were also analyzed. **Results:** From Nov. 2011 to Jun. 2013, 20 pts (median CD4 count D0 : 242 /$\mu$L) were enrolled. Before CT (n=20), IL-7 induced a significant increase of CD4 count (median relative change : +148.1% in IL-7 groups vs +9.9% in placebo [Wilcoxon, p=0.002]), CD8 as well as naïve and memory T cell subsets. During CT (n=11), IL-7 increased CD4 count (+58.6% in IL-7 group vs -2.4% in pbo group [p=0.121]), as well as CD8CD45RO memory cells. CYT107 was well tolerated with injection site reactions as the main AE, no anti-IL-7 antibodies, and no IL-7-related ≥ Grade 3 AE. Interestingly, IL-7 during CT reduced the incidence of Grade 3 haemotological AE compared to placebo (0 vs 5 events, respectively). With a median follow-up of 14 [7-15] months, 6/10 and 2/10 deaths were observed in the groups having received pbo or IL-7 before CT, respectively. 3 objective responses (OR) were observed in pts receiving IL-7 (before and/or during CT) vs 1 OR in pts receiving only pbo. Survival data will be presented at the meeting. **Conclusions:** IL-7 treatment was safe, restored CD4 and T cell subsets in lymphopenic pts with severe haematological toxicity. Further investigations of IL-7 in oncology are warranted. Clinical trial information: NCT01368107.

**3034 General Poster Session (Board #101), Sun, 8:00 AM-11:45 AM**

**Dose-seeking phase I trials (DSP1T) for currently approved molecular-targeted therapies (MTT): We are still far from using appropriate designs.** *Presenting Author: Nuria Kotecki, Centre Oscar Lambret, Lille, France*

**Background:** To explore the use of innovative and more appropriate designs (Continual Reassessment method [CRM], dose-escalation driven by PK or target inhibition . . .). **Methods:** We have reviewed fully published (2001-2013) single-agent DSPT1 (n=38) investigating MTT (n=20), currently approved for solid tumors treatment. **Results:** Eligible criteria included target expression/molecular profiling in only 6 trials (15%). In all cases but one, the trials were based on dose-escalation, mainly toxicity-driven (36 trials, 94%). In 33 trials, the period for assessing DLTs was ≤28 days (87%). DLTs were defined in 31 DSPT1; these definitions took into account the drugs mechanism of action in only 8 cases (25%). In 23 trials, the definitions were strictly similar to those used for cytotoxic agents (75%). "3+3 design", CRM and randomization were used in 17 (44%), 2 (5%) and 3 (8%) DSPTA, respectively. The dose increment was based on "Fibonacci-like" schema, PK or CRM in 25 (65%), 3 (8%) and 2 (5%) DSPT1, respectively. Median numbers of pts and dose-levels were 53 (12-206) and 6 (1-21). There was an expanded cohort at P2RD in 24 trials (63%) with a median number of pts of 12 (3-82). The P2RD was defined in 22 trials (58%). P2RD was identical to the latter approved dose in only 20 trials. The selection of the P2RD also integrated clinical activity (10 trials, 26%), PK (31, 81%), target inhibition or PD (4, 11%) and the results of parallel DSP1T (3, 8%). The probability to experience DLT at the P2RD was ranged from 0% to 33% (median 14%). **Conclusions:** Most of the designs of DSP1T investigating MTT are old-fashioned. The period for assessing DLTs was too short and might be not appropriate in the perspective of long-term drug administration scheduling. This may underestimate the MTT toxicity profile. It is of utmost importance to move ahead to more adapted and innovative designs.

**3035 General Poster Session (Board #102), Sun, 8:00 AM-11:45 AM**

**Cancer patients (pts) being replaced in dose-seeking phase I trials (DSP1T): Occurrence, outcome, and risk factors.** *Presenting Author: Sophie Cousin, Centre Oscar Lambret, Lille, France*

**Background:** Selection of pts entering in DSPT1 remains challenging. Some predictive scores for early death (within 90 days) or overall survival (OS) have been validated. There is currently no predictive model for identifying pts that will be replaced, whereas this condition interferes with the dose-escalation process and recruitment. **Methods:** We retrospectively reviewed all consecutive pts enrolled in DSP1T in 4 centers. Royal Marsden Score (RMS) was calculated as follows: 1 point for each of the following parameters: albumin<35 g/l, LDH>ULN and ≥2 metastatic sites (Olmos JCO 2012). Using logistic regression and decision-tree analyses, we have developed a predictive model for excluding pts of high-risk for being replaced. This model maximized the Specificity (Sp) and the Negative predictive value (NPV). **Results:** Of 332 enrolled pts, 16 pts had to be replaced (4.8%). In all cases, the main reason for early study discontinuation was rapid deterioration of general condition. The median duration of study participation was 18 vs 66 days (p=0.001). The median OS was 45 days vs 480 days (p<0.0001). The 90-day mortality rates were 6/16 (37.5%) vs 19/316 (6.0%). In univariate analysis, the risk factors for being replaced were performance status (PS)=2 (RR=8.2 [2.1-37.4), RMS=3 (RR=35.4 [8.3-150.5]), and enrolment in a study investigating a combination (RR=6.29 [1.98-20.0]). Multivariate analysis had retained PS≥2 and RMS=3 as independent predictive factors for being replaced. We have identified 2 pt subgroups: low-risk of being replaced (RMS≤2 and PS≤1) and high-risk for being replaced (RMS=3 or PS≥2). Rate of being replaced were 8/247 (3.2%) and 8/22 (36.4%) in low and high-risk pts, respectively. Sp and NPV were 94.5% and 94.4%, respectively. **Conclusions:** About 5% of enrolled pts have to be replaced. These pts experienced very poor outcome. RMS=3 or PS≥2 are predictive for being replaced.

**3036 General Poster Session (Board #103), Sun, 8:00 AM-11:45 AM**

**Cancer genomics-based approach for development of new immunotherapeutics for lung cancers.** *Presenting Author: Yataro Daigo, Institute of Medical Science, University of Tokyo, Tokyo, Japan*

**Background:** Oncoantigens are oncogenic and high immunogenicity proteins specifically expressed in cancer cells, and are promising targets for immunotherapy. **Methods:** We have established a strategy as follows to identify new oncoantigens; (1) screening of highly expressed genes in the majority of 120 llung cancers using cDNA microarray representing 27,648 genes, (2) verification of no expression of each gene in normal tissues, (3) validation of the clinicopathological significance of its high level of expression with tissue microarray covering 400 lung cancers, (4) characterization of a critical role of each gene in the growth or invasiveness of cancer cells by RNAi and cell growth/invasion assays, (5) screening of the epitope peptides recognized by HLA-A*0201- or A*2402-restricted cytotoxic T lymphocyte (CTL) for clinical trials. **Results:** We identified 40 oncoantigens and identified dozens of 10-amino-acid peptides, each of which was a candidate to be presented on the surface of HLA-A*0201 or HLA-A*2402 that induced *in vitro* CTL response. We conducted a phase I study for HLA-A*2402-positive, advanced non-small cell lung cancer patients who failed to standard therapy, using the combination of 1, 2 or 3 mg/body of each peptides from LY6K, CDCA1, and KIF20A mixed with adjuvant once a week. 18 evaluable patients have been enrolled, and this cancer vaccine therapy demonstrated tolerability and had very high immunogenicity of even 1 mg/body dose to induce antigen-specific CTLs in cancer patients. The clinical response of the vaccination was evaluated according to RECIST; one complete response case was observed, 8 patients showed stable disease, and 9 showed progressive disease, indicating that disease control rate was 50%. We are also screening predictive and monitoring biomarkers for peptide vaccine therapy through immunogenomics approach by analyzing pattern of CTL response, genomic/proteomic profiles of CTLs and cancer tissues, and genetic variation of patients. **Conclusions:** The cancer vaccine therapy using the cocktail of three peptides demonstrated good tolerability as well as the promising disease control rate, and therefore warrants further clinical studies with screening of their companion diagnostics. Clinical trial information: NCT01069575.

**3037 General Poster Session (Board #104), Sun, 8:00 AM-11:45 AM**

**Prognostic significance of the neutrophil-lymphocyte ratio (NLR) in phase 1 clinical trial patients.** *Presenting Author: Rajiv Kumar, The Institute of Cancer Research, London, United Kingdom*

**Background:** Inflammation has a critical role in the pathogenesis and progression of tumours. A high pre-treatment NLR has been associated with a poor prognosis. Its prognostic utility in patients (pts) being treated on Phase I trials remains uncertain. **Methods:** We identified 300 pts treated on Phase 1 clinical trials at the RMH, between January 2007 and November 2013. Data was collected on pt, treatment and tumour characteristics, including baseline RMH score, neutrophil count and lymphocyte count. **Results:** Overall, 47% of the pts were male; 35% had ECOG 0 and 64% ECOG 1. Tumour types included 15% breast, 13% colorectal, 13% ovarian, 13% non-small cell lung, 14% prostate and 32% other. The RMH score was 0 in 23%, 1 in 43%, 2 in 31% and 3 in 3%. The median NLR was 3.08 (IQR 2.06 – 4.49). Median overall survival (OS) for the NLR quartiles was 10.5 mths for quartile 1, 10.3 mths for quartile 2, 7.9 mths for quartile 3 and 6.5 mths for quartile 4 ($P<0.0001$ for trend). In a univariate model for OS, median OS for a low vs high RMH score was 10.6 vs 5.8 mths (HR 0.55, $P<0.0001$). In addition, ECOG (0 vs 1-2) was significant (HR 0.62, $P=0.002$), as was the NLR when assessed for the binary thresholds defined by the quartiles (NLR25: HR 0.79, $P = 0.04$; NLR 50: HR 0.57, $P = 0.0001$; NLR 75: HR 0.50, $P= 0.0001$). Age, gender and steroid use, were not significant. In a multivariate model for OS, the RMH score and ECOG remained significant (HR 0.63, P=0.002 and HR 0.71, P 0.03, respectively). When the NLR measures were added, NLR (continuous variable) remained a significant prognostic factor (HR 1.06, P <0.0001) as did $Log_{10}$NLR (HR 2.61, P=0.001. The interaction test between the RMH score and the NLR measures was negative. ROC curve analysis showed that the RMH score had a C-index of 0.630, P = 0.0002. The models assessed included: RMH + NLR, RMH + $Log_{10}$NLR, RMH x NLR, and RMH x $Log_{10}$NLR. However, pairwise comparisons of the C-indices from these models to the RMH score alone showed no significant improvement in C-index. **Conclusions:** NLR is prognostic for OS in a Phase I population, independent of the RMH score, in a multivariate analysis.

**3038 General Poster Session (Board #105), Sun, 8:00 AM-11:45 AM**

**Biomarkers for immunotherapy: Results from the analysis of an HLA-status double-blind, biologically randomized phase II study of five therapeutic epitope-peptides with oxaliplatin-based chemotherapy as first-line therapy for advanced colorectal cancer (FXV study).** *Presenting Author: Shoichi Hazama, Digestive Surgey and Surgical Oncology, Yamaguchi University Graduate School of Medicine, Ube, Japan*

**Background:** Biomarkers to predict the efficacy of immunotherapy have been awaited. A phase II study of five therapeutic epitope-peptides with oxaliplatin-based chemotherapy as first-line therapy for advanced colorectal cancer (CRC) using five novel HLA-A*2402-binding peptides derived from not only three oncoantigens, RNF43, TOMM34, and KOC1 but also antiangiogenic cancer vaccine targeting VEGFR1 and VEGFR2 was presented at 2013 ASCO Oral Abstract Session (No. 3006). We further explored the predictive biomarker for the response to immunotherapy. **Methods:** Between February 2009 and November 2012, 96 chemotherapy naïve CRC pts were enrolled in this study. Each of the five peptides (3 mg each) was mixed with 1.5 ml of IFA and subcutaneously administered weekly for 12 weeks and after then biweekly. Chemotherapy was performed simultaneously as mFOLFOX6 (n=93) or XELOX (n=3) with bevacizumab (n=5). All enrolled pts had received the therapy without knowing HLA-A status double-blindly, and the HLA-A genotypes were key-opened at analysis point. Pretreatment serum IL-6 and CRP, lymphocyte%, neutrophil/lymphocyte (N/L) ratio and comprehensive expression profiles microRNA of the tumor were evaluated between HLA-A*2402 positive (treatment) group and HLA-A*2402 negative (placebo) group. **Results:** IL-6 <1.0 (pg/ml) and Lymphocyte% >15% were the significant predictive markers (p=0.007, 0.034) for the long survival, which was observed only in HLA-A*2402 positive group. In the patients with IL-6 <1.0 or lymphocyte% >15, obvious trend to long survival in HLA-A*2402 positive group was observed. MiR-a and miR-b (will be opened in the meeting) were selected for the predictive biomarkers. Patients with low miR-a (<550) or low miR-b (<350) were significantly survived longer than high miR groups (p=0.002, 0.012), which significances were observer only in HLA-A*2402 group. **Conclusions:** Serum IL-6, Lymphocyte%, and miRs expression were the predictive biomarkers for the response to peptides vaccine and the selection of patients. Clinical trial information: UMIN000001791.

**3039 General Poster Session (Board #106), Sun, 8:00 AM-11:45 AM**

**Tumor cells/leukocytes ratio (TLR) in peritoneal fluids as a biomarker in patients with peritoneal metastasis of gastric cancer.** *Presenting Author: Joji Kitayama, Department of Surgical Oncology, University of Tokyo, Tokyo, Japan*

**Background:** Peritoneal carcinomatosis (PC) is the most frequent and life-threatening types of metastasis in patients with gastric cancer (GC). Although the presence of tumor cells in peritoneal cavity is evaluated with microscopic observation by pathologists (Cy) or detection of mRNA of tumor specific molecules, no reliable method is available to quantify the accurate frequency of tumor cells. **Methods:** A total of 380 samples of acsites or peritoneal lavages were recovered from 243 patients with GC and 22 patients with liver cirrhosis (LC). Peritoneal fluids were obtained by laparotomy or paracentesis, and from subcutaneous intraperitoneal access port in case of the patients who received repeated intraperitoneal (IP) chemotherapy for PC. Cells were recovered by centrifugation of peritoneal fluids and immunostained with mAbs to CD45 and to CD326 (EpCAM). Using flowcytometry, the number of CD326(+)CD45(-) and CD45(+)CD326(-) cells, which were determined as tumor cells (T) and leukocytes (L), respectively, were calculated in $10^4$~$10^5$acquired cells, and T/L ratio (TLR) was calculated. **Results:** Median (M) of TLR of the GC patients with PC(+) patients was 0.19% (0%-1868.44%, n=281), which was significantly higher than those of PC(-) patients (M=0%, 0%-0.30%, n=77, p<0.001) and LC (M=0%, 0%-0.028%, n=22, p<0.001). In PC(+) patients, 168 samples which was determined as positive cytology (Cy+) showed higher TLR as compared with 113 samples with Cy (-) (M=1.33%, 0%-1868.44% vs M=0%, 0%-1.13%, p<0.0001). In 37 patients who underwent repeated IP chemotherapy, TLR was markedly decreased after chemotherapy and the response was more sensitive than the changes in Cy or mRNA of CEA. Moreover, TLR of the patients with PC(+) GC before chemotherapy was significantly associated with their outcome. Median survival times (MST) of the patients whose initial TLR were <1.0%, 1.0%~10%, <10% were 765, 394, 271 days, respectively (p<0.001). **Conclusions:** TLR measured with flowcytometry well reflects the relative volume of living tumor cells in peritoneal cavity and thus could be a useful biomarker to predict the prognosis as well as the effectiveness of IP chemotherapy in patients with PC.

**3040 General Poster Session (Board #107), Sun, 8:00 AM-11:45 AM**

**Comprehensive reassessment of plasma VEGFA (pVEGFA) as a candidate predictive biomarker for bevacizumab (Bv) in 13 pivotal trials (seven indications).** *Presenting Author: Carlos Bais, Genentech Inc., South San Francisco, CA*

**Background:** Baseline (BL) pVEGFA level has been investigated as a predictive biomarker for the clinical efficacy of anti-VEGF therapy with Bv in 13 trials (7 indications).Three studies, AVADO (breast cancer [BC]), AVAGAST (gastric cancer), and AVITA (pancreatic cancer [PC]), reported that a high BL pVEGFA level was associated with prolonged PFS or OS, but contrasting data were obtained in other Bv clinical trials. Therefore, pVEGFA as a potential predictive factor of Bv activity in specific oncological indications and individual pts remains poorly understood. **Methods:** To investigate the potential value of BL pVEGFA level (from EDTA-plasma) as a predictive biomarker for Bv activity, sensitivity analyses were carried out on pVEGFA assay data from 13 pivotal Bv trials. In all trials, a VEGFA assay with preferred sensitivity toward the short VEGFA isoforms was used (IMPACT platform, currently used for pt stratification in the MERiDiAN BC trial). **Results:** In the AVADO study, a high BL pVEGFA level was associated with improved PFS in pts treated with Bv 7.5mg/kg but not Bv 15mg/kg. Additionally, while BL pVEGFA levels were predictive of OS and PFS in the AVITA trial, these results were not replicated in a second PC trial (CALGB 80303). Parallel sensitivity analyses of the IMPACT VEGFA assay and assays that recognize all VEGFA isoforms similarly, suggested that preferential detection of the short isoform of VEGFA was not required to assess outcome correlations (AVADO trial). Sensitivity analysis of pVEGFA data from the AVADO trial also indicated an 11% difference in Spearman's rank correlation between different VEGFA assays, which resulted in a loss of the interaction p-value. Finally, longitudinal analysis of VEGFA level in plasma samples from healthy donors showed substantial intra-pt variability in pVEGFA concentration over time. **Conclusions:** These data suggest that pVEGFA level is not a robust predictive biomarker for Bv activity; stratification of pts based on a single BL measurement of pVEGFA is unlikely to be successfully implemented in clinical practice. Further assessment of this hypothesis awaits the prospective analysis of pVEGFA data from MERiDiAN.

**3041 General Poster Session (Board #108), Sun, 8:00 AM-11:45 AM**

**Predictive markers for clinical outcome after neoadjuvant radiochemotherapy in breast cancer patients.** *Presenting Author: Christiane Matuschek, University of Düsseldorf, Düsseldorf, Germany*

**Background:** Neoadjuvant radiochemotherapy (NRT-CHX) in locally advanced noninflammatory breast cancer (LABC) is still under debate. Proliferation markers are the majority of genes included in RNA-based prognostic gene signatures applied for breast cancer patients. **Methods:** During 1991-1998, a total of 315 LABC patients (cT1-cT4/cN0-N1) were treated with NRT-CHX. Preoperative radiotherapy (RT) consisted of external beam radiation therapy (EBRT) of 50 Gy (5 × 2 Gy/week) to the breast and the supra-/infraclavicular lymph nodes combined with an electron boost in 214 cases afterwards or -in case of breast conservation- a 10-Gy interstitial boost with (192)Ir after loading before EBRT. Chemotherapy was given prior to RT in 192 patients, and concomitantly in 113; 10 patients received no chemotherapy. The impact of age, tumor grade, nodal status, hormone and growth factor receptor status (ER, PR, EGFR), p53, ki-67, HER2/neu, and bcl-2 on pathological complete response pCR and disease-free survival were examined in uni- and multivariate terms. **Results:** Hormone receptor status, proliferative activity, bcl-2, EGFR-status and clinical tumor size had a significant impact on clinical outcome. Age, cN, grading, p53, and HER2/neu status failed to reach a significant correlation to complete remission. All examined immunohistochemical factors with the exception of EGFR, and all clinical factors displayed an univariately significant impact on DSF. Particularly, while HER-2/neu had no predictive value for pCR it displayed the highest impact on DSFafter complete response (n=92) , even in a multivariate setting with clinical tumor size and nodal status. Complementary, p53 was the most superior immunhistochemical factor for prognosis after neoadjuvant incomplete remission (n=223). **Conclusions:** Her2/neu is a predictive marker for overall survival independent from the pCR. Furthermore it has no predictive value for the pCR. P53 is a prognostic marker for patients with incomplete remission. Prospective studies are needed to evaluate their use for decisions to further individualize adjuvant treatment after neoadjuvant radiochemotherapy.

**3042 General Poster Session (Board #109), Sun, 8:00 AM-11:45 AM**

**Evaluation of changes on tumor-infiltrating lymphocytes and regulatory T-cells in tissue and peripheral blood after neoadjuvant chemotherapy in breast cancer patients and relation with pathologic complete response.** *Presenting Author: Luis de la Cruz Merino, Clinical Oncology Department. Hospital Universitario Virgen Macarena, Seville, Spain*

**Background:** Some clinical trials in breast cancer have reported imppressive outcomes related to laboratory immune findings in the neoadjuvant setting. We designed a protocol to analyze immune profile before, during and after neoadjuvant chemotherapy (CT) in breast cancer in blood and tissue, and their eventual relation with pathological complete response (pCR). **Methods:** From March 2011 to January 2014, 47 patients (18 Her2+/ 29 Her2-) with T2-4 N0-3 breast carcinoma treated with neoadjuvant chemotherapy in the Breast Cancer Unit of the Hospital Universitario Virgen Macarena (Seville, Spain) were included in the study. CD3+, CD8+, CD8-16-56+ and Foxp3+ cell infiltrates were detected by immunohistochemistry before and after neoadjuvant CT in tissue specimens. Blood samples were collected in EDTA-K3 tubes before every cycle of CT to determine the immunophenotype profile. Cell populations were determined by flow cytometry analysis of whole blood, including the study of CD3-CD4-CD25low and CD3-CD4-CD25high (regulatory) T cells. **Results:** By January 2014, 47 patients (18 Her2+/29 Her2-) were operated. Pathological complete responses (pCR) or near pCR (grade 4/5 Myller&Payne) were attained in 20 patients (42,6%). pCR was achieved in 66,66% (12/18) of tumors overexpressing Her2, but in only a 27,5% (8/29) of Her2-negative tumors. Absence and/or disappearance of Tregs in tissue (Black grading system=0) was more frequent after neoadjuvant CT (11,11 vs 62,2%). Average whole blood CD3-CD4-CD25high (regulatory) T cells were 126,36 before CT and 91,19 cells/microliter after neoadjuvant CT (p 0,010). Overall Tregs diminished in the pCR and non pCR groups without statistically significant differences. **Conclusions:** Neoadjuvant CT decreases Tregs immunosuppressive infiltrates in tissue and CD3-CD4-CD25high (regulatory) T cells in peripheral blood in all the population. Although differences among subgroups (pCR/non-pCR and Her2+/Her2-) were not statistically significant, these data support the role of Tregs as an interesting biomarker with eventual therapeutic implications.

**3043 General Poster Session (Board #110), Sun, 8:00 AM-11:45 AM**

**Development of an IHC-based detection method for studying indoleamine 2,3-dioxygenase 1 (IDO1) expression in human cancers.** *Presenting Author: Alton Hiscox, Ventana Medical Systems, Tucson, AZ*

**Background:** Indoleamine 2,3-dioxygenase-1 (IDO1) mediates oxidative cleavage of tryptophan, an amino acid essential for cell proliferation and survival. The depletion of tryptophan and the generation of tryptophan metabolites have been shown to suppress immune functions via several cellular mechanisms, allowing tumor escape from host immune surveillance. IDO1 is induced by interferons and TLR agonists and is expressed in a variety of human cancers as well as the invading immune infiltrate and the tumor-draining lymph nodes. High IDO1 expression is significantly associated with more rapid disease progression and poor prognosis in multiple cancer types. Thus, inhibition of IDO1 activity may have therapeutic potential in cancer and furthermore, IDO1 expression could serve as a biomarker for selecting patients that are responsive to an IDO1 inhibitor-based treatment regimen. **Methods:** We generated and selected an anti-human IDO1 rabbit monoclonal antibody. The specificity of the antibody for IDO1 was confirmed using Western blot analyses of lysates from cells expressing human IDO1, IDO2, or TDO. **Results:** INCB024360, a novel IDO1-selective inhibitor, is currently being evaluated in clinical trials of cancer patients. To support the clinical development of INCB024360, we developed an immunohistochemistry (IHC)-based method for the detection of IDO1 protein in human tissues. To further evaluate the specificity and reactivity of the antibody against IDO1 in human tissues, an IHC staining protocol was established, standardized and used to stain various human normal and tumor tissues, as well as IDO1-expressing cells. We have examined IDO1 expression in several human tumors including lung, ovarian, melanoma, gastric, and pancreatic cancers. **Conclusions:** In summary, we have developed and standardized an IHC-based method for the specific detection of IDO1 protein in human tissues. The method will be useful to determine the prevalence of IDO1 expression in a variety of human cancers. Furthermore, incorporating this detection method into ongoing clinical trials may identify patients that are likely responsive to IDO1 inhibitor-based treatment regimens.

**3044 General Poster Session (Board #111), Sun, 8:00 AM-11:45 AM**

**Enhancement of cetuximab-induced antibody-dependent cellular cytotoxicity (ADCC) with lenalidomide in advanced solid tumors: A phase 1 trial.** *Presenting Author: Erin Marie Bertino, The Ohio State University Comprehensive Cancer Center, Columbus, OH*

**Background:** Antibody-dependent cellular cytotoxicity (ADCC) is one mechanism of action of monoclonal antibody therapy. ADCC occurs via the innate immune system's ability to recognize mAb coated cancer cells and activate effector cells. Lenalidomide is an immunomodulatory agent with capacity to stimulate T cell proliferation, activate natural killer cells, and effect immune cytokines including IL-2, IL-12, and interferon gamma (INF-g). Pre-clinical and clinical data demonstrate the ability of lenalidomide to increase ADCC activity of mAb therapy. This phase 1 trial evaluated the combination of cetuximab with lenalidomide to enhance ADCC activity in advanced colorectal (CRC) and head and neck squamous cell cancers (HNSCC). **Methods:** This phase 1 dose escalation (3+3) trial included pts with metastatic CRC or HNSCC. Treatment consisted of cetuximab 500 mg/m2 IV every 2 weeks with lenalidomide orally days 1-21 every 28 days. Three dose levels of lenalidomide were evaluated (15, 20, and 25 mg). Correlative studies include measurement of ADCC using an in vitro chromium release assay, bioplex cytokine profiles, and Fc gamma receptor (FcR) polymorphisms. For ADCC assay, target cell line was HT29 (CRC KRAS WT cell line). **Results:** 22 pts were treated (19 CRC, 3 HNSCC); 20 pts had received prior cetuximab or panitumumab. Grade 3 fatigue was the only DLT. One partial response was observed and 7 patients had stable disease as best response.The recommended phase II dose is cetuximab 500 mg/m2 with lenalidomide 25 mg daily. ADCC assay demonstrated increased cell lysis with increasing doses of lenalidomide, particularly with lenalidomide 25 mg. Patient with PR demonstrated increase in ADCC as well as upregulation of IL-2, IL-12, INF-g with downregulation of FGF and VEGF. No high affinity FcR polymorphisms were identified. **Conclusions:** Cetuximab and lenalidomide are well-tolerated with minimal toxicity. There was evidence of anti-tumor activity and clinical efficacy. Correlative studies also demonstrate improved immunologic activity as demonstrated by ADCC assays with increasing doses of lenalidomide although no high affinity FcR polymorphisms were identified. Clinical trial information: NCT01254617.

**3045 General Poster Session (Board #112), Sun, 8:00 AM-11:45 AM**

**Endogenous anti-$\beta$-glucan antibodies as a potential predictive biomarker for clinical response to imprime PGG immunotherapy in non-small cell lung cancer (NSCLC) patients.** *Presenting Author: Nandita Bose, Biothera, Inc., Eagan, MN*

**Background:** Imprime PGG (IPGG) is a yeast-derived $\beta$-1,3/1,6 glucan that primes innate immune cells to kill antibody-targeted cancer cells via a complement receptor 3 (CR3)-dependent mechanism. In humans, naturally occurring anti-$\beta$-glucan antibodies (ABA) are required for binding of IPGG to CR3 and subsequent changes in innate cell functions. **Methods:** In a 32-donor healthy volunteer study, using a qualified quantitative ELISA assay, ABA levels and the threshold for binding and modulation of innate immune functions were evaluated, including a) complement activation, b) complement receptor expression, c) activation marker modulation, and d) selective chemokine production. The potential of the ABA level as a clinical biomarker for clinical response to IPGG was evaluated in a Phase 2 clinical trial by retrospectively segregating subjects into populations at or above the ABA threshold (biomarker positive; $BM^+$) or below the ABA threshold (biomarker negative; $BM^-$). Advanced NSCLC patients received cetuximab, carboplatin and paclitaxel without (Control) or with IPGG 4mg/kg on Days 1, 8 and 15 of each 3-week treatment cycle for the first 4 to 6 cycles. Maintenance treatment with cetuximab alone or with IPGG was continued in subjects achieving radiographic disease control (RECIST 1.0). **Results:** The objective response rate (ORR; primary endpoint) was 23% in the control group (6/26), 48% in the entire IPGG group (22/46; p= 0.047 *vs* control), 67% in the $BM^+$ IPGG group (10/15; p=0.009 *vs* control) and 39% in the $BM^-$ IPGG group (12/31; p=0.26 *vs* control). Median overall survival was 11.3 mo in the control group, 12.4 mo in the entire IPGG group (HR 1.04; p=0.88 *vs* control), 16.7 mo in the $BM^+$ IPGG group (HR 0.70; p=0.37 *vs* control) and 9.4 mo in the $BM^-$ IPGG group (HR 1.28; p=0.43 *vs* control). Three-year survival was 0% in the control group, 7% in the entire IPGG group, 17% in the $BM^+$ IPGG group and 0% in the $BM^-$ IPGG group. **Conclusions:** In summary, the addition of Imprime PGG to carboplatin, paclitaxel and cetuximab resulted in improved outcomes in $BM^+$ patients, suggesting the potential clinical use of ABA level as a predictive biomarker for response to Imprime PGG. Clinical trial information: NCT00874848.

**3046 General Poster Session (Board #113), Sun, 8:00 AM-11:45 AM**

**Clinical and pathologic correlation of the activated form of the estrogen receptor beta (ER$\beta$) in breast cancer (BC).** *Presenting Author: Emilie Hutt, Centre Oscar Lambret, Lille, France*

**Background:** ER$\beta$ is antagonized by anti-estrogens and has been associated with a better prognosis although its role is unclear. Experimentally, ER$\beta$ has a nuclear biology common to the steroid nuclear receptors. In the absence of estrogenic ligand, it is evenly distributed in nuclei; when exposed to ligand, ER$\beta$ migrates to form sub-nuclear aggregates that can be detected by immunofluorescence microscopy. Thus, two distinct nuclear patterns, diffuse (D) or aggregated (A) are observed which correspond to the receptors' functional states. Similarly to previous work on ER$\alpha$ and PR (ASCO 2013 abstr.# e11535 & 593), an immunohistochemistry (IHC) method has been developed to characterize the nuclear distribution patterns which may indicate whether ER$\beta$ is transcriptionally active or not in PEFF tissues. The goal of the study is to analyze whether activated ER$\beta$ is associated with anti-estrogen treatment outcome. **Methods:** 662 archived BC biopsies have been obtained along with clinical and pathological data. Biopsies were analyzed for standard HES, ER$\alpha$, ER$\beta$, PR and Ki67. ER$\beta$ positivity was determined with the 14C8 antibody (Abcam) and the nuclear distribution pattern analyzed at x1000 magnification. **Results:** 392 cases have been analyzed to date. Mean Age: 57 (17-89). Median follow up 36 months (mo). Histology: ductal 82% lobular 15% other 3%; $ER\alpha^{pos}$ 78% $PR^{pos}$ 78%. Adjuvant chemotherapy 46%, Hormone therapy 85%. Stage I 44%, II 48%, III 8%. Grade I 25%, II 50%, III 25%. ER$\beta$ was positive in 57% of the cases ($ER\beta^{pos}$). ER$\beta$ was activated (A- ER$\beta$) in 35% of the $ER\beta^{pos}$ biopsies, and non-activated (D- ER$\beta$) in 65% $ER\beta^{pos}$ . A-ER$\beta$ was associated with higher grade ($p < 0.000$, $p = 0.007$); ER$\beta$, PR, HER2, Ki67, staging were not associated with $ER\beta^{pos}$ nor A-ER$\beta$. Local or distant Progressive disease (PD) was evident in 19% of cases and was not associated with $ER\beta^{pos}$ or A-ER$\beta$ (p=0.87). With DFS defined as time to PD or death (5 year cut-off), neither $ER\beta^{pos}$nor A-ER$\beta$ were associated with a better DFS (HR: 1.02 and 0.98). **Conclusions:** In contrast to ER$\alpha$, preliminary results show that ER$\beta$ positivity and ER$\beta$ activation status were associated with higher pathological grade but not with other pathological or clinical variables.

**3047 General Poster Session (Board #114), Sun, 8:00 AM-11:45 AM**

**Expansion of peptide-specific T cells from human melanoma-draining lymph nodes.** *Presenting Author: Madeleine Strohl, Case Western Reserve University School of Medicine, Cleveland, OH*

**Background:** Adoptive immunotherapy using T lymphocytes is a novel therapy under investigation in patients with advanced stage melanoma. We have evidence that melanoma-draining lymph nodes (MDLN) from patients with stage III disease can be cultured to result in the generation of melanoma specific T cells. These T cells have demonstrated the ability to stop and reverse the progression of disease *in vitro* and in mouse models. We hypothesized that a proportion of our cultured T cells from MDLNs will demonstrate specific, measurable responses to one or more of known melanoma antigens *in vitro*. **Methods:** Human lymph nodes derived from patients with melanoma (IRB CASE 3610) containing T cells, B cells, monocyte/macrophages and dendritic cells were cultured with anti-CD3/CD28 beads, IL-2 and VEGF-blocking antibody. On day 11, cells were cultured with overlapping peptides spanning the sequences of four known melanoma antigens. Cells were incubated for 72 hours prior to undergoing FACS analysis to characterize intracellular IFN-$\gamma$, TNF-$\alpha$ and IL-2 expression in $CD4^+$ and $CD8^+$ subpopulations. Stimulation indexes were calculated as stimulated sample /MDLN alone sample expression. **Results:** Coculture of $CD4^+$ (helper T) cells with MAGEA1, NY-ESO1 and Prame/OIP4 resulted in a TNF-$\alpha$ stimulation index of 1.65,1.6 and 3, respectively. Coculture of $CD4^+$ cells with Melan-A/MART-1 and NY-ESO1 resulted in an IL-2 stimulation indexes of 1.66 and 2.73. $CD8^+$ (cytotoxic T) cells cocultured with MAGEA1 and Prame/OIP4 resulted in TNF-$\alpha$ stimulation indexes of 1.85 and 3.85, while coculturing with Melan-A/MART-1 and NY-ESO1 resulted in IL-2 stimulated indexes of 1.56 and 2.22. **Conclusions:** This data demonstrates that activated T cells which recognize defined melanoma peptide antigens can be generated from melanoma draining lymph nodes. Development of a novel assay to identify peptide-specific T cells will have significant applications to monitoring immune responses in patients with melanoma. Our goal will be to incorporate the use of this assay in immune monitoring of peripheral blood T cells in patients enrolled into a Phase I clinical trial of T cell therapy in patients with advanced melanoma.

**3048 General Poster Session (Board #115), Sun, 8:00 AM-11:45 AM**

**Preclinical evaluation of anti-RON antibody-drug maytansinoid conjugates (anti-RON ADC) for targeted colorectal cacner therapy.** *Presenting Author: Liang Feng, School of Pharmacy, Texas Tech University Health Science Center, Amarillo, TX*

**Background:** The receptor tyrosine kinase RON is critical in tumorigenesis and a validated drug target for cancer therapy. Here we report the development and therapeutic efficacy of anti-RON mAb Zt/g4-maytansinoid conjugates (Zt/g4-DM1) with enhanced cytotoxicity against colorectal cancer cells (CRC) in mouse xenograft tumor models. **Methods:** Zt/g4 (IgG1a/κ) was selected as the drug carrier for its ability to induce RON endocytosis in CRC cells. Zt/g4 was conjugated to DM1 via the thioether link to form antibody-drug conjugate Zt/g4-DM1 with an antibody-drug ratio of 1:4 molecules. CRC HCT116, HT29, and SW620 cells were used as the model for in vitro and in vivo studies. **Results:** Zt/g4-DM1 retains the intrinsic activity that causes rapid RON internalization. Targeted payload delivery induced cell cycle arrest at G2/M phase, reduced cell viability with $IC_{50}$ values at ~1.2 μg/ml, which results in massive cell death within a period of 72h. The cytotoxic effect of Zt/g4-DM1 was negligible in cancer cells with minimal RON expression. Studies from the mouse CRC xenograft model revealed that Zt/g4-DM1 is highly effective in delaying HT29 cell-mediated tumor growth in athymic nude mice. In a single cycle of q 4 days x 5 with Zt/g4-DM1 at 1, 3, 7, 10, and 15 mg/kg body weight, we observed significant tumor inhibition (>70% tumor growth delay) when Zt/g4-DM1 was used at 7 mg/kg. Significantly, more than 95% of tumor growth was inhibited at 10 mg/kg or 15 mg/kg of Zt/g4-DM1. Continued observation after last treatment showed that the inhibitory effect of Zt/g4-DM1 is long lasting up to 20 days without signs of tumor regrowth. The prepared Zt/g4-DM1 is stable *in vitro* and has a minimal toxic effect *in vivo*when Zt/g4-DM1 was used below 40 mg/kg. Zt/g4 has been sequenced and a 3D model of antigen-binding domains in variable regions in both heavy and light chains has been created. Zt/g4 is currently under humanization for potential clinical trials. **Conclusions:** Zt/g4-DM1 is a highly effective biotherapeutics for inhibition of CRC growth in mouse xenograft models. The development of humanized Zt/g4-DM1 opens an avenue for potential clincal trials for various types of cancers harboring aberrant RON expression.

**3049 General Poster Session (Board #116), Sun, 8:00 AM-11:45 AM**

**A novel method for identifying downstream signals in tumor-reactive T cells following PD-1 engagement and monitoring endogenous tumor immunity and immunotherapy.** *Presenting Author: Haidong Dong, College of Medicine, Mayo Clinic, Rochester, MN*

**Background:** Therapies targeting programmed cell death 1 (PD-1) or its ligand B7-H1 (aka PD-L1) have yielded promising therapeutic effects in various solid and hematologic malignancies. A reliable method to determine whether PD-1 on T cells has engaged its ligand B7-H1 on tumor cells is highly desirable as it may have significance as a predictive marker for PD-1 targeted therapy. **Methods:** Endogenous tumor-reactive CD8+ T cells were identified by their high expression of PD-1 and CD11a CD8+ T cells and their expression of Bim, a pro-apoptotic molecule, in the peripheral blood of 26 patients with metastatic melanoma and 11 patients with metastatic prostate cancer or healthy donors using flow cytometry. Soluble PD-L1 in patients' sera was quantified using ELISA. **Results:** The target-cell engaged CD8+ T cell population was significantly higher in patients with melanoma and prostate cancer compared to healthy donors, as assessed by CD11a and PD-1 expression. Bim expression was higher in CD8+ T cells in both cancer patients than healthy controls ($p<0.01$). In patients with advanced melanoma, Bim was significantly higher in the PD-1(+) target cell-engaged CD8+ T cells than the PD-1(-) CD-8+ T cells ($P<0.01$). Bim levels above the base line levels of healthy donors in the CD8+ T cells correlated with decreased survival in patients with melanoma (8.9 months v. 13.8 months, $p<0.05$). Our data suggest that the Bim level is dependent on PD-1 expression, and that higher Bim expression may be indicative of PD-1(+) CD8+ T cells which have engaged B7-H1 (PD-L1), either soluble (peripheral blood) or membrane bound (tumor cells), and are susceptible to apoptotic death. **Conclusions:** PD-1+ CD11a high CD8+ T cells identify a unique population of effector cells responsive to target tumor cells in cancer patients. Elevated Bim expression in CD8+ T cells may indicate the active immune inhibiting effects of PD-1/B7-H1 signaling on endogenous antitumor T cell responses. Bim expression can serve as a signaling biomarker for PD-1 function and may be useful in selecting patients who may benefit from checkpoint blockade therapy.

**3050 General Poster Session (Board #117), Sun, 8:00 AM-11:45 AM**

**Antibody-mediated modulation of the IgM B-cell receptor (BCR) expression and signaling.** *Presenting Author: Sydney Welt, Welt Bio-Molecular Pharmaceutical, LLC, Armonk, NY*

**Background:** Targeting the BCR signaling pathway in B-cell malignancies has been shown to be therapeutic, but inhibition of the BCR itself has remained elusive due to serum IgM (sIgM) sequence homology. A unique sequence in the extracellular domain of membrane IgM (ECD-mIgM), designated proximal domain (PD), is not expressed in sIgM. Anti-PD monoclonal antibodies (mAbs) can be used to purify ECD-mIgM for mAb generation. Here we identify an ECD-mIgM conformational epitope not detected in sIgM. **Methods:** High affinity anti-PD monoclonal antibodies (mAbs) were generated by proprietary immunization techniques. These mAbs are shown by ELIZA, Western blots and Scanning Immuno-Electron Microscopy (SEM) to bind to mIgM protein and mIgM+ expressing cell lines (CA 46, SU-DHL-5, CRL-1596, CRL-1432, CRL-1642). Using these high affinity anti-PD mAbs, mIgM was immune-affinity purified. Second generation mAbs detecting mIgM conformational epitopes and not reacting with sIgM in ELIZA/Western/SEM assays were collected. Clonogenic assays were done by limiting dilution/MTT. **Results:** Cell surface binding assays demonstrated the specificity of these mAbs by testing against a panel of mIgM + vs mIgM- (mIgG+) cells. Normal sera failed to block or reduce mAb binding to mIgM+ cells. MAb1-1, mAb2-2b and mAb3-2b internalize mIgM but do not modulate cell growth inhibition. Second generation mAb4-2b mediates BCR internalization and in low density cultures, cell growth inhibition, anti-clonogenic activity and apoptosis are observed. Apoptosis is seen in a variety of malignant B-cell lines including high and low mIgM/Igα/β expressers. **Conclusions:** These data support the contention that BCR internalization is insufficient to interrupt the BCR signaling cascade despite the lack of detectable residual mIgM. Upon mAb4-2b binding to a non-ligand binding site on mIgM, it induces both BCR internalization and in another distinct event, apoptosis. These mAbs are candidates for development as drug/radioisotope targeting agents and/or as a mediator of inhibition of the BCR signaling pathway (mAb 4-2b). These mAbs have a high level of specificity as they do not bind to non-mIgM B-cells, normal lymphocytes and non-lymphatic tissue, thus reducing toxicity.

**3051 General Poster Session (Board #118), Sun, 8:00 AM-11:45 AM**

**Potentiation of immune checkpoint blockade cancer immunotherapy with oncolytic virus.** *Presenting Author: Dmitriy Zamarin, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Therapeutic efficacy of agents targeting immune checkpoints has been limited to a subset of patients and cancer types. Preexisting lymphocytic infiltration of tumors has emerged as an important biomarker predictive of clinical benefit, suggesting that therapeutic effect could be enhanced through strategies that induce tumor inflammation. Here we explored whether the inflammatory responses generated by oncolytic viruses could be harnessed to improve systemic therapeutic efficacy of agents targeting immunologic checkpoints. **Methods:** For our studies we utilized Newcastle Disease Virus (NDV), an avian virus with robust type I IFN-inducing properties. Metastatic disease was modeled by using bilateral flank B16 mouse melanoma model, with NDV administered unilaterally, allowing us to characterize the immune responses in both virus-injected and distant tumors. Therapeutic efficacy and immune responses utilizing intratumoral NDV with systemic immune checkpoint blocking antibodies were further characterized in several mouse models. **Results:** Localized intratumoral therapy of B16 melanoma with NDV induced CD4+ and CD8+ lymphocytic infiltrates and anti-tumor effect in distant (non-virally infected) tumors without viral spread to these sites. Combination therapy with localized NDV and systemic immune checkpoint blockade led to distant tumor rejection in both NDV-susceptible and resistant tumor models and protected the animals from tumor re-challenge. This effect was associated with marked tumor infiltration with activated effector, but not regulatory T cells, and was dependent on CD8 and NK cells, and type I and II interferons. To further enhance the T cell effector function in tumors, we genetically-engineered NDVs expressing co-stimulatory ligands and demonstrated further increase in therapeutic efficacy of the combination therapy in several tumor models. **Conclusions:** In summary, in mouse tumor models, localized therapy with NDV induces inflammatory infiltrates in distant tumors, making them susceptible to systemic therapy with immunomodulatory antibodies. This provides a strong rationale for investigation of combination therapies utilizing NDV and immune checkpoint blockade in clinic.

**3052^ General Poster Session (Board #119), Sun, 8:00 AM-11:45 AM**

**Phase 1 study of VX15/2503, a humanized IgG4 anti-SEMA4D antibody, in advanced cancer patients (pts).** *Presenting Author: Amita Patnaik, START Center for Cancer Care, San Antonio, TX*

**Background:** Semaphorin 4D (SEMA4D) regulates cellular adhesion, motility and activation of cells of the nervous, vascular and immune systems; it also promotes tumor progression and metastasis. SEMA4D and its receptor plexin B1 are widely expressed in human tumors; the interaction of plexin B1 with MET and ERBB2 leads to SEMA4D-mediated transactivation of these membrane receptor kinases promoting tumor cell migration and invasive growth. The murine progenitor of VX15/2503 suppressed tumor growth in syngeneic and transgenic tumors. No toxicologic effects were noted in studies of VX15/2503 using rats and primates and PK/PD profiles were generally predictive of data from clinical trial subjects. **Methods:** A multiple ascending dose trial was initiated in adult pts with advanced refractory solid tumors; pts were administered weekly IV doses of VX15/2503 until progression. Dose levels were 0.3 to 20 mg/kg. Tumors were assessed by RECIST 1.1 after each 8 dose cycle. Biomarkers assessed were SEMA4D, VEGF, HGF, PLGF, and MET. **Results:** Enrollment has been concluded (n=42 Pts); sex 40.5%M/59.5%F. Mean age (yrs) 64.8; ECOG 0/1/2 are 28.6% /69%/4%. No MTD was found. One DLT (grade 3 GGT elevation; 15 mg/kg) was reported in a pancreatic cancer pt with disease progression. As of 12/16/2013 the most frequent treatment-related AE's (n=42 pts) included grade 1/2 nausea (11.7%), arthralgia (7.3%), decreased appetite (7.3%), and fatigue (7.3%); 15 drug unrelated SAE's were reported in 11 pts. No CR/PR were observed. Thirteen of 42 pts at all dose levels exhibited stable disease for at least 8 weeks. Pts with the longest duration of treatment included: 48-55 weeks (colorectal; 9 mg/kg) (breast; 15 mg/kg) (papillary thyroid; 20 mg/kg); these pts had relatively high T or B cell levels. VX15/2503 serum concentrations of $\geq$ 0.3 $\mu$g/mL produced complete T cell SEMA4D saturation. HAHA responses (titer $>$ 100) with possible effects on PK were observed in 4 of 41 pts (10%); in only 1 pt (2%) was an effect of HAHA on PD observed. VX15/2503 half-life was roughly 4-5 days at doses $\geq$1.0 mg/kg. **Conclusions:** VX15/2503 was well tolerated at dose levels up to 20 mg/kg, with 450 doses administered to 42 pts. Future studies will be combination trials in selected tumor types. Clinical trial information: NCT01313065.

**3053 General Poster Session (Board #120), Sun, 8:00 AM-11:45 AM**

**Association between immune-checkpoint inhibitor induced tumor shrinkage and overall survival in advanced melanoma and NSCLC.** *Presenting Author: Yan Feng, Bristol-Myers Squibb, Princeton, NJ*

**Background:** Immune checkpoint inhibitors enhance immunologic antitumor activity and ongoing studies are exploring the potential of such inhibitors to provide long term (OS) benefits across several cancer types. We describe an exploratory analysis of the association between tumor shrinkage (TS) and OS in patients (pts) with melanoma or NSCLC receiving ipilimumab or nivolumab, immune checkpoint inhibitors that augment T-cell activity by blocking CTLA-4 and programmed death-1 receptors, respectively. **Methods:** TS and OS associations for ipilimumab in pts with advanced melanoma were assessed using data from 4 phase II studies (CA184-004/007/008/022, n=351). TS and OS associations for nivolumab were assessed in pts with advanced melanoma (n=97) or NSCLC (n=112) using data from cohorts of a phase I study (CA209-003). A nonlinear mixed-effects model was used to describe longitudinal tumor burden data; TS was determined from the model as % decrease from baseline. The relationship between TS and OS was determined by a multivariate Cox proportional-hazards model. **Results:** Across the pt populations tested, the risk of death decreased with increasing % TS (hazard ratio [HR] coefficients in all 3 models and associated 95% confidence intervals [CIs] $<$1.0). At 30% TS (corresponding to magnitude of RECIST partial response), the association between TS and OS for pts with melanoma was comparable for ipilimumab or nivolumab treatment (HR [95% CI] of 0.602 [0.543–0.668] and 0.502 [0.381–0.662], respectively, relative to no change in % TS). At 30% TS, the association between TS and OS for NSCLC pts treated with nivolumab was comparable with that seen for melanoma pts (HR [95% CI] of 0.361 [0.252–0.517]). **Conclusions:** An association was found between the extent of TS and OS across melanoma pts receiving ipilimumab or nivolumab and NSCLC pts receiving nivolumab in this exploratory retrospective analysis. Measuring the extent and timing of TS may have use in predicting potential OS benefits of immune checkpoint inhibitors; however, this observation would need to be prospectively evaluated in data from a well-controlled study. Additional exploratory analyses are ongoing to assess correlates to OS benefit.

**3054 General Poster Session (Board #121), Sun, 8:00 AM-11:45 AM**

**Immune escape mechanisms associated with tumor recurrence after adoptive cell transfer immunotherapy.** *Presenting Author: Marco Donia, Center for Cancer Immune Therapy, Copenhagen University Hospital Herlev, Herlev, Denmark*

**Background:** Adoptive cell transfer immunotherapy (ACT) with tumor infiltrating lymphocytes (TILs) results in unprecedented rates of durable clinical responses but some patients initially responding achieve only a temporary disease remission before tumor recurrence. **Methods:** Disease relapse in a case of metastatic melanoma experiencing tumor recurrence after complete response to treatment with TILs was characterized at the cellular and molecular level using primary tumor cell lines and tumor infiltrating lymphocytes derived from metastatic lesions resected at different time points. **Results:** Multiple mechanisms linked to tumor-intrinsic evolutional phenomena associated with tumor re-growth despite durable persistence of peripheral antitumor responses were identified. Tumor-cell intrinsic alterations led to both impaired immune sensitivity and universally reduced immune recognition associated with multiple defects in antigen processing machinery, but not to antigen loss or increased expression of immune suppressive molecules such as PD-L1. In addition, cell lines from tumor recurrence were characterized by increased in vivo malignancy independent of immune response sensitivity, in the absence of new known melanoma driver mutations. **Conclusions:** Data from this study brings direct evidence that tumor cell evolutionary mechanisms responsible for immune escape, and associated with disease recurrence in human metastatic tumors after effective immunotherapies targeting multiple antigens, are extraordinarily complex and multifactorial. Future strategies to extend duration of responses to immunotherapy should consider targeting this complexity

**3055 General Poster Session (Board #122), Sun, 8:00 AM-11:45 AM**

**Interim analysis of a phase I/II open label, dose-escalating study to investigate safety, tolerability, and preliminary efficacy of the trifunctional anti-HER2/neu x anti-CD3 antibody ertumaxomab in patients with HER2/neu expressing solid tumors progressing after standard therapy.** *Presenting Author: Nicole Haense, Krankenhaus Nordwest, University Cancer Center, Frankfurt, Germany*

**Background:** Ertumaxomab (ertu) is a bispecific, trifunctional antibody (ab) targeting HER2/neu, CD3 and the Fc$\gamma$-receptors I, IIa, and III forming a tri-cell complex between tumor cell, T cell and accessory cells. Patients (pts) with HER2/neu (1+/SISH positive, 2+ and 3+) expressing tumors progressing after standard therapy are treated to investigate safety, tolerability and preliminary efficacy. **Methods:** In this ongoing investigator driven, non-randomized study, ertu is applied i.v. in 2 cycles following a predefined dose escalating scheme. Each cycle consists of 5 ascending doses (10-500$\mu$g) applied weekly within 28 days with a 21 day treatment-free interval. If 2 pts experience a dose limiting toxicity at a given dose level, the maximum tolerated dose (MTD) will have been exceeded. **Results:** So far, 11 heavily pretreated pts (e.g. breast, rectal, gastric cancer) have been enrolled in the first 4 main cohorts. 1 (9%) pt had a partial remission at end of study (EoS), 2 (18%) pts had a stable disease after the first cycle and PD (progressive disease) at EoS. 7 (63%) pts had a PD after the first cycle and were not further treated. 1 (9%) pt had to be replaced. To date, no therapy related serious adverse event was detected and consequently the MTD is not yet reached. All adverse events (AE) were transient and completely reversible. Most frequent AEs were fatigue (11/11), gastrointestinal disorders (10/11), pyrexia (8/11) and cephalgia (8/11). Single doses up to 300$\mu$g were well tolerated in this dose scheme (total dose up to 800 $\mu$g per cycle). All pts showed a transient decrease of the CD3+lymphocyte count 24h after infusion. 3/4 analyzed pts developed an anti-tumor immune response demonstrated by the induction of either anti-HER2/neu-abs (3/3) or anti-EpCAM-abs (1/3). **Conclusions:** Doses up to 300$\mu$g were safely administered in an escalating dose scheme. First signs of efficacy with mild and reversible AEs warrant further increasing of dosing. The development of anti-HER2/neu and anti-EpCAM abs suggests the promotion of an immunologic memory. Clinical trial information: NCT01569412.

**3056 General Poster Session (Board #123), Sun, 8:00 AM-11:45 AM**

**Effect of interferon-$\alpha$ on redirected T-cell killing of pancreatic and gastric cancers.** *Presenting Author: David M. Goldenberg, Center for Molecular Medicine and Immunology, Morris Plains, NJ*

**Background:** Trop-2 is highly expressed in diverse epithelial cancers with limited presence on normal tissues. (E1)-3s is a T-cell redirecting trivalent bsAb, which comprises an anti-CD3 scFv covalently linked to a stabilized dimer of a Trop-2-targeting Fab (Rossi et al., *mAbs*, 2014; 6(2), in press). IFN$\alpha$ has demonstrated clinical efficacy in multiple solid cancers, and is approved for melanoma, Kaposi sarcoma and various hematologic cancers. We studied the effects of IFN$\alpha$ on (E1)-3s-mediated T-cell killing of gastric and pancreatic cancer cell lines. **Methods:** DOCK-AND-LOCK was used to link an anti-CD3 scFv to a stabilized Fab dimer of the humanized anti-Trop-2 mAb, hRS7. T-cell activation, cytokine induction and cytotoxicity were evaluated ex vivo using PBMCs or purified T cells with NCI-N87 gastric cancer as target cells. In vivo activity was assayed with NCI-N87 and Capan-1 (pancreatic) xenografts. **Results:** In presence of target cells and PBMCs, (E1)-3s did not cause excess cytokine production. When combined with (E1)-3s, peginterferonalfa-2a, which alone did not increase T-cell activation or raise cytokine levels over baseline, enhanced T-cell activation, but did not significantly increase cytokine induction. In vitro, (E1)-3s mediated a highly potent ($IC_{50}$=0.37 pM) T-cell lysis of NCI-N87 target cells. Inclusion of peginterferonalfa-2a potentiated the activity of (E1)-3s, improving the $IC_{50}$ (0.14 pM) by more than 2.5-fold ($P$=.0001). A more potent form of IFN$\alpha$, 20*-2b, enhanced the potency of (E1)-3s by more than 7-fold ($IC_{50}$=0.05 pM; $P$<.0001). In vivo, combining peginterferonalfa-2a with (E1)-3s delayed Capan-1 tumor out-growth longer than each single agent ($P$<0.0007, log-rank), with all animals cured in the combination group (MST>57 d), versus 18% and 14% in the (E1)-3s (MST=50 d) and peginterferonalfa-2a (MST=53 d) groups, respectively. Combination therapy delayed tumor out-growth of NCI-N87 compared to (E1)-3s or peginterferonalfa-2a single-treatment groups (MST>66 vs. 49 or 35 days, respectively; $P$<0.0094). **Conclusions:** T-cell-mediated killing of Trop-2-expressing pancreatic and gastric cancer was effectively induced by (E1)-3s and enhanced significantly with IFN$\alpha$.

**3057 General Poster Session (Board #124), Sun, 8:00 AM-11:45 AM**

**A systematic review of immune-related adverse event (irAE) reporting in clinical trials of immune checkpoint inhibitors (ICIs).** *Presenting Author: Wei-Wu Chen, Drug Development Program, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

**Background:** ICIs are active in various solid tumors. irAEs are associated with ICI therapy that can affect multiple organ systems. Limited data exist regarding the quality of irAE reporting in ICI clinical trial publications. **Methods:** A systematic search of citations from MEDLINE, EMBASE and Cochrane databases identified prospective clinical trials involving ICIs in advanced solid tumors from 2003-2013. A 21-point (pt) (title, abstract, introduction 3 pts; methods 6 pts; results 9 pts and discussion 3 pts) quality score (QS) was adapted from the CONSORT harms extension statement. Items included in the 21-pt QS addressed: methods of irAE assessment; duration of irAE evaluation; time of onset, management, and resolution of irAEs; and consistency of safety reporting with authors' conclusion. Two reviewers independently scored all trials and differences were resolved by consensus. Linear regression was used to identify factors associated with quality reporting. **Results:** After review of 2628 articles, 50 trial reports were included (50% phase I, 38% phase II, 6% phase III, and 6% not specified) with ICIs as monotherapy (52%) or combination treatments (48%). The median QS was 11.25 pts (range 3.5-17.5 pts). The median grade 3/4 toxicity rate reported was 20.5% (range 0-66%) and 29/50 (58%) of trials concluded that irAEs were tolerable. Of these 29 studies, 5 had grade 3/4 toxicity rates that exceeded 33%. Thirteen (26%) studies did not report any details on the outcome of irAEs and 22% did not provide information on how irAEs were managed. Six trials concluded that the ICI tested had reversible or manageable irAEs without presenting any data on irAE treatment or resolution. Multivariate regression analysis revealed that year of publication (within last 5 years) and journal impact factor >15 were significantly associated with a higher QS (p=0.002 for both). **Conclusions:** The reporting of irAEs due to ICIs is often incomplete. A standardized reporting method of irAEs that accounts for tolerability, management and reversibility is needed to ensure completeness and transparency of published trial data. This would enable a more precise evaluation of the therapeutic risk benefit ratio of ICIs.

**3058 General Poster Session (Board #125), Sun, 8:00 AM-11:45 AM**

**Antitumor efficacy of poxvirus-based active immunotherapy alone and in combination with subtherapeutic dosing with immune checkpoint inhibitors.** *Presenting Author: Susan P Foy, Bavarian Nordic Inc., Mountain View, CA*

**Background**: PROSTVAC PSA-targeted immunotherapy for metastatic castration-resistant prostate cancer is being tested in the PROSPECT phase 3 trial. Another poxvirus-based immunotherapy product, MVA-BN-HER2, was tested in early phase clinical trials for breast cancer. We hypothesized that active immunotherapy in combination with immune checkpoint inhibitors (ICI) CTLA-4, PD-1, PDL-1, or LAG-3 would yield significant synergistic benefit for anti-tumor efficacy in non-clinical models compared to any approach alone. Due to toxicities that are associated with some high dose ICI regimens that provide clinical benefit, we tested poxvirus-based immunotherapy combined with lower dose ICI regimens for anti-tumor efficacy. **Methods**: In therapeutic CT26-HER2 solid and metastatic tumor models, mice were administered MVA-BN-HER2 immunotherapy alone or in combination with single and double CTLA-4, PD-1, PD-L1, or LAG-3 ICI regimens. Dose regimens (10, 3, and 1 mg/kg) of ICIs alone and in combination with targeted active immunotherapy were also evaluated. **Results:** Synergistic benefit for anti-tumor efficacy in therapeutic mouse models was observed with various regimens combining poxvirus-based active immunotherapy with single and double ICI dosing. Complete tumor regression resulted from combining MVA-BN-HER2 immunotherapy with anti-PD-1 plus anti-LAG-3. In addition, ICI dose reduction retained significant improvement in survival in combination with MVA-BN-HER2 poxvirus active immunotherapy, even at 1 mg/kg dose. When given without MVA-BN-HER2, ICIs were ineffective at improving survival in lower dose regimens. **Conclusions**: Overall survival following poxvirus-based active immunotherapy shows synergy with single and dual combinations of ICIs in solid and metastatic tumor models. Lowering ICI doses to sub-therapeutic benefit levels still yields survival benefit when combined with poxvirus-based immunotherapy. Therefore, combination therapy of reduced-dose ICIs with poxvirus-based active immunotherapy is predicted to support improved clinical benefit, safety and tolerability over ICI therapy alone.

**3059 General Poster Session (Board #126), Sun, 8:00 AM-11:45 AM**

**Pretreatment serum levels of circulating myeloid-derived suppressor cells (MDSC) as a prognostic indicator in patients with gastrointestinal cancer.** *Presenting Author: Masahiko Shibata, Saitama Medical University, Saitama, Japan*

**Background:** A suppression of cell mediated immunity and malnutrition are commonly seen in patients with advanced cancer and it has been reported that chronic inflammation plays a key role in induction of these conditions. We have reported that MDSC: myeloid-derived suppressor cells, found as a new type of immune suppressor cells that is closely related to chronic inflammation, is increased in patients with various types of cancer including gastrointestinal, hepatopancreatic, breast, thyroid and ovarian cancers, and the levels of MDSC were closely related to systemic inflammation, immunosuppression and nutritional impairment. **Methods:** Peripheral blood mononuclear cells (PBMC) were collected from 123 preoperative patients with gastrointestinal cancer including 18 patients with esophageal, 43 with gastric, 62 with colorectal cancers, and these cells were used for the detection of MDSC (CD11b+CD14-CD33+) by flow cytometry. The circulating levels of MDSC were divided with 1.02% of PBMC which is the median level in healthy volunteer, and the prognosis of these patients was analysed with Kaplan-Meier method. **Results:** In patients with stage IV disease, the overall survival (OS) was significantly shorter (p<0.05) in patients with high MDSC levels than in those with low MDSC levels. Although in patients with high MDSC levels, both of OS and DFS (disease free survival) of the patients with stage IV diseases were shorter (both p<0.001) than those with stages I, II, and III diseases, there were no significant difference in those with low MDSC levels. Furthermore, in patients with colorectal cancer, the OS was shorter in stage IV patients with high MDSC levels than in stage IV patients with low MDSC levels. However, OS was not significantly different with MDSC levels in patients with Stages I, II, and III diseases. **Conclusions:** Therefore, the pretreatment levels of MDSC is effective as a good prognostic indicator especially in patients with advanced gastrointestinal cancers.

**3060 General Poster Session (Board #127), Sun, 8:00 AM-11:45 AM**

**Long-term survival benefit from ipilimumab treatment in metastatic uveal melanoma patients.** *Presenting Author: Mugdha Anand Deo, Universite Catholique de Louvain, Brussels, Belgium*

**Background:** Uveal melanoma is the most common intraocular malignant tumor with an incidence of approximately 5 cases per million per year. Around 50% of the patients relapse after a curative-intended local treatment. Liver metastasis is the most common site of recurrence. The standard treatment is a systemic chemotherapy with an alkylating agent but does not show an overall survival benefit. In this study, we assessed the overall survival benefit from ipilimumab treatment in metastatic uveal melanoma (MUM) patients based on its success in improving overall survival in cutaneous melanoma patients. **Methods:** A retrospective analysis was performed at the Cliniques Universitaires Saint-Luc to assess the long term survival benefit from ipilimumab treatment in previously treated MUM patients. The patients progressing after a first-line chemotherapy were sequentially included if their ECOG score was $\leq 2$. They received 3mg/kg of ipilimumab every 3 weeks with the median cycle number of 3.92. Tumor response was assessed every 3 months using CT scan according to RECIST. Progression free survival (PFS), overall survival (OS) and objective response (OR) were calculated using Kaplan-Meier and median duration of follow-up was calculated by univariate analysis. **Results:** Twenty-four previously treated MUM patients were included in this analysis. No OR was observed in 23 (96%) patients, while 1(4%) patient showed a late partial response after 9 months. Four (17%) patients showed a stable disease lasting $\geq 3$ months. With a median follow-up of 7.3 months, the median PFS was 2.8 months. The median OS was 9.7 months and OS rates at 12 and 24 months were 45.6% and 11.4%, respectively. **Conclusions:** Our findings confirm the very low response rate of ipilimumab in MUM patients. However, this drug has a clear benefit in increasing the overall survival for some patients than that obtained with standard chemotherapy. Most of the published data assessing the efficacy of ipilimumab in ocular melanoma are focused on response rate and median overall survival. We do think that looking at the survival rate at 1-2 years is more relevant to assess the efficacy of ipilimumab. How to select patients benefiting from ipilimumab remains a challenge.

**3061 General Poster Session (Board #128), Sun, 8:00 AM-11:45 AM**

**Phase I trial of ImmunoBody in melanoma patients.** *Presenting Author: Poulam M. Patel, University of Nottingham, Nottingham, United Kingdom*

**Background:** ImmunoBody is a DNA vaccine encoding a human IgG1 antibody with T cell epitopes grafted into its CDR regions. SCIB1 has 3 epitopes grafted from gp100 and one from TRP-2 antigens. The vaccine targets dendritic cells in vivo and stimulates high avidity T cells which result in elimination of established tumors in pre-clinical models. A clinical trial was conducted to determine safety and its ability to induce cellular immune responses. **Methods:** The vaccine was administered via Intramuscular injection with electroporation at 3 weekly intervals for 3 vaccinations, then at 3 and 6 months. In part 1 of the study,one patient with Stage III and 8 with stage IV melanoma were given escalating doses of SCIB1. The 4mg dose was selected for an expansion cohort (part 2) in fully resected patients, 8 with stage III and 6 with stage IV melanoma. Due to lack of toxicity a five further patients with stage IV M1b disease were given 8mg doses. **Results:** No dose-limiting toxicities were observed. The most common adverse event was injection site pain. 4/6 patients in the 2mg/4mg cohorts who received $>3$ doses of SCIB1, are still alive with a median survival time of 26 months. One patient had multiple tumor lesions which all decreased in size or disappeared following treatment except for one lesion which was resected. Immunohistochemistry demonstrated strong expression of PD.L1 on the tumor cells. All patients in part 2 remain alive and only three have progressed. The median survival time in Part 2 is 17 months from study entry and 22 months from diagnosis of metastatic disease. In part 1, one patient in the 0.4mg cohort, all three patients in the 2mg dose cohort and two patients in the 4mg dose cohort mounted an immune response to the vaccine-encoded antigens. 4/5 patients in the 8mg cohort made a $\gamma$IFN elispot response after T cell expansion in-vitro with frequencies exceeding 2% of blood lymphocytes. In part 2, all 14 patients responded immunologically. Six patients responded to all 4 epitopes, five patients responded to 3 epitopes and 3 patients responded to 2 epitopes. **Conclusions:** We demonstrate that SCIB1 is safe. Of 25 evaluable patients, 23 have shown immune responses following repeat dosing with 2 -8 mg of SCIB1. Detection of an objective clinical response and overall survival times are encouraging. Clinical trial information: NCT01138410.

**3062 General Poster Session (Board #129), Sun, 8:00 AM-11:45 AM**

**$\gamma\delta$ T cells in combination with Newcastle disease virus and dendritic cell therapy as a novel immunotherapeutic approach in treating of advanced lung cancer.** *Presenting Author: Jan Nesselhut, Praxisgemeinschaft fuer Zelltherapie, Duderstadt, Germany*

**Background:** $\gamma\delta$ T cells represent a minority white cell in blood, which expand dramatically in acute infections. $\gamma\delta$ T cells recognize antigens usually in a non-MHC-restricted fashion. A number of trials have shown that epithelial tumors were susceptible to $\gamma\delta$ T cell lysis. A combination of $\gamma\delta$ T cells with other cell based immune therapies such as Newcastle disease virus (NDV) or dendritic cell therapy (DC) may enhance their therapeutic efficacy. **Methods:** Peripheral blood mononuclear cells (PBMC) were isolated from 200 ml whole blood for treatment of n=6 patients with advanced metastatic lung cancer. $\gamma\delta$ T cells were expanded ex vivo with an amino –bisphosphonate (5 mM Zometa) and IL-2 (100 U/ml). After 10 to 12 days,$\gamma\delta$ T cells were harvested by MACS techniques. Purity and activity were analyzed by flow cytometry. $\gamma\delta$ T cells was administered to patients intravenously at monthly intervals. Additionally, patients receive a treatment with NDV and DC one day prior to the $\gamma\delta$ T cell application. **Results:** The mean percentage of $\gamma\delta$ T cells within the isolated PBMC was 2.3%. After in-vitro expansion the mean percentage increased to 70% with expansion rates up to 268 fold. Further purification by MACS leads to a mean percentage of 92% (highest 99.6%). The mean number of infused $\gamma\delta$ T cells was $3.82 \times 10^8$ for each treatment. Patients are 2-12 months under treatment to date. 2 patients had disease stabilization and are still alive (8 and 11 months). Another patient with bilateral SCLC and liver metastases showed a complete remission of the lung lesions and a remission of the liver metastases after two treatment cycles and is still alive (12 months). **Conclusions:** $\gamma\delta$ T cells can be efficiently expanded and purified. A combination of DC based therapy, NDV and treatment with $\gamma\delta$ T cells may improve the clinical outcome for advanced lung cancer patients .

**3063 General Poster Session (Board #130), Sun, 8:00 AM-11:45 AM**

**Specific increase in T-cell potency via structure-based design of a T-cell receptor for adoptive immunotherapy.** *Presenting Author: Karolina Malecek, NYU Medical School, New York, NY*

**Background:** Adoptive immunotherapy with antigen-specific T lymphocytes is a powerful strategy for cancer treatment. However, most tumor antigens are non-reactive "self" proteins, which presents an immunotherapy design challenge. Studies have shown that tumor-specific T cell receptors (TCRs) can be transduced into normal peripheral blood lymphocytes, which persist after transfer in about 30% of patients and effectively destroy tumor cells. Still, recent clinical trial with affinity-enhanced TCRs has resulted in severe effects due to cross reactivity to an unrelated peptide. Thus, the challenge for targeted T cell therapy remains to increase T-cell potency in order to improve clinical responses and ensure on-target specificity by avoiding unwanted cross reactivity. **Methods:** We used structure based design to predict point mutations of a TCR (DMF5) that enhance its binding affinity for an agonist tumor differentiation antigen-major histocompatibility complex (pMHC), Mart-1(27L) HLA-A2, which elicits full T cell activation to trigger immune responses. Structural based approaches have been used to increase TCR affinity, however their potential cross-reactivity has not been reported. Here, we analyzed the effects of selected TCR point mutations alone and in combination on T cell activation potency. Further, we analyzed their specificity and cross-reactivity with related antigens presented by different melanoma cell lines and donor-derived antigen presenting cells. **Results:** Our structure-based approach allowed us to rationally design sequence substitutions that improve binding in contact areas between the TCR and pMHC without increasing cross-reactivity with a wide variety of self-antigens. We identified and evaluated point mutations in critical TCR positions resulting in more potent T cell activation but maintaining overall specificity. When double and triple combination mutations were introduced, they exhibited an additive enhancement that further improved T cell activation while retaining a high degree of specificity. **Conclusions:** Such affinity-optimized TCRs could potentially be used in adoptive immunotherapy to treat melanoma while avoiding adverse autoimmunity effects.

**3064 General Poster Session (Board #131), Sun, 8:00 AM-11:45 AM**

**Phase I open-label, multiple ascending dose trial of MSB0010718C, an anti-PD-L1 monoclonal antibody, in advanced solid malignancies.** *Presenting Author: Christopher Ryan Heery, Laboratory of Tumor Immunology and Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD*

**Background:** MSB0010718C is a fully human IgG1 monoclonal antibody targeting the coregulatory protein Programmed Death (PD)-Ligand 1 (PD-L1). PD-1/PD-L1 interactions induce T-cell anergy, protecting tumor cells from elimination by the immune system. MSB0010718C is expected to have antitumor activity by restoring immune system activity and through ADCC. **Objectives:** Assess the safety of MSB0010718C and determine its maximum tolerated dose, and analyze its pharmacokinetic (PK) profile and target receptor occupancy (RO). **Methods:** Twenty-seven patients (pts) with refractory malignancies have been enrolled and treated to date. Dose escalation (3+3 design) has been performed for 4 dose levels (1, 3, 10, and 20 mg/kg, q2w). After dose-level safety was determined, accrual of additional pts was allowed in order to generate additional safety, PK, and RO data. **Results:** Four, 11, 6, and 6 pts have been accrued to dose levels 1–4, respectively. Median pt age is 64 years (range 34–77), ECOG 0–1, with a median of 2 prior lines of therapy for metastatic disease (range 0–5). Eleven pts received prior immunotherapy (range 1–2 lines). Twenty-three pts have been followed for at least 4 weeks by Jan 7, 2014. To date, 12 pts (52.2%) have come off study: 9 (39.1%) for progression, 2 (8.7%) for adverse events (AEs), and 1 (4.3%) for death. Grade ≥3 AEs attributable to drug comprised laboratory abnormalities in 3 pts (2 pts with grade 3 AEs; 1 pt with a grade 4 AE). One DLT was observed in 1 pt at dose level 4: an immune-related AE with creatine kinase increase, myositis and myocarditis. Data from 25 pts were evaluable for PK and RO analysis. Median time to maximum concentration for all doses was approximately 1.5 to 2 h after infusion, with a linear PK. Half-life was 63.4, 80.7, 93.9, and 115.1 h for dose levels 1, 2, 3, and 4, respectively, as measured by ELISA. Target RO data were available for 13 pts, as measured by PD-L1 binding on peripheral leukocytes via flow cytometry. Mean RO prior to second infusion was 75.7, 93.8, and 93.2% for dose levels 1, 2, and 3, respectively. **Conclusions:** MSB0010718C can be safely administered in doses up to 20 mg/kg IV every 2 weeks. Clinical trial information: NCT01772004.

**3065 General Poster Session (Board #132), Sun, 8:00 AM-11:45 AM**

**A phase II, single arm clinical trial involving an alternative cancer treatment psorinum therapy in patients with metastatic renal cell carcinoma.** *Presenting Author: Aradeep Chatterjee, Critical Cancer Management Research Centre and Clinic, Kolkata, India*

**Background:** We prospectively studied the clinical efficacy of an alternative cancer treatment "psorinum therapy" in treating metastatic renal cell carcinoma (mRCC). **Methods:** Our study was phase II, open level, single arm and single stage. Participants' eligibility criteria included (1) pathological confirmation of the malignancy (2) metastatic disease status (3) no prior conventional cancer treatments (4) Karnofsky performance status between 40- 70%. The primary outcome measures of the study were (1) to assess the radiological tumor response rate (using CT scanning procedure and following the RECIST criteria; (2) to assess how many participants survived at least 1 yr, 2yrs, 3yrs, 4yrs and finally, after 5 years. The secondary outcome measure was to assess the side effects of the investigational anti-cancer drug (psorinum) if any. Psorinum (an alcoholic extract of scabies slough and pus cells) was administered orally at a dose of 0.04ml/ Kg body weight/ day as a single dose on an empty stomach for a complete course duration of 2 yrs to all the participants along with allopathic and homeopathic supportive cares. **Results:** 78 participants included in the final analysis at the end of the study. According to the RECIST criteria complete response occurred in 11 (14.10%) cases and partial response occurred in 29 (37.18%) cases. 64 (82.05%) of them survived at least 1yr, 48 (61.54%) survived at least for 2yrs, 41 (52.56%) survived at least 3yrs, 29 (37.18%) survived at least 4yrs, 24 (30.77%) survived at least for 5yrs. These participants didn't receive conventional or any other investigational cancer treatments. **Conclusions:** The results of the study show clinical efficacy of psorinum therapy in treating patients with mRCC. The investigational drug psorinum is non- toxic. Randomized controlled clinical trial should be conducted for further investigation of this alternative cancer treatment in treating metastatic renal cell carcinoma to integrate it into the mainstream oncology.

**3066 General Poster Session (Board #133), Sun, 8:00 AM-11:45 AM**

**Fynomer-antibody fusions targeting HER2 and CD3 for selective killing of HER2 overexpressing tumor cells.** *Presenting Author: Richard Woods, Covagen AG, Zurich-Schlieren, Switzerland*

**Background:** A promising approach in the immunotherapy of cancer is to recruit T cells to attack tumor cells using bispecific therapeutics targeting a tumor-associated surface antigen and CD3 on T cells. Such therapeutics elicit T cell mediated lysis of tumor cells independent of T cell specificity. Fynomers are small 7 kDa globular proteins derived from the SH3 domain of the human Fyn kinase (Fyn SH3) that can be engineered to bind with antibody-like affinity and specificity to virtually any target of choice. Fynomers can be fused to N-terminal and/or C-terminal ends of antibodies to generate bispecific therapeutics (FynomAbs) with tailored architectures. Here, we describe the generation and characterization of anti-CD3/HER2 FynomAbs. **Methods:** Using phage display technology we have isolated Fynomers binding to HER2. After genetic fusion of these Fynomers to anti-CD3 antibodies the resulting bispecific fusion proteins were evaluated for their anti-tumoral activity. **Results:** We have generated novel bispecific FynomAbs which can simultaneously bind HER2 on tumor cells and CD3 on T cells. The bispecific HER2/CD3 targeting FynomAbs potently redirect T cells to HER2 expressing tumor cells showing picomolar tumor cell lysis activity on multiple cell lines. The activity was found to be highly specific, as no lysis of cells was observed in the absence of HER2 expression. In addition, the FynomAbs demonstrate an antibody-like pharmacokinetic profile in mice, which may translate into a convenient administration route without the need for continuous infusion. **Conclusions:** FynomAbs represent an attractive platform to generate bispecific molecules and can be produced using standard antibody technology (GMP production yield of 3.3 g/L at 1000 L scale achieved). We show here the successful generation of bispecific T cell recruiting FynomAbs with antibody-like biophysical and pharmacokinetic properties that allow the redirection of T cells specifically to tumor cells.

**3067 General Poster Session (Board #134), Sun, 8:00 AM-11:45 AM**

**A phase I study with LTX-315, an immunogenic cell death inducer, in patients with transdermally accessible tumors.** *Presenting Author: Paal Brunsvig, Oslo University Hospital, Oslo, Norway*

**Background:** LTX-315, a chemically modified 9-mer peptide derived from naturally occurring membrane-active host defence peptides, induces the release of potent danger signals (i.e. HMGB1) and tumor-associated antigens from treated tumor cells. Preclinical animal studies have demonstrated that treatment of a single tumor with LTX-315 generated a systemic anti-tumor immune response that eradicated distant lesions and prevented reoccurrence following tumor rechallenge. A phase I dose escalating open label, single centre study was designed to evaluate safety profile and determine recommended dose as measured by assessment of adverse events, laboratory values and tumor necrosis. Immunological responses to the injections were exploratory endpoints. **Methods:** Patients received weekly ultrasound guided injections of LTX-315 into a single tumor for a maximum of six injections. Cohorts 1 and 2 received 10% of the tumor volume until DLT or ≥ 50% necrosis of target tumor was observed. In cohort 3, a fixed dose of 4 mg was injected. **Results:** Fourteen patients with lymphomas, malignant melanomas or breast cancer were enrolled. The main safety issue was primarily flushing and transient hypotension related to the dose of study drug and independent of tumor type. Two patients experienced a DLT (hypotension grade 3 and 4). Tumor necrosis was seen in 5 patients. Two of the patients had a reduction in tumor volume ≥ 50%. Tissue necrosis and presence of tumor infiltrating lymphocytes (TILs) was observed in a breast cancer tumor. **Conclusions:** Based on the safety information it seems as LTX-315 is causing reactions that can be controlled by limiting the dose injected into the tumor; dosages ≤ 4.0 mg are well tolerated. The signs of tumor necrosis, presence of TILs and tumor regression without accompanying severe reactions confirms the rationale and the potential benefit of intratumoral injections with LTX-315. A new intratumoral study with LTX-315 at four European sites is ongoing with detailed characterization of immune response. Clinical trial information: NCT01058616.

**3068^ General Poster Session (Board #135), Sun, 8:00 AM-11:45 AM**

**First-in-human study of MM-141: A novel tetravalent monoclonal antibody targeting IGF-1R and ErbB3.** *Presenting Author: Steven J. Isakoff, Massachusetts General Hospital Cancer Center, Boston, MA*

**Background:** MM-141 is a novel tetravalent bi-specific monoclonal antibody that binds IGF-1R and ErbB3, and blocks both ligand dependent and independent IGF-1R/ErbB3/PI3K/AKT/mTOR signaling. In preclinical xenograft models, MM-141 was more active than a combination of anti-ErbB3 and anti-IGF-1R monoclonal antibodies. MM-141 potentiated the activity of gemcitabine, paclitaxel, docetaxel, tamoxifen, and everolimus. These results support the clinical development of MM-141 and a multi-arm Phase 1 study is underway. The completed monotherapy arm of this trial will be reported **Methods:** This is a Phase 1 dose-escalation study evaluating safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) properties of MM-141 as monotherapy (Arm A, n=15) and in combination with everolimus (Arm B) or with nab-paclitaxel and gemcitabine (Arm C). Patients in Arm A were dosed in a "3+3" design at weekly doses of 6 mg/kg (n=3), 12 mg/kg (n=4), or 20 mg/kg (n=4), or at biweekly doses of 40 mg/kg (n=4). Doses were escalated until the maximum tolerated dose (MTD) was identified, or until MM-141 was shown to be tolerable at the highest planned dose. **Results:** Arm A enrolled 15 patients with advanced solid tumors into the dose escalation portion of the study. No dose-limiting toxicities were observed at weekly dose levels of 6mg/kg, 12mg/kg, and 20mg/kg, or at the biweekly dose of 40mg/kg. Adverse events, regardless of relationship, that were reported with a frequency >15% included: vomiting (7/15), nausea (6/15), fatigue (4/15), abdominal pain (4/15), increased AP (4/15), dyspnea (4/15), diarrhea (3/15), anemia (3/15), increased AST (3/15), and rash (3/15). The safety, tolerability, PK and PD profile support weekly and biweekly MM-141 dosing. Detailed PK and PD data will be presented for all cohorts. Disease stabilization was observed in patients with Ewing's Sarcoma (1) and parotid gland carcinoma (1). An expansion cohort at a weekly dose of 20mg/kg (Arm D) is ongoing in patients with hepatocellular carcinoma. Data summarized here are from a data lock at 01/15/2014. **Conclusions:** A recommended dose level for MM-141 on each of weekly and bi-weekly schedules was established. Clinical trial information: NCT01733004.

**3069 General Poster Session (Board #136), Sun, 8:00 AM-11:45 AM**

**Regulatory T-cell inhibition plus antitumor immunotherapy targeted against cytomegalovirus (CMV) in patients with newly diagnosed glioblastoma multiforme (GBM).** *Presenting Author: Gordana Vlahovic, Duke University Medical Center, Durham, NC*

**Background:** Despite aggressive surgery, high-dose focused radiation, and toxic, multimechanistic chemotherapy, malignant gliomas (MG) remain almost universally fatal. The inherent biologic specificity of immunotherapy offers the prospect of targeting neoplastic cells more precisely. Dendritic cells (DCs) are endowed with an extraordinary ability to activate CD4+ and CD8+ T-cells, and DCs loaded with antigens derived from tumor cells (CMV pp65-LAMP mRNA) have the potential to induce potent antitumor immunity. Furthermore, regulatory T-cells (TRegs) which induce a state of reversible immunosuppression in MG and can be functionally inactivated with anti-CD25 antibody (Ab), while dramatically enhancing vaccine-induced immune responses. **Methods:** Eligible were gross totally resected patients (pts) with newly diagnosed GBM. Pts underwent leukapheresis followed by standard of care radiation/temozolomide (XRT/TMZ) therapy. After completion of XRT/TMZ, up to 12 cycles of TMZ 200 mg/m2/x5d were administered. Around Day 21 of the 1st cycle pts also received: anti-CD25 Ab treatment, vaccine #1, and non-specific autologous lymphocyte transfer (ALT). Vaccines #2 and #3 were given biweekly following vaccine#1. A 2nd leukapheresis was conducted prior to the 2nd cycle of TMZ. On Day 21 of the 2$^{nd}$TMZ cycle Vaccine #4 was administered. Pts were followed with serial MRIs until disease progression. **Results:** 7 patients (5 males) were treated. No adverse events attributable to vaccine treatment were observed. Median progression free survival was 23.5 months (95% CI:1.7 to 54.1). Median overall survival was 30.3 months (95% CI:11.8 to 60.8). Overall survival was calculated from the start of vaccine therapy to time of death or last contact if alive. **Conclusions:** Treatment with XRT/TMZ, DC vaccine and anti- CD25 Ab was well tolerated and results are promising. Due to the lack of adverse events, the protocol has been amended for future patients in this ongoing study. The number of vaccines had been increased to 8 (vs. 4) and anti-CD25 antibody is being given with the first two cycles (vs. with 1$^{st}$ cycle only) of adjuvant TMZ. Clinical trial information: 00626483.

**3070 General Poster Session (Board #137), Sun, 8:00 AM-11:45 AM**

**Development of a personalized cellular ex vivo CBL-b silencing cancer immune therapy.** *Presenting Author: Marc Oliver Salzberg, Apeiron Biologics AG, Vienna, Austria*

**Background:** The E3 ubiquitin ligase cbl-b has been identified as an important gatekeeper limiting T cell activation. Concordantly, the immune system of cbl-b deficient mice can effectively fight tumors, thereby validating cbl-b as an excellent target to enhance anti-tumor immune activity. We have recently shown in proof-of-concept experiments that transfer of transiently cbl-b silenced murine T cells had efficacy to enhance the anti-tumor immune response in mouse models. **Methods:** A design algorithm was used to screen for siRNAs that are highly effective to silence cbl-b, and the optimized siRNA was produced at a GMP manufacturer. PBMCs were isolated from healthy donors or cancer patients, transfected with siRNA by electroporation and immune cell phenotype and activation was determined by FACS and ELISA. For enhancement of DC vaccination responses, PBMCs were ex vivo silenced, and co-administrated with the DC preparations intranodally to the cancer patient. **Results:** We have established a highly efficient transfection protocol using a commercial electroporation device enabling us to simultaneously transfect T, B, NK cells and monocytes with minimal cell damage. Using this protocol, we have identified a siRNA that was able to shut down cbl-b expression for more than 7 days in stimulated human T cells, resulting in strong enhancement of T cell activation, cytokine production and proliferation. Moreover, simultaneous silencing of cbl-b in all immune cells of the PBMCs yielded additional advantages, most notably enhancing NK cell reactivity against tumor cell and IL-2 stimulation. Silencing of cancer patient PBMCs yielded similar results ex vivo and intranodal transfer of autologous cbl-b silenced cells together with activated DCs to patients with advanced cancers was feasible and well tolerated. **Conclusions:** To enable the clinical implementation of a cbl-b ex vivo silencing treatment, we have established and tested a protocol that can be easily performed on any clinical unit that applies adoptive cell therapies to patients. Based on these results, a Phase I trial for the systemic administration of cbl-b silenced PBMCs to patients with advanced cancers will be initiated.

**3071 General Poster Session (Board #138), Sun, 8:00 AM-11:45 AM**

**NY-ESO-1 specific CD4$^+$ $T_{helper}1$ cells for immunotherapy of cancer.** *Presenting Author: Simone Kayser, University Children's Hospital, Tübingen, Germany*

**Background:** NY-ESO-1 is an attractive target for adoptive T cell transfer (ACT) as it is expressed on a variety of tumors, but not in normal tissue except germline cells. Immune attack against cancer is mediated by cell lysis or induction of growth arrest through paralysis directly in tumor cells. The latter can be achieved by CD4$^+$, IFN-$\gamma$-producing $T_{helper}1$ (Th1) cells. Translation of this immune mediated mechanisms into clinical application has been limited by complex in vitro protocols and regulatory hurdles. **Methods:** We established a short protocol according to good manufacturing practice (GMP) to generate NY-ESO-1 specific T cells with focus on Th1 cells. After presensitization with overlapping NY-ESO-1-peptides, IL-2 and IL-7, T cells were enriched based on IFN-$\gamma$ capture technique. Cells were expanded using autologous feeder cells and IL-2, IL-7 and IL-15 and T-cell specificity and function was analyzed. **Results:** Large numbers of specific NY-ESO-1 CD4$^+$ T cells with a Th1 cytokine profile and lower numbers of cytokine secreting CD8$^+$ T cells could be generated with a sustained expansion potential. Manufactured CD4$^+$ T cells show strong specific responses with IFN-$\gamma^+$, TNF-$\alpha^+$ and IL-2$^+$ and induce growth arrest and apoptosis in tumor cells. The T-cell products did not include alloreactive or regulatory T cells. Specificity was confirmed with a new identified MHC class II matched NY-ESO-1 derived peptide and recognition of processed NY-ESO-1 Protein was demonstrated. **Conclusions:** Adoptive T-cell transfer by a novel cancer treatment-approach with tumor-antigen specific CD4$^+$ Th1 lymphocytes can be performed to boost anti-cancer immunity and is feasible with T cells from healthy allogeneic donors as well as with autologous T cells from cancer patients. The T-cell generation process was approved by the regulatory authorities. Due to the frequent expression of NY-ESO-1 in tumors the therapy is applicable to a large patient collective in different cancer entities.

**3072 General Poster Session (Board #139), Sun, 8:00 AM-11:45 AM**

**A phase Ib/IIa study of NEO-102: A therapeutic antibody for the treatment of advanced pancreatic and colorectal cancer.** *Presenting Author: Sandip Pravin Patel, Duke University Medical Center, Durham, NC*

**Background:** We have developed a chimeric monoclonal antibody (mAb) that targets a variant of MUC5AC that is expressed specifically by human pancreatic (P) and colorectal (C) tumors with minimal reactivity to normal GI mucosa. In the phase (ph) I trial of the initial formulation NEO-101, 5/19 patients (pts) had stable disease (SD) after completing their 1st course of treatment (tx) (4 doses) and overall survival (OS) of >12 months (mos) observed in 3 C and 2 P pts despite disease progression on standard (std) of care tx regimens. The current study utilizes NEO-102, a glycoengineered form of NEO-101 with improved stability and decreased RBC agglutination. **Methods:** A Ph Ib/IIa open label, multi-center dose-escalation clinical trial with NEO-102 is enrolling pts with advanced P and C cancer refractory to std therapy. NEO-102 is administered every 2 weeks with initial restaging at 8 weeks (after 4 doses) and every 8 weeks after if no progression. Primary objectives: measure efficacy by analysis of CT scans using RECIST criteria, OS, laboratory tests, and physical examination. Secondary objectives: determine safety and tolerability of escalating doses of NEO-102; assess pharmacokinetics (PK) and select immune responses to the mAb. Analyses of pt PBMCs for ADCC and immune cytokine profiling are underway to assess for immunologic outcome and for correlation with clinical benefit. **Results:** 12 pts are evaluable for toxicity (10 C, 2 P) and no DLT has been encountered. Grade 3 adverse events possibly related to NEO-102 are diarrhea and anemia. 8 pts are evaluable for efficacy at day 57, with 5 patients with SD (4/6 C, 1/2 P) and 3 with PD. The maximum number of doses administered is 9+ and the median duration of treatment has been 56+ days (Range 29-131+). **Conclusions:** Preliminary results with NEO-102 mAb have demonstrated signs of clinical activity based on stabilization of disease in heavily pretreated pts with P and C cancer. Safety has been established at the 3 mg/kg dose level and patients are currently being accrued to the 4 mg/kg dose level. If no DLT is observed at the current dose level, we will proceed with 4mg/kg as the dose utilized for expansion cohorts in P (30 pts) and C (40 pts). Clinical trial information: NCT01040000.

**3073 General Poster Session (Board #140), Sun, 8:00 AM-11:45 AM**

**Phase II trial evaluating HER2 targeted activated T cells in advanced HER2 low expressing breast cancer patients.** *Presenting Author: Deepa Bai Jagtap, Karmanos Cancer Institute, Wayne State University, Detroit, MI*

**Background: :** Despite improvements in the treatment of metastatic breast cancer (MBC), there are no curative treatment options. Anti-CD3 monoclonal antibody (mAb) activated T cells (ATC) armed with anti-CD3 x anti-HER2 bispecific antibody (HER2Bi) exhibit anti-HER2 cytotoxicity, proliferate, and secrete immunokines upon tumor engagement. Here we report preliminary results of a phase II immunotherapy trial in which 29 HER2 low expressing(0- 2+) patients (pts) with advanced breast cancer who received infusions of HER2Bi armed ATC (aATC) . Pts were evaluated for time to progression (TTP), overall survival (OS), and immune responses as end points. **Methods:** Peripheral blood mononuclear cells (PBMC) obtained by leukapheresis were activated with anti-CD3 mAb and expanded with IL-2. aATC were harvested, armed with HER2Bi and cryopreserved in aliquots with a target dose of ≥ 48 billion cells. Pts received oncologist's choice of chemotherapy (4 cycles or 4 months) followed by 3-4 infusions of aATC. A subset of 5 pts received 250 mg/m$^2$cyclophosphamide to create immunologic space prior to aATC infusions. The median age was 53.5 yrs (range 29-75yrs) with 59% of pts over the age of 50yrs. **Results:** Nineteen pts were ER positive and had received ≥ 2 lines of endocrine therapy and 16 out of 19 ER positive pts had also received at least 2 lines of chemotherapy for MBC . The overall response rate was 31% defined as stable disease . Anti-tumor immune responses were detected in these pts. The K-M curve for all of the pts who received armed ATC reveals a median OS of 16.7 months (from enrollment). In pts who were evaluable (received ≥ 48 billion aATC), 5 of 16 (31%) were stable at 4 months after all aATC infusions. In pts who received < 48 billion aATC, 2 of 8 (25%) pts were stable at 4 months after aATC infusions. Six severe adverse events (grade ≥3), were documented as probably or definitely related to infusions, in 5 different patients. **Conclusions:** These clinical results suggest that targeting the high risk HER2 low expressing tumors by this approach may provide survival benefit without excessive toxicity. Clinical trial information: NCT01022138.

**3074 General Poster Session (Board #141), Sun, 8:00 AM-11:45 AM**

**An adoptive immunotherapy approach for colorectal cancer (CRC) patients.** *Presenting Author: Marco Bregni, Ospedale di Circolo, Busto Arsizio, Italy*

**Background:** Adoptive T-cell transfer (ACT) refers to an immunotherapeutic approach in which anti-tumor T lymphocytes are identified, grown *ex vivo* and re-infused into the cancer patients. This strategy was successfully applied in metastatic melanoma and renal cell carcinoma. However, adoptive immunotherapy do not play an important role in the treatment of advanced CRC. We developed an ACT protocol for CRC using as source of tumor antigens the irradiated primary CRC cell lines, captured by dendritic cells (DC) to stimulate *in vitro* a specific autologus activation of patient's T cytotoxic lymphocytes (CTL) against tumor. **Methods:** 78 CRC patients were enrolled. Tumor tissues were obtained at surgery, together with 100 ml of heparinized peripheral blood. Tumors were mechanically dissociated to a single-cell suspension and cultured to obtain a primary cell line from each patient. DCs were generated from monocytes, cultured with recombinant human Interleukin-4 and recombinant human Granulocyte- Macrophage Colony-Stimulating Factor for 6-7 days. Anti-tumor CTLs were elicited in co/micro-cultures using DCs, autologous apoptotic tumor cells and T CD8+ lymphocytes enriched effectors, in presence of weakly irradiated T CD4+ lymphocytes, Interleukin 7 and Interleukin 12, with weekly stimulation. CTLs Interferon-$\gamma$ (IFN-$\gamma$) secretion was assessed by ELISpot assay. **Results:** Primary tumor cell lines were obtained from 20 out of 78 patients, with a success rate of 25,6%. DCs were generated from 26 patients, and 6 had the corresponding primary tumor cell line. Co/micro-cultures were set up for 6 patients. ELISpot results showed a strong and significant IFN-$\gamma$ secretion at the third, fourth and fifth stimulations for one patient and at the second for another patient, whereas for three patients a weak secretion was detected during the second and third stimulations. **Conclusions:** The percentage of success in the establishment of primary colon cell lines was higher than those reported in literature, although the intestinal flora adversely affected their obtainment. The generation of tumor-specific CTLs could be useful for supporting an ACT approach in CRC.

**3075 General Poster Session (Board #142), Sun, 8:00 AM-11:45 AM**

**Long-term follow up for a phase I trial HER2/neu-targeted T cells in women with advanced breast cancer.** *Presenting Author: Lawrence G. Lum, Karmanos Cancer Institute, Wayne State University, Detroit, MI*

**Background:** Anti-CD3 x anti-Her2 bispecific antibody (Her2Bi) retargeting transforms activated T cells (ATC) into non-restricted MHC specific cytotoxic T cells. This study reports a phase I immunotherapy trial beginning in 2001 (NCT00027807) in 23 women with Her2 0-3+ metastatic breast cancer consisting of 8 infusions of HER2Bi armed ATC (aATC) in combination with interleukin 2 (IL-2) and granulocyte-macrophage-colony stimulating factor to evaluate safety, feasibility, time to progression, median overall survival (OS), T cell trafficking and immune responses. **Methods:** ATC were expanded in IL-2 after anti-CD3 stimulation of mononuclear cells obtained from leukapheresis. Groups of 3 patients (pts) received 5, 10, 20, or 40 x 10e9 aATC per infusion. **Results:** Total episodes of Grade III-IV side effects for 23pts in decreasing order were chills, headache, nausea/vomiting, back pain, hypertension, and death of 1 pt from congestive heart failure due to digoxin toxicity. aATC persisted in the blood for a week or more and trafficked to tumors. Twelve out of 22 (54.5%) had stable disease (SD) or better. OS was 36.2 months (m) for all pts, 57.4 m for Her2 3+ pts (n=7), and 27.4 m for Her2 0-2+ pts (n=16) with a median follow-up of 36.2 m. For pts with SD, the OS was 57.9 m in the HER2 3+ pts (n=4) and 40 m in the HER2 0-2+ pts (n=7). For pts with progressive disease (PD), OS was 36.6 m in the Her2 3+ pts (n=3) and 21.3 m in the Her2 0-2+ pts (n=9). There was 1 partial response. aATC infusions induced anti-tumor cytotoxicity that persisted >4 m, Th1 cytokines, and increases in IL-12 after 2 weeks. Phenotyping, imaging of In labeled aATC, and tumor biopsies show that aATC circulate > 96 hrs, localize and persist in tumors. **Conclusions:** aATC infusions are safe with manageable side effects. The OS of 36.2 m is encouraging in heavily pretreated pts. Targeting HER2 positive and negative tumors with aATC induced anti-tumor responses, increased Th1 cytokines, and IL-12 serum levels. The clinical responses suggest that aATC infusions may provide a survival benefit in pts with both stable and progressive disease. These results provide the rationale for conducting phase II trials. Clinical trial information: NCT00027807.

**3076 General Poster Session (Board #143), Sun, 8:00 AM-11:45 AM**

**A phase 1 study of MM-121 (a fully human monoclonal antibody targeting the epidermal growth factor receptor family member ErbB3) in combination with cetuximab and irinotecan in patients with advanced cancers.** *Presenting Author: James M. Cleary, Dana-Farber Cancer Institute, Boston, MA*

**Background:** ErbB3-EGFR heterodimers have been implicated in resistance to targeted and conventional therapies across multiple malignancies. **Methods:** This phase 1 trial assessed the safety, tolerability, and pharmacokinetic (PK) properties of MM-121 in combination with cetuximab (Part 1) or with cetuximab and irinotecan (Part 2) in patients (pts) with advanced solid cancers. Pts were dosed in a "3+3" design with escalating doses of MM-121 and cetuximab without (Pat 1) or with (Part 2) biweekly irinotecan. **Results:** Part 1 enrolled 34 pts with a median age of 60. Common (>25%) adverse events (AE) of any grade were: fatigue (64.7%), dermatitis acneiform (47.1%), hypomagnesemia (47.1%), diarrhea (44.1%), decreased appetite (32.4%) and hypokalemia (26.5%). One DLT was observed in the first cohort of Part 1 (G3 lung infection) and dose escalation was able to continue to the highest recommended doses of MM121 and cetuximab. One pts (CRC) had a complete response (CR), and three pts (NCSLC (2), cholangiocarcinoma) had a partial response (PR). Twelve pts had a best response of stable disease (SD). Part 2 enrolled 14 pts with a median age of 58. Common (>25%) AEs of any grade were: diarrhea (92.9%), hypokalemia (57.1%), nausea (50%), fatigue (42.9%), hypomagnesemia (37.5%), decreased appetite (35.7%), dermatitis acneiform (28.6%), mucosal inflammation (28.6%), dehydration (28.6%), and weight decrease (28.6%). Three DLTs were observed in Part 2: one at the first dose level (G3 diarrhea), and two at the second dose level (G3 mucositis with G4 neutropenia and G3 UTI, dehydration, and diarrhea with G4 neutropenia and cardiac arrest and G5 respiratory failure) and an MTD was reached. One CRC pts who previously had developed acquired resistance to cetuximab had a PR, and one pts had a best response of SD in Part 2 of the study. Mandatory pre- and post-treatment biopsies are analyzed to assess the PD correlates of response and resistance to this combination. **Conclusions:** The HER3 antibody, MM121, can be combined with cetuximab +/- irinotecan and had modest activity in a population of refractory solid tumor pts. Clinical trial information: NCT01451632.

**3077 General Poster Session (Board #144), Sun, 8:00 AM-11:45 AM**

**Survival effect of bi-shRNA$^{furin}$/GMCSF DNA-based immunotherapy (FANG) in 123 advanced cancer patients to $\alpha$-interferon-ELISPTOT response.** *Presenting Author: John J. Nemunaitis, Mary Crowley Cancer Research Centers, Dallas, TX*

**Background:** Over the last 3 years, follow up in a series of Phase I (study # CL-PTL-101) and phase II studies (study # CL-PTL-105, -107, -114, -110, -112) involving FANG (BB-IND 14205) have been performed involving 123 advanced cancer patients, most of whom previously failed prior systemic therapy. ELISPOT assay which quantitatively measures responding mononuclear cell $\gamma$IFN release to patient personal tumor was utilized to track immunotherapy activity. **Methods:** Sequential ELISPOT assessment utilizing patient blood mononuclear cells and autologous tumor tissue as antigen source (harvested prior to immune therapy) were measured at baseline and sequentially afterward. **Results:** Sixty-four advanced cancer patients received monthly intradermal injections of FANG and 53 had FANG constructed but elected other therapy (No FANG group). Median survival of FANG treated patients was 729 days vs. No FANG patients 260 days, p=0.001. Patients (4%) who were ELISPOT positive at baseline or before receiving FANG or who crossed over (1%) from No FANG to FANG as part of Phase II trial were excluded. Forty-seven patients received FANG and had sequential ELISPOT analysis. Thirty-five were ELISPOT positive, and 12 were ELISPOT negative. Median survival of the FANG ELISPOT positive patients was 995 days vs. 554 days of the ELISPOT negative patients (p=0.011). No significant toxic effect was demonstrated to FANG over the three year follow up period. Seventy-one percent of the ELISPOT positive FANG treated patients were alive at 2 years and 44% were alive at 3 years. By comparison, only 25% of the FANG treated patients who were ELISPOT negative were alive at 2 years and none have reached 3 year survival. **Conclusions:** Treatment with FANG demonstrates safety and suggests survival benefit in coordination with $\gamma$-interferon ELISPOT assessment. Randomized phase II assessment is ongoing. Updated results will be presented. Clinical trial information: NCT01061840, NCT01309230, NCT01505166, NCT01453361, NCT01867086, NCT01551745.

**3078^ General Poster Session (Board #145), Sun, 8:00 AM-11:45 AM**

**Ascending dose trials of a retroviral replicating vector (Toca 511) in patients with recurrent high-grade glioma.** *Presenting Author: Joan M. Robbins, Tocagen Inc., San Diego, CA*

**Background:** We are conducting ascending dose trials in subjects with High Grade Glioma (HGG, NCT01156584 and NCT01470794), using an investigational retroviral replicating vector (Toca 511, vocimagene amiretrorepvec). Toca 511 encodes an optimized yeast cytosine deaminase that converts 5-fluorocytosine (5-FC) to the anticancer drug 5-FU in infected tumors. Preclinical models provide support for a dual mechanism of action of Toca 511+5-FC that includes both direct killing of tumor by locally produced 5-FU, and induction of a local and systemic immunotherapeutic response resulting in: 1) long term survival after cessation of 5-FC treatment and 2) resistance to tumor re-challenge. **Methods:** Toca 511 is administered once, followed by repeat courses of oral Toca FC (an extended-release formulation of 5-FC). One trial employs direct intratumoral injection of Toca 511 and the other administration into the cavity wall after resection of a recurrent tumor. **Results:** Over 30 patients have been treated in each of these dose escalation trials with 6 and 5 viral dose levels respectively studied to date. Treatment at all dose levels has been well tolerated. Post-treatment resection in some patients showed viral protein and DNA and RNA sequences including the CD protein and gene, suggesting viral spread and persistence. MRI changes consistent with tumor regression and clinical improvements were observed in some patients post-Toca FC dosing. Pooled survival data in these ongoing studies show 82% (28/34) and 46% (13/28) survival at 6 months and 12 months, respectively. **Conclusions:** Completion of these studies is planned, including further dose escalation of Toca 511 and of Toca FC. A third ascending dose study, NCT01985256, in patients with HGG, will evaluate the safety and tolerability of Toca 511 injected intravenously followed by injections into the cavity wall after resection and repeated courses of Toca FC. The current studies provide evidence for the same dual mechanism of action noted in preclinical studies and survival data warrant investigation in a larger clinical trial. Clinical trial information: NCT01156584, NCT01470794, NCT01985256.

**3079 General Poster Session (Board #146), Sun, 8:00 AM-11:45 AM**

**Rapid cell expansion (RACE) technology for production of engineered autologous T-cell therapy: Path toward manageable multicenter clinical trials in aggressive NHL with anti-CD19 CAR.** *Presenting Author: Marc Better, Kite Pharma, Santa Monica, CA*

**Background:** Engineered autologous T cell therapy is proving to be a promising method to treat a variety of tumor types. An ongoing National Cancer Institute (NCI) Phase 1/2a study in patients with refractory B cell malignancies has been particularly encouraging, with data presented most recently at the ASH 2013 annual meeting. To prepare for Kite-sponsored multicenter trials, a rapid and compliant manufacturing process has been developed. Because refractory B cell malignancies can progress quickly, it is important to reduce the time between apheresis of patient PBMCs and administration of the engineered T cells. **Methods:** PBMCs from normal donors and patients with B cell malignancies were stimulated in vitro with anti-CD3 antibody in the presence of IL-2 to initiate T cell growth. The cells were then transduced with a gamma-retroviral vector containing an anti-CD19 CAR gene and propagated in culture to generate sufficient engineered T cells for administration. **Results:** We have developed a 6-day manufacturing process in serum-free media without the use of CD3/CD28 beads. Development studies have demonstrated in vitro analytical comparability to cells produced using an open system at the NCI. **Conclusions:** Kite in conjunction with the NCI Surgery Branch has developed a rapid and efficient proprietary process for the generation of anti-CD19 CAR cells. A Kite-sponsored multicenter clinical trial in patients with aggressive non-Hodgkin lymphoma using T cells generated by this new manufacturing process is expected to begin in early 2015.

**3080 General Poster Session (Board #147), Sun, 8:00 AM-11:45 AM**

**PROSTVAC, PSA-targeted immunotherapy: New evidence for mechanism of action.** *Presenting Author: Stefanie J Mandl, Bavarian Nordic Inc., Mountain View, CA*

**Background:** PROSTVAC is being tested for treatment of metastatic castration-resistant prostate cancer in the PROSPECT phase 3 trial. PROSTVAC immunotherapy comprises subcutaneous dosing in a heterologous prime-boost regimen with recombinant vaccinia virus (PROSTVAC-V) for priming plus recombinant fowlpox virus (PROSTVAC-F) for boosting doses. Both products encode transgenes for PSA as the target tumor antigen plus TRICOM (B7-1, ICAM-1 and LFA-3) to enhance immune activation. Data from clinical and nonclinical studies provide evidence for mechanism of action potentially leading to improved overall survival following PROSTVAC immunotherapy. **Methods:** Subjects from a randomized double-blind placebo controlled Phase 2 study (NCT00078585) received PROSTVAC or empty vector. IFN-$\gamma$ ELISPOT was performed on archived samples meeting viability requirements. Immune responses in therapeutic prostate cancer mouse studies were evaluated by immunoassays. **Results:** Subjects demonstrated significant enhancement of PSA-specific T cell responses following PROSTVAC immunotherapy compared to control subjects. T cells against endogenous, non-PSA tumor antigens (antigen spread) were also elevated following PROSTVAC immunotherapy. Treatment with PROSTVAC-V/F in mice amplified the magnitude and quality of activated PSA-specific T cells following heterologous vs. homologous prime-boost dosing regimen. Tumor-infiltrating CD4 and CD8 T cells were highly functional as evidenced by expression of activation markers, production of multiple cytokines and amplified cytotoxic T cell activity. In vivo CD4 and CD8 T cell depletion revealed that both subsets contributed to anti-tumor efficacy. PROSTVAC immunotherapy also resulted in reduced Treg suppressor cells among total tumor-infiltrating T cells. **Conclusions:** PROSTVAC immunotherapy activates broad, highly functional T cell immunity to PSA directly elicited by active immunotherapy and to endogenous tumor antigens via immune-mediated antigen spreading. These results from clinical and nonclinical studies are predicted to explain improved overall survival following PROSTVAC immunotherapy in a phase 2 trial in advance of evidence from the ongoing phase 3 PROSPECT trial. Clinical trial information: NCT00078585.

**3081 General Poster Session (Board #148), Sun, 8:00 AM-11:45 AM**

**NCI experience using yeast-brachyury vaccine (GI-6301) in patients (pts) with advanced chordoma.** *Presenting Author: Christopher Ryan Heery, Laboratory of Tumor Immunology and Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD*

**Background:** Saccharomyces cerevisiae has been genetically modified to express Brachyury (Br) protein and developed under a CRADA with GlobeImmune/NCI as a heat-killed immune-stimulating therapeutic cancer vaccine (GI-6301). Br is a member of the T-box family of transcription factors and is a key factor in embryonic (mesoderm) development. Chordoma, a rare tumor of the notochord (derived from mesoderm) is known to overexpress Br while expression in normal adult tissue is minimal or not present. Preclinical work has demonstrated Br specific T cells can lyse human Chordoma cells expressing Br in an MHC restricted fashion. **Methods:** We enrolled a cohort of 7 pts with advanced Chordoma on an expansion cohort of a phase I study (NCT01519817) and evaluated their clinical and immunologic outcomes. All pts had undergone previous radiation (median 470 days since radiation: range 111-1883). All received 40 yeast units of vaccine every 2 weeks x 7 with first restaging at day 85. If stable, pts went on to monthly dosing with restaging scans every 2 months. The primary endpoint was safety, but clinical outcomes were followed as well. Br-specific T cell responses were also analyzed by flow-cytometry intracellular staining (ICS) of CD4 and CD8 T lymphocytes for the cytokines IFN-g, TNF, and IL-2. **Results:** All 7 pts had undergone extensive previous treatment. Median age was 59 (41-66). Two pts had relatively stable disease for 6 and 12 months, respectively, coming on the study, and both remain stable at day 141 and 197 restaging, respectively. The remaining 5 had progressive disease at enrollment. Of those 5, 1 had a decrease in index lesions $>$30% at day 141 with a confirmed PR on repeat scan 4 weeks later. 1 has stable disease through day 141 restaging. The other 3 progressed at day 141 restaging. Adverse events were minimal with injection site reaction being the most common (13 events in 63 doses (21%), 6 of 7 pts (86%)). Two of 7 pts had a Br-specific T cell response by ICS. **Conclusions:** This cohort of pts with advanced Chordoma in the phase I study with GI-6301 vaccine demonstrated safety and enhanced immune response with a confirmed PR. These findings are encouraging and warrant further study using this vaccine in pts with Chordoma. Clinical trial information: NCT01519817.

**3082 General Poster Session (Board #149), Sun, 8:00 AM-11:45 AM**

**Combination between a long-acting engineered cytokine (NKTR-214) and checkpoint inhibitors anti-CTLA-4 or anti-PD1 in murine tumor models.** *Presenting Author: Seema S. Kantak, Nektar Therapeutics, San Francisco, CA*

**Background:** Durability of response is the hallmark of immunotherapy but only a fraction of patients experience this prolonged benefit. Recent studies suggest more patients may benefit from combining agents with complementary immunological mechanisms. NKTR-214 is an engineered form of IL-2 that directly activates cytotoxic T cells by targeting the IL-2 receptor beta subunit and exhibits a pharmacokinetic profile that is more like an antibody than a cytokine. Anti-CTLA-4 and anti-PD1 are antibodies that block negative regulation of T cells. Here we show that combining either antibody with NKTR-214, provides significant tumor growth inhibition in resistant mouse models. **Methods:** For combination studies, BALB/c mice bearing established CT-26 (Colon Carcinoma) or EMT6 (Mammary Carcinoma) tumors were treated with single agent NKTR-214, murine anti-CTLA-4 antibody, murine anti-PD-1 or the two agents in combination. **Results:** NKTR-214 exhibits a plasma and tumor exposure that is 600-fold and 500-fold greater respectively, than an equivalent dose of the original IL-2 cytokine. The optimized PK profile allows q9d dosing schedule instead of bid; the latter being typical for cytokines. In both the EMT-6 and the CT-26 models, the combination of NKTR-214 with anti-CTLA-4 provided 10/12 and 8/12 tumor-free animals respectively, up to 40 days after the last dose and showed clear synergy compared to either agent alone. The combination with anti-PD1 was also synergistic and showed tumor regression in 5/10 animals. Single agent administration did not show any significant tumor growth inhibition in these models. The combinations were well tolerated with no body weight loss or other clinical signs. **Conclusions:** NKTR-214 directly stimulates cytotoxic T cells and is therefore complementary to the mechanism of checkpoint inhibition using antibodies. The favorable pharmacokinetics of NKTR-214 enables dosing schedules that are more like an antibody allowing convenient combination with other antibodies. Combining NKTR-214 mediated T cell activation with CTLA-4 or PD1 blockade is synergistic in murine models of cancer and holds the promise for durable responses in humans.

**3083 General Poster Session (Board #150), Sun, 8:00 AM-11:45 AM**

**Immunomodulatory effects of 5-azacytidine in acute myeloid leukemia.** *Presenting Author: Anne Letsch, Hematology,Oncology and Tumorimmunology, Charité CBF, Berlin, Germany*

**Background:** Specific immunotherapeutic approaches in acute myeloid leukemia have recently attracted interest. Several leukemia associated antigens have been identified and early vaccine trials demonstrated promising efficacy. However vaccination strategies might be improved by combination with current standard treatment or other reagents with immunomodulatory activity in order to enhance leukemia directed immune responses. An attractive combination partner is 5-Azacytidine (5-AZA). In preparation of combination studies of specific immunostimulation in concert with 5-AZA, the immunomodulatory effects of 5-AZA on leukemic cells have been analyzed. **Methods:** The leukemic cell lines ML-2, HL-60, TF-1, Oci-AML5, UT-7, THP-1, NB4, SigM5, and HEL as well as blasts from 3 leukemic patients have been incubated with 2$\mu$M 5-AZA for 9 days. Before and during stimulation (day 5, 7 and 9) the following markers have been analyzed by flow cytometry: CD80, CD86, HLA-DR, HLA-ABC, CXCR4, PD-L1, PI-9 and INDO. Mean fluorescence intensity (MFI) of the single markers were compared at different time points. **Results:** The data obtained on the 9 cell lines and blasts from 3 leukemic patients stimulated by 5-AZA have been heterogenous, but some phenomena were observed in a majority of cell lines and patients. Generally in favour of immune control of leukemic cells are the following mechanism: a) Upregulation of CD86 in 8 of 9 cell lines (8/9) and 0 of 3 patients (0/3), b) downregulation of INDO (7/9 and 1/3), and c) downregulation of PI-9 (3/9 and 2/3). On the other hand we observed mechanisms, which would theoretically enhance immune evasion of leukemic cells: a) downregulation of MHC-class-I molecules (7/9 and 2/3), b) upregulation of PD-L1 (4/9 and 2/3) and c) increase of CXCR4 (8/9 and 2/3) by incubation with 5-AZA. The other markers remained generally unchanged. **Conclusions:** Results should be confirmed on mRNA-level and by functional analyses. Nevertheless our current data already points to interesting immunomodulatory effects of 5-AZA, being an attractive candidate as adjuvant in combination therapies with other immune interventions in leukemia and other malignancies. Potential leukemic and tumor promoting effects of 5-AZA have to be further evaluated.

**3084 General Poster Session (Board #151), Sun, 8:00 AM-11:45 AM**

**18F-fluorodeoxyglucose PET/CT imaging for predicting treatment response in patients with advanced melanoma treated with anti-PD1 immunotherapy.** *Presenting Author: Miguel Hernandez Pampaloni, University of California San Francisco, San Francisco, CA*

**Background:** Immune checkpoint inhibitors have dramatically altered the landscape of melanoma therapeutics over the past few years. Anti-PD1 therapy has been reported to produce durable tumor regression in phase 1 trials. Development of biomarkers to evaluate treatment response are pivotal for optimizing individual therapy. We aim to evaluate whether pretreatment 18F-fluorodeoxyglucose (FDG) PET/CT imaging can be a predictor of tumor response or disease progression in patients on anti-PD1 therapy as a marker of tumoral increased glucose utilization rate. **Methods:** Twenty-three patients (15 males) with BRAF wild type mutation advanced melanoma who failed prior treatment with antineoplastic regimens and started therapy with MK-3475 alone were included in the study. Standard of care whole-body FDG PET/CT imaging was performed at baseline before the anti-PD1 therapy was initiated (10 $\pm$ 5 days interval time between FDG PET/CT imaging and therapy start date). FDG uptake was semi-quantitatively measured by maximum standardized uptake value (SUV). Treatment response was evaluated with computed tomography imaging by central radiologic review according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. **Results:** Sixteen patients showed significant and stable tumor regression to date while seven patients demonstrated tumor progression by conventional imaging wtihin 6 months of the therapy starting date. All patients with treatment response remain currently on MK-3475 monotherapy. Of the seven patients who showed disease progression, all had at least 2 or more abnormal hypermetabolic foci by FDG PET/CT imaging (SUV max 9.44). Interestingly, of the 16 patients with maintained tumor regression, 8 patients did not showed any hypermetabolic finding, while the remaining 8 patients showed hypermetabolic lesions. (SUV max 6.0). **Conclusions:** Absence of abnormally increased FDG uptake by PET/CT imaging may be a useful tool to predict durable anti-PD1 immunotherapy response, while pre-therapy, single time point increased glucose utilization rate could represent a necessary but insufficient step for the assessment of disease progression.

**3085 General Poster Session (Board #152), Sun, 8:00 AM-11:45 AM**

**Intratumoral vaccination with activated allogeneic dendritic cells in patients with newly diganosed metastatic renal cell carcinoma (mRCC).** *Presenting Author: Anders Magnusson, Department of Radiology, Uppsala University, Uppsala, Sweden*

**Background:** Accumulating data indicate that the efficient induction of antigen-specific CTLs characterizing viral infections is caused by cross-priming where infected DCs produce an unique set of inflammatory factors that recruit and activate non-infected "bystander" DCs. Accordingly, we have developed a cellular adjuvant consisting of activated DCs producing high levels of DC-recruiting and DC-maturating factors in a sustained fashion. This concept doesn´t require MHC-compatibility between injected cells and the patient and therefore introduces the possibility of using pre-produced and freeze-stored DCs from healthy blood donors as an "off-the-shelf" anti-tumor vaccine when injected intratumorally. **Methods:** 12 patients with newly diagnosed mRCC (5 with poor prognosis according to Heng criteria) where included in a clinical phase I/II study. Vaccine cells (50 doses) were produced from a leukapheresis-product from one healthy blood donor and subsequently deep-frozen. 5-20 x 10(6) vaccine cells were injected intratumorally twice with 2 weeks interval before nephrectomy. **Results:** No vaccine-related severe adverse events were observed. 9 out of 11 evaluated patients exhibited an increase in circulating tumor-specific lymphocytes (IFN-gamma ELISPOT) after vaccination. A strong infiltration of CD8+ T cells was found in 7 out of 12 removed kidney tumors, of which 5 tumors, to the best of our knowledge, exhibit the most intensive and general infiltration of CD8+ T cells ever reported in any human solid tumor. Median overall survival (mOS) in the poor prognosis (PP) group is still not reached but has already passed (without addition of targeted therapy) the expected mOS in poor prognosis patients on targeted therapy (9.8 vs 7.8 months). 40% of the patients in the PP-group have to date (Jan 2014) survived for more than 17 months (without addition of targeted therapy) compared to an expected 17 months-survival of 20% in PP patient groups on targeted therapy. **Conclusions:** Our findings indicate that intratumoral injections of pre-activated allogeneic DCs is safe and induce a systemic CTL-mediated anti-tumor response that may prolong survival in mRCC patients. Clinical trial information: NCT01525017.

**3087 General Poster Session (Board #154), Sun, 8:00 AM-11:45 AM**

**Randomized phase II study of personalized peptide vaccination with cyclophosphamide pretreatment in refractory advanced biliary tract cancer patients.** *Presenting Author: Tetsuro Sasada, Department of Immunology and Immunotherapy, Kurume University School of Medicine, Kurume, Japan*

**Background:** We previously demonstrated the feasibility of personalized peptide vaccination (PPV), in which appropriate vaccine peptides are individually selected for each patient to boost anti-cancer immunity, in advanced biliary tract cancer (BTC) patients. This study was conducted to assess whether cyclophosphamide (CYP) pretreatment could improve the clinical efficacy of PPV in refractory advanced BTC patients. **Methods:** We conducted a randomized phase II study to examine the effect of CYP pretreatment (100 mg, daily for 7 days before each cycle of 6 vaccinations) on PPV for advanced BTC patients, who failed or progressed after standard chemotherapy regimens. For PPV treatment, a maximum of 4 peptides were selected from 31 candidate peptides based on the HLA class I types and antigen-specific humoral immune responses before vaccination, and subcutaneously administered (6 vaccinations, weekly; thereafter, by-weekly). The primary and secondary endpoints were to examine the immunological responses to vaccine antigens and overall survival (OS), respectively, after PPV with and without CYP pretreatment (PPV plus CYP and PPV alone, respectively). **Results:** Thirty-four BTC patients were randomly assigned; 16 and 18 patients were assigned to the PPV plus CYP and PPV alone groups, respectively. No severe adverse events were observed in the treated patients. There were no statistically significant differences between the two groups with regard to the numbers of patients, who showed increased peptide-specific CTL or IgG responses. However, CTL frequencies in the patients with positive CTL responses were significantly higher in the PPV plus CYP group, compared to those in the PPV alone group. OS in the PPV plus CYP group was significantly longer than that in the PPV alone group ($P = 0.03$ by Fleming-Harrington test). The median OS was 397 and 190 days in the PPV plus CYP and PPV alone groups, respectively. **Conclusions:** Pretreatment with CYP did not enhance antigen-specific immune responses, but might improve the prognosis after PPV in refractory advanced BTC patients. Further larger scale, randomized trials would be needed to confirm this encouraging result. Clinical trial information: 000006249.

**3088 General Poster Session (Board #155), Sun, 8:00 AM-11:45 AM**

**Phase I study to evaluate toxicity and feasibility of intratumoral injection of alpha-gal glycolipids in patients with advanced melanoma.** *Presenting Author: Mark R. Albertini, University of Wisconsin, Madison, WI*

**Background:** Effective uptake of tumor cells by antigen-presenting cells is achieved pre-clinically by labeling them with $\alpha$-gal glycolipids ($\alpha$-gal) that bind the natural anti-Gal antibody. We aimed to evaluate toxicity and feasibility of intratumoral injections of $\alpha$-gal as an autologous tumor vaccine in advanced melanoma patients (pts). **Methods:** Pts with unresectable metastatic melanoma, at least one readily resectable cutaneous, subcutaneous, or palpable lymph node metastasis, and serum anti-Gal titer $\geq$ 1:50 were eligible for treatment with 2 intratumoral injections of $\alpha$-gal given 4 weeks apart on a 3x3 dose escalation schedule (Level I: 0.1 mg/injection; Level II: 1.0 mg/injection; Level III: 10 mg/injection). Monitoring included blood for clinical, autoimmune, and immunological analyses and core tumor biopsies. Overall treatment response was determined 8 weeks after the first $\alpha$-gal injection. **Results:** Nine pts received 2 intratumoral injections of $\alpha$-gal (3 pts/dose level). Vaccine site toxicity was mild, and no systemic toxicity could be attributed to the vaccine. Dose-limiting toxicity was not seen. There was no clinical autoimmunity and no induction of pathologic autoantibodies. Two pts (Level I (1 pt) and Level II (1 pt)) had stable disease by RECIST lasting 8 and 7 months, respectively. All other pts had progressive disease. Tumor nodule biopsies revealed minimal to no change in inflammatory infiltrate between pre and post-treatment biopsies with the exception of 1 pt in dose level III with a post-treatment inflammatory infiltrate. Pretreatment biopsies showed focal tumor cell necrosis in 2 of 9 pts. Two and 4 weeks post injection, target nodules (5 of 9 pts) exhibited tumor cell necrosis without neutrophilic or lymphocytic inflammatory response. Non-target tumor nodules (2 of 4 pts) showed necrosis, which was diffuse in 1 pt. **Conclusions:** Repeated intratumoral injections of $\alpha$-gal are well tolerated, and tumor necrosis was seen in some melanoma pts after tumor injection with $\alpha$-gal. If intratumoral injections of $\alpha$-gal glycolipids can induce anti-melanoma immunity, subsequent investigation in combination with immune checkpoint inhibitors could be informative. Clinical trial information: nct00668382.

**3089 General Poster Session (Board #156), Sun, 8:00 AM-11:45 AM**

**Pilot trial of a WT-1 analog peptide vaccine in patients with high-risk myeloid neoplasms.** *Presenting Author: Jason B. Brayer, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

**Background:** Tumor vaccines targeting known tumor-associated antigens (TAA) represent an exciting concept and, more importantly, a reasonable approach to engaging the immune system. WT-1 is once such TAA well-documented to provoke immune sensitization in myeloid tumors, and thus may serve as an ideal vaccine target. The purpose of this pilot study was to demonstrate the safety and tolerability as well as to assess for immunogenicity of a polyvalent WT-1 peptide vaccine. **Methods:** Patient enrollment included individuals with high-risk MDS or AML after at least 2 prior lines of therapy. The vaccine combined native and synthetic analog peptides derived from the WT-1 protein and emulsified in Montanide ISA 51 VG adjuvant, and coupled with GM-CSF injections to amplify immunogenicity. Six vaccinations were delivered over 12 weeks, then continued monthly until 12 vaccinations were delivered or until evidence of disease relapse or progression. Therapeutic efficacy was evaluated in terms of progression-free and overall survival. Interval quantitative PCR measurements of WT1 transcript levels acted as a surrogate marker of disease burden. Immune responses were evaluated by delayed-type hypersensitivity testing, T cell proliferation, and $CD8^+$T cell IFN$\gamma$ ELISPOT at specified intervals. **Results:** In total, 13 patients received at least 1 vaccination and 4 completed the full course of vaccinations. Vaccinations were well tolerated with no discontinuations due to adverse reaction or vaccine-induced toxicity. One of 2 patients with high-risk MDS experienced a transient decrease in transfusion dependence. Two of 11 AML patients experienced prolonged relapse-free survival greater than a year. Both patients were in CR#2 at time of vaccination and the duration of their remission exceeded the duration of their first remission, suggesting a potential benefit. **Conclusions:** Vaccination against WT-1 using a polyvalent peptide-based approach can be safely administered at well-tolerated doses. The subjective evidence in several patients suggests elicitation of an immune response. Although encouraging, the limited response rate and durability indicate a need for further optimization in future trials. Clinical trial information: NCT00665002.

**3090 General Poster Session (Board #157), Sun, 8:00 AM-11:45 AM**

**Long-term survival for patients with detectable metastatic melanoma at time of treatment with patient-specific tumor stem cell vaccines.** *Presenting Author: Robert Owen Dillman, Hoag Institute for Research and Education, Newport Beach, CA*

**Background:** Autologous, proliferating, self-renewing cancer cells (tumor stem cells) express numerous tumor-associated antigens including unique neoantigens. They are an excellent antigen-source for patient-specific polyvalent vaccines. Data from two single-arm phase II trials, (*Cancer Biother Radiopharm 2007, 2009*) and a 42-patient randomized trial, [*J Immunother 2012]* showed that metastatic melanoma patients treated with autologous dendritic cells loaded with antigens from autologous proliferating tumor cells (DC/TC) had better overall survival (OS) than patients injected with irradiated, proliferating, autologous tumor cells (TC). A survival benefit for DC/TC was seen in patients who had no evidence of disease (NED) at the time of treatment. [*AACR 2014*] In this study we addressed whether better survival was associated with DC/TC in NED-patients. **Methods:** To increase numbers for subset analyses, data for all 170 patients from the 3 trials were pooled. 27 TC-patients were excluded to decrease inter-patient differences associated with poor survival. Remaining patients were classified as NED or non-NED; this report focuses on the non-NED (n=73). Survival curves were generated for 39 treated with DC/TC and 34 treated with TC, and compared by log-rank test. **Results:** 5-year OS for all 73 non-NED patients was 27% (median 25.5 months). No patients were lost to follow up; 15/23 survivors had been followed for at least 5 years. Median ages were 54 and 53 years in the DC/TC and TC cohorts respectively; male gender accounted for 69% and 65%. M1c disease constituted a higher proportion of patients in the DC/TC cohort (44% vs 35%, p=0.071). OS was better in the DC/TC cohort (HR=0.65) with median survival 38.8 vs 14.7 months and 5-year OS 33% vs 20% (p=0.025). In patients with measurable disease by RECIST criteria, survival was better for DC/TC (p=0.035). **Conclusions:** This subset analysis suggests that active specific immunotherapy with DC/TC is associated with longer survivor than TC in patients who have detectable metastatic melanoma at the time of treatment. (*NCI-V01-1646,* NCT00436930) Supported by the Hoag Hospital Foundation and the Cancer Biotherapy Research Group.

**3091 General Poster Session (Board #158), Sun, 8:00 AM-11:45 AM**

**Tolerability, humoral immune response, and disease control in phase 1 patients receiving ONT-10, a MUC1 liposomal vaccine.** *Presenting Author: John J. Nemunaitis, Mary Crowley Cancer Research Centers, Dallas, TX*

**Background:** MUC1 is a high molecular weight glycoprotein overexpressed and aberrantly glycosylated in many cancers. ONT-10, a liposomal vaccine incorporating a synthetic glycolipopeptide MUC1 antigen and the novel synthetic toll-like receptor 4 agonist PET Lipid A, induces strong anti-MUC1 humoral and cellular responses in preclinical models. **Methods:** This phase 1 study is evaluating ONT-10 safety, immune response, and antitumor activity. Pts with end-stage solid tumors associated with MUC1 expression are eligible. Cyclophosphamide 250 mg/m$^2$IV is given on day -3 followed by ONT-10 (250, 500, 1000, or 2000 $\mu$g) SC day 1 and then Q2W for 4 doses or QW for 8 doses using a 3+3 design. Humoral immune response is assessed by ELISA for MUC1 specific antibodies (Ab) and cellular by ELISPOT for MUC1 specific IFN-$\gamma$. Tumor response is per RECIST 1.1 and irRC. Pts without progressive disease at week 12 can receive maintenance ONT-10 every 6 weeks **Results:** 42 pts have been treated: ovarian (n=13), breast (n=6), colorectal (n=6), pancreatic (n=5), endometrial (n=4), lung (n=4), other (n=4), all ECOG 0/1. Median age 62 (35-77); median prior therapies 4 (1-11). There have been no DLTs. All treatment-related AEs have been Grade 1-2, the most common, fatigue (26%) and injection site reactions (16%). MUC1 specific Ab have been seen in the majority of pts at titers up to $>$ 51,200, with the highest IgG responses seen at the higher-dose QW schedules. Cellular analysis is ongoing. Best tumor response has been SD in 23/34 evaluable pts (68%); 12 pts to date have been progression free for $>$ 6 mo (6.4 – 21+ mo). 2 pts with ovarian cancer have had reduced tumor volume (16% at week 9 and 44% at week 34, respectively). 22/36 (61%) eligible pts have gone to maintenance ONT-10. **Conclusions:** ONT-10 has been well tolerated at all doses with no DLTs. Humoral responses have been seen in most pts, with an apparent dose response for IgG on the QW schedule. Encouraging disease control has been seen with SD in 68% of pts, of whom over half have been progression free for $>$ 6 mo. Clinical trial information: NCT01556789.

**3092 General Poster Session (Board #159), Sun, 8:00 AM-11:45 AM**

**Randomized phase II study of personalized peptide vaccination in patients with advanced bladder cancer progressing after chemotherapy.** *Presenting Author: Masanori Noguchi, Division of Clinical Research, Research Center for Cancer Treatment, Kurume University School of Medicine, Kurume, Japan*

**Background:** A personalized selection of the right peptides for each patient could be a novel approach for a cancer vaccine to boost anti-cancer immunity in the majority of patients along with the potential of survival benefits. The purpose of this study was to assess the efficacy and toxicity of personalized peptide vaccination (PPV) as second-line therapy in patients with advanced metastatic bladder cancer. **Methods:** We conducted a multicenter, randomized phase II study to compare PPV plus best supportive care (BSC) with BSC alone in patients with advanced metastatic bladder cancer who failed or progressed after first-line platinum-containing regimens. PPV treatment was using maximum of four peptides chosen from 31 candidate peptides according to human leukocyte antigen (HLA) types and peptide-reactive immunoglobulin (IgG) titers, for 12 times of subcutaneously injections (8 injections, weekly; 4 injections, by-weekly). Primary outcome was progression free survival (PFS). Secondary outcomes were overall survival (OS), immune response and toxicity. **Results:** From 2010 to 2013, 80 patients were randomly assigned; 38 patients were assigned to PPV plus BSC, and 42 patients were assigned to BSC alone. After median follow-up of 4.5 months, the median OS was 8.3 months on PPV plus BSC versus 4.2 months on BSC alone (hazard ratio [HR], 0.533; log-rank p = 0.0423). PFS was not significantly longer on PPV plus BSC (HR, 0.622; log-rank p = 0.0621). Both treatments were well tolerated, without serious adverse drug reactions. Peptide-specific IgG or cytotoxic T-lymphocyte responses were observed in 20 of 26 patients (77%), or 8 of 19 patients (42%) on PPV plus BSC, respectively. **Conclusions:** PPV as second-line therapy in patients with advanced bladder cancer is active and well tolerated improving survival with immune responses. Further large scale, randomized trials are needed to confirm our preliminary results. Clinical trial information: UMIN000003157.

**3093 General Poster Session (Board #160), Sun, 8:00 AM-11:45 AM**

**Immunotherapeutic treatment of metastatic colorectal cancer using ETBX-011.** *Presenting Author: Elizabeth Susan Gabitzsch, Etubics Corporation, Seattle, WA*

**Background:** Cell mediated immune (CMI) induction has become a prominent component of potential immunotherapy of cancer. We have reported on a Phase 1/2 single agent clinical trial of the immunotherapeutic ETBX-011 for the treatment of mCRC. We now report on long-tem immunity to CEA and survival data to provide further insight into the responses following treatment with ETBX-011. **Methods:** Cohorts of patients with advanced colorectal cancer, refractory to prior therapies, received escalating doses from $10^9$ to $5x10^{11}$VP of ETBX-011 (Ad5 [E1-, E2B-]-CEA(6D)) subcutaneously every 3 weeks for 3 immunizations. The induction of CEA-specific cell mediated immunity was measured by ELISPOT and overall survival was determined. Also, in a subset of the ETBX-011 treated mCRC patients the number of T-regs as the percent of CD4 cells and the ratio of T-effector cells to Tregs was determined. **Results:** ETBX-011 was found to be well-tolerated at all doses and there were no drop outs due to treatment. Specific anti-CEA immune responses were observed in the majority of patients and median overall-survival was 11 months. We now report on long term follow-up of the patients. Forty-four percent (48%) of patients still survived at 12 month follow-up and 28% at 18 months following treatments. One patients who developed significant CEA specific cellular immune response also showed a decrease in the Treg:T-effector ratio on follow-up and still survived at 2 years post treatment. **Conclusions:** These results demonstrate that mCRC patients treated with ETBX-011 immunotherapeutic is safe and can be easily administered to patients. ETBX-011 treatment generated significant CMI induction to the tolerated tumor associated antigen CEA and may experience increased overall survival. A single agent randomized, multicenter Phase 2b trial is being initiated to further evaluate the clinical effectiveness. Clinical trial information: NCT01147965.

**3094 General Poster Session (Board #161), Sun, 8:00 AM-11:45 AM**

**Phase II clinical trial of multiple peptide vaccination for advanced head and neck cancer patients with induced immune responses and a prolonged OS.** *Presenting Author: Yoshihiro Yoshitake, Department of Oral & Maxillofacial Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto City, Japan*

**Background:** The peptides derived from ideal cancer-testis antigens, including LY6K, CDCA1 and IMP3 (identified using genome-wide cDNA microarray analyses), were utilized in immunotherapy for head and neck squamous cell cancer (HNSCC). In this trial, we analyzed the immune response to and safety and efficacy of vaccine therapy. **Methods:** A total of 37 patients with advanced HNSCC were enrolled in this trial of peptide vaccine therapy, and the OS, PFS and immunological response were evaluated using enzyme-linked ImmunoSpot (ELISPOT) and pentamer assays. The peptides were subcutaneously administered weekly with IFA. The primary endpoints were evaluated based on differences between *HLA-A*2402*-positive (A24(+)) patients treated with peptide vaccine therapy and –negative (A24(-)) patients treated without peptide vaccine therapy among those with advanced HNSCC. **Results:** Our cancer vaccine therapy was well tolerated. The OS of the A24(+)vaccinated group (n = 37) was statistically significantly longer than that of the A24(-) group (n=18) (MST 4.9 vs. 3.5 month, respectively, $p<0.05$). One of the patients exhibited a complete response. In the A24(+) vaccinated group, the ELISPOT assay identified LY6K-, CDCA1- and IMP3-specific CTL responses in 85.7%, 64.3% and 42.9% of the patients, respectively. The patients showing LY6K- and CDCA1-specific CTL responses demonstrated a longer OS than those without CTL induction. Moreover, the patients exhibiting CTL induction for multiple peptides demonstrated better clinical responses. **Conclusions:** The immune response induced by this vaccine may improve the prognosis of patients with advanced HNSCC. Clinical trial information: 000008379.

**3095 General Poster Session (Board #162), Sun, 8:00 AM-11:45 AM**

**Combined chemoimmunotherapy of castrate-resistant prostate cancer with dendritic-cell based vaccine DCVAC/Pca.** *Presenting Author: Michal Podrazil, 2nd Medical School Charles University, Prague, Czech Republic*

**Background:** Appropriate combination of tumor mass reduction and neutralization of tumor-induced immunosuppression might potentiate the induction of anti-tumor immunity. We performed an open label, single arm Phase I/II clinical trial in patients with metastatic castrate resistant prostate cancer (mCRPC) eligible for docetaxel using autologous mature dendritic cells pulsed with killed LNCap prostate cancer cell line, DCVAC/PCa. **Methods:** Eligible patients had progressive mCRPC despite androgen deprivation. None of the patients received abiraterone or enzalutamide. DCVAC/PCa treatment consisted of, on average ten doses of $1x10^7$ dendritic cells injected s.c. Treatment comprised of initial 7d administration of metronomic cyclophosphamide, and subsequent 2 doses of DCVAC/PCa. Patients then started docetaxel (75 mg/m$^2$) and prednisone (5 mg twice daily) treatment administered every 3-weeks and DCVAC/PCa was given every 6 weeks up to a maximum number of doses manufactured from one leukapheresis. The primary end point was safety, the secondary end-point immune response. Overall survival (OS) was compared to the predicted OS according to Halabi and MSKCC nomograms. **Results:** Data from twenty-five patients were evaluated. The mean age at the start of immunotherapy was 67 years, median PSA 109 ng/ml and Hb 11,9 g/dl. 48% patients had GS $\geq$8. No serious DCVAC/PCa-related adverse events have been reported. There were no clinical or laboratory signs of autoimmunity. Median OS was 19 months (95% CI: 14.69-23.31) while the predicted median OS was 12 months (95% CI: 11.19-12.81). We observed no significant changes of the peripheral blood Tregs and MDSCs during the course of the trial. Long-term administration of DCVAC/PCa led to the induction and maintenance of the stable levels of T cells specific against multiple tumor antigens including PSA, NY-ESO1, MAGE-A1 and MAGE-A3. **Conclusions:** In patients with mCRPC, the alternate administration of DCVAC/PCa cancer immunotherapy and docetaxel results in the stabilization of the disease progression and longer than expected survival. Chemotherapy does not preclude the induction of tumor specific T cells. Clinical trial information: 2009-017259-24.

**3096 General Poster Session (Board #163), Sun, 8:00 AM-11:45 AM**

**Long-term survival of patients suffering from solid extra-cranial neoplasias after dendritic cell-based cancer immune therapy.** *Presenting Author: Friedrich Erhart, St. Anna Children's Cancer Research Institute, Vienna, Austria*

**Background:** Cancer immunotherapy (CIT) based on Dendritic Cells (DC) is developing into a more mature therapy option as clinical trials progress. Our approach involves the microbial danger molecule Lipopolysaccharide (LPS) in connection with Interferon-Gamma (IFNg) to generate mature DCs that release Interleukin-12 (IL12). As the IL12 production is limited to a timespan of about twenty-four hours, we inject DCs that have been exposed to LPS/IFNg for six hours in order to ensure that IL12 release is still ongoing during the in vivo interaction with T cells. **Methods:** We here report an analysis of 27 patients with advanced solid extra-cranial metastatic malignancies that received our DC CIT approximately ten years ago. The patients come from two phase I clinical trials and were age-matched and disease-matched. To explore potential factors contributing to the extended survival of certain patient groups, we studied a set of immunological variables in the peripheral blood mononuclear cells and the vaccine, where available from these patients. Methods used were flow cytometry, Elispot assays, Cytometric Bead Arrays and qRT-PCR. Statistical techniques included Student's T test, Pearson's correlation, Kaplan-Meier curves and Cox regression. **Results:** Of the total 27 study participants, six (~22%) were still alive. 20 patients of one of those two phase I trials have already been reported in an interim analysis in 2007. In spring 2013, which is approximately ten years after the advent of the trial, five of the twenty (1/4=25%) were still alive. Immunological variables with significantly different values in patients alive at the time of review include RORgt mRNA levels, GATA3 mRNA levels, CD94+ cells and IL-17 production. **Conclusions:** Long-term survival has been reached in a subset of patients with advanced metastatic disease that received our DC CIT approximately ten years ago. The immunological variables we studied might be a first hint at future biomarkers that can identify potential long-term survivors. Further studies with an increased number of patients are needed to consolidate our observations.

**3097 General Poster Session (Board #164), Sun, 8:00 AM-11:45 AM**

**Phase I/IIa study of therapeutic p16$^{INK4a}$ vaccination in patients with HPV-associated cancers.** *Presenting Author: Miriam Reuschenbach, Department of Applied Tumor Biology, Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany*

**Background:** Therapeutic strategies specifically targeting HPV-associated cancers are lacking. The cellular protein p16$^{INK4a}$ is strongly overexpressed in HPV-associated cancers, while in normal tissues p16$^{INK4a}$ expression is barely detectable. Therefore targeting of p16$^{INK4a}$ by vaccination could represent an interesting immune therapeutic approach for patients with HPV-associated cancers. We performed a phase I/IIa trial to monitor toxicity and immunogenicity of p16$^{INK4a}$vaccination (Vicoryx). **Methods:** Patients with advanced p16$^{INK4a}$-overexpressing, HPV DNA-positive cancer (anogenital region, head and neck) were included after completion of standard treatment. The protocolcomprised a total of 12 subcutaneous injections of a synthetic p16$^{INK4}$ peptide mixed with Montanide ISA-51 VG in weekly intervals. Objectives of the trial were clinical safety and changes of humoral and cellular immune responses against the p16$^{INK4a}$peptide. T cell responses were monitored by interferon-gamma ELISpot and antibodies by ELISA from peripheral blood. **Results:** Phase I is completed with 10 patients, phase IIa is ongoing with 14 patients recruited of 16 planned. No toxicity was observed during and after vaccination that was regarded as related to vaccination with the auto-antigen p16$^{INK4a}$ in any of the patients. While pre-existing baseline T cell and antibody responses against the p16$^{INK4a}$ peptide were rare, p16$^{INK4a}$-reactive T cells and antibodies were successfully induced in 8 of 16 patients analyzed to date. So far one head and neck cancer patient with lung metastases completed the entire study protocol with stable disease for now 18 months after the last vaccination. The remaining 9 patients of phase I had progressive disease. **Conclusions:** This is the first study demonstrating that p16$^{INK4a}$ peptide vaccination is safe and well tolerated and that immune responses against p16$^{INK4a}$ can be induced by p16$^{INK4a}$ peptide vaccination and are not accompanied by clinical autoimmune symptoms. Further trials will be designed to assess whether this approach may be an adjuvant therapeutic strategy for patients with HPV-associated cancers. Clinical trial information: NCT01462838.

**3098 General Poster Session (Board #165), Sun, 8:00 AM-11:45 AM**

**Synthetic IL-33 DNA as anti-tumor adjuvant in vivo.** *Presenting Author: Daniel Villarreal, University of Pennsylvania, Philadelphia, PA*

**Background:** Antigen specific CD4+ and CD8+ T cell responses have been generated in 78-90% of volunteers in two recent HPV and HIV clinical studies using our highly optimized DNA immunogens delivered using *in vivo* electroporation. IL-12 DNA was shown to augment T-cell responses in a prophylactic HIV clinical trial as compared to using antigen alone (increase in response rates of 36.4% and 18.6% in the CD4+ and CD8+ T cell compartments respectively) which could prove critical as available FDA-licensed adjuvants are limited, and include aluminum salts, or more recently, LPS formulations and do not improve CD8$^+$T cell immunity. **Methods:** Here we describe an advance to augment the immune responses of DNA delivered by electroporation in the cancer immunotherapy arena. IL-33 has two different biologically active forms known as full-length IL-33 and mature IL-33. **Results:** Full-length IL-33 is thought to be the biologically most active form to promote inflammation, while the function of the mature cleaved form of IL-33 in modulating the immune responses remains more elusive. The potential ability of both isoforms to influence the adaptive immune response and act as an adjuvant has not previously been explored. We show that both isoforms of IL-33 are capable of enhancing potent antigen specific effector and memory T cell immunity in vivo when used in a DNA immunotherapy for HPV16. We also show that while both forms of IL-33 drove robust HPV specific IFNy responses (~2000 SFU), neither form drove high secretion of IL-4 (<250 SFU). Moreover, both isoforms augmented polyfunctional CD4$^+$ and CD8$^+$ T cell responses when compared to antigen alone (24-25% vs 18% and 66-67% vs 56%, respectively) and resulted in higher antigen-specific CD8$^+$ degranulation. Co-administration with IL-33 conferred 100% protection against challenge with HPV E6/E7-expressing tumors (TC1 cell challenge). Both the full length and mature IL-33 adjuvant isoforms prevented or delayed the growth of tumors and/or expedited the rate of complete tumor regression and cured 10/10 and 9/10 animals, respectively. **Conclusions:** The data support that IL-33 DNA can act as a novel adjuvant for HPV-specific DNA immunotherapy, and is a strong candidate to be examined clinically in the context of anti-tumor immune-based therapy.

**3099 General Poster Session (Board #166), Sun, 8:00 AM-11:45 AM**

**Cancer immunotherapy of patients with the biochemical relapse of the prostate cancer using dendritic cell-based vaccine DCVAC/PCa.** *Presenting Author: Radek Spisek, Sotio, Prague, Czech Republic*

**Background:** Effect of cancer immunotherapy at the minimal residual disease stage can be evaluated in patients with the biochemical relapse of the prostate cancer. We performed a Phase I/II clinical trial in patients with the biochemical relapse of the prostate cancer using autologous mature dendritic cells pulsed with killed LNCap prostate cancer cell line, DCVAC/PCa. **Methods:** Eligible patients had a biochemical relapse of the prostate cancer after primary prostatectomy or after radical prostatectomy and salvage radiotherapy. Absence of hormonal therapy was required. DCVAC/PCa treatment consisted of twelve doses of 1x10$^7$dendritic cells injected s.c. Treatment comprised of initial 2 doses in 2 weeks interval and DCVAC/PCa was then administered every four weeks for a total of twelve doses. Patients experiencing significant prolongation/stabilization of PSA-DT were eligible for an additional treatment cycle. Primary goal of the study was to assess safety. Secondary goals were PSA kinetics and presence of tumor specific immunity. **Results:** Twenty one patients were evaluated after receiving 12 doses of DCVAC/PCa. Administration of DCVAC/PCa did not lead to any significant side effects. Continuous cancer immunotherapy by DCVAC/PCa significantly prolonged the PSA doubling time (PSA-DT) in all treated patients. Median PSA-DT increased from 7,86 months prior to the treatment, to 26,08 months after completing 12 doses of DCVAC/PCa, $p<0.001$. Eight of 21 patients had stable PSA levels during the treatment duration (PSA-DT>36 months) and PSA-DT remained stable during the additional cycle of the treatment (average PSA-DT of 48,13 months). Long-term administration of DCVAC/PCa led to the induction and maintenance of T cells specific against multiple tumor antigens including PSA, MAGE-A1 and MAGE-A3. **Conclusions:** This study indicates that the cancer immunotherapy with DCVAC/PCa represents a promising approach for prostate cancer patients with biochemical relapse. This study supports the use of immunotherapy early in the course of the disease, provided that relevant surrogate endpoints predictive of improved prognosis of early stage patients will be identified. Clinical trial information: 2009-017259-91.

**3100 General Poster Session (Board #167), Sun, 8:00 AM-11:45 AM**

**Antitumor effects of a nanoparticle-based vaccine targeted at human aspartyl (Asparaginyl) $\beta$-hydroxylase (HAAH).** *Presenting Author: Hossein A. Ghanbari, Panacea Pharmaceuticals, Inc., Gaithersburg, MD*

**Background:** HAAH is an established target for cancer therapy. It is over-expressed on cancer cells and plays a role in cancer cell growth, motility and invasiveness. Treatment of cancer cells to inhibit HAAH expression (siRNA) or neutralize its activity (mAb) returns cells to a normal phenotype. Moreover, tumor growth in xenograft models of human cancer is significantly (>80%) inhibited by anti-HAAH mAbs. HAAH is an oncofetal protein, important during development but not adult life, and thus, is a promising target for immunotherapy. However, as a self antigen, standard vaccination methods are ineffective in eliciting a sufficient immune response. **Methods:** We have designed and developed a nanoparticle based anti-cancer vaccine targeting HAAH. This vaccine incorporates a segment of the extracellular domain of HAAH fused to the gpD protein of $\lambda$-phage which is known to help to overcome immune tolerance. **Results:** The manufactured vaccine demonstrated high levels of immunogenicity in mice. Animals injected with 5x10$^7$-5x10$^9$ nanoparticles showed dose-dependent HAAH-specific antibody responses after 3 injections (day 0, 7, and 14). Sera from these animals demonstrated antigen specific binding to HAAH presented as either recombinant protein (ELISA) or on the surface of tumor cells (ELISA and FACS). The nanoparticle-based vaccine was further tested for efficacy against a mouse hepatocellular cancer line (BNLT3) injected subcutaneously into BALB/c mice in both a prophylactic and treatment modality. In the prophylactic model, mice (n=20) were vaccinated with 5 subcutaneous doses of nanoparticles (5x10$^{10}$) on days 0, 7, 14, 46, and 62 and were challenged with 5x10$^4$ BNLT3 cells on day 46. By day 70, 100% of control mice (n=5) had developed tumors with a mean tumor volume of >300mm$^3$. In contrast, only 85% of vaccinated mice had tumors, with a mean tumor volume of <100mm$^3$. In the treatment model, tumor cells (5x10$^3$) and vaccine (10$^{10}$) were co-administered on day 0 and animals were boosted on days 7 and 14. By day 50, 60% of control mice (n=5) had developed tumors with a mean volume of >20mm$^3$, while none of the vaccinated mice had palpable tumors. **Conclusions:** These data support further development of this novel nanoparticle vaccine.

**3101 General Poster Session (Board #168), Sun, 8:00 AM-11:45 AM**

**Boosting of cellular and humoral immune responses to HPV16/18 antigens by VGX-3100: A follow-on phase I trial.** *Presenting Author: Matthew P Morrow, Inovio Pharmaceuticals, Blue Bell, PA*

**Background:** Despite the development of highly effective prophylactic vaccines against human papillomavirus (HPV) types 16 and 18, prevention of cervical dysplasia and cancer in women infected with high-risk HPV types remains an unmet medical need. We have previously reported data from a phase 1 dose escalation study for a therapeutic HPV16/18 vaccine, VGX-3100, delivered by in vivo electroporation (EP). Immunization in that study drove seroconversion as gauged by ELISA to at least one vaccine antigen in 100% of patients while 78% mounted an Interferon Gamma (IFNg)ELISpot response to the vaccine antigens.. **Methods:** Of the 18 patients enrolled in that trial, 13 were rolled into a second phase 1 immunogenicity trial entailing a single 6.0mg boost of VGX-3100 administered using EP. **Results:** Increases in immune reactivity following the boost were noted, as eleven patients showed boost-driven increases in ELISA titers and the mean ELISpot magnitude increased by at least 2-fold in seven patients irrespective of the dose of VGX-3100 they received in the first clinical trial. Additional Flow Cytometric analyses of cellular responses revealed increased HPV specific IFNg and TNFa production as compared to prior to the boost (0.34% to 0.57% and 0.27% to 0.60%, respectively) with contribution from both the CD4+ and CD8+ T cell compartments. Additionally, HPV specific CD8+ T cells expressing Fas Ligand concomitantly with either cytokine or the degranulation marker CD107a increased from 0.19% to 0.28% following the boost. Employment of staining for the activation marker CD137 (41BB) showed that patient CD8+ T cells continued to activate efficiently in response to HPV antigens following the boost, including a statistically significant increase in co-expression of Granzyme B and Perforin within the activated T cell subset ($p=0.026$). **Conclusions:** Taken together these data suggest that immunization with VGX-3100 drives immune responses that have the ability to be further boosted by additional administrations. Current studies are underway in an untreated HPV 16/18 associated CIN2/3 setting to assess whether these significant immune responses can translate into clinically effective treatment options to surgery. Clinical trial information: NCT01188850.

**3102 General Poster Session (Board #169), Sun, 8:00 AM-11:45 AM**

**Impact of new oncolytic herpes simplex virus vector armed with interleukine-12 for cervical cancer therapy.** *Presenting Author: Masahiro Kagabu, Iwate Medical University School of Medicine, Morioka, Japan*

**Background:** Cervical cancer is the third most common cancer in women, and the seventh overall, the incidence and mortality of cervical cancer in the world was approximately 530,000 and 275,000 respectively according to a database of the Agency for Research on Cancer (IARC) in 2008. Requirement of new treatments it is mandatory to improve the outcome of the pathology. Replication-selective oncolytic herpes simplex viruses (oHSV) have emerged as a new platform for cancer therapy. Accumulating evidence indicates that, aside from the extent of replication capability within the tumor, the efficacy of an oncolytic HSV-1 depends on the extent of induction of host antitumor immune responses. We analyzed therapeutic potential of third-generation of oncolytic HSV-1 termed T-01 and Replication-competent HSV-1 vectors expressing IL-12 (T-mfIL12) for cervical cancer in mouse model. **Methods:** (1) In vitro, we investigated cytotoxicity reaction of human and mouse cervical cancer cell lines (TC-1, SKG-IIIa, CaSki, HeLa). (2) In vivo, we analyzed TC-1 cell lines in immune-competent models. Animals were challenged with a lethal dose of TC-1, 17 days after the first intratumoral (i.t.) administration of T-01 or T-mfIL12 was performed. Intratumoral administration of T-01 or T-mfIL12 were performed 4-5 days interval total 6 times. **Results:** T-01 and T-mfIL12 has great cytotoxicity for human and mouse cervical cancer cell lines. In addition, our results indicate that administration of T-01 and T-mfIL12 produced greatest antitumor effects in cervical cancer models. Furthermore, in immune-competent models, we found an increase of the number of cancer specific CD8+ T-cell in spleen of mice treated with T-01 in comparison with the control treated mice. **Conclusions:** Our data suggest that administration of T-01 and T-mfIL12 is an effective treatment against cervical cancer model. It may potentially be translated into the clinical area.

**3103 General Poster Session (Board #170), Sun, 8:00 AM-11:45 AM**

**A first-in-class, first-in-human phase I study of enadenotucirev, an oncolytic Ad11/Ad3 chimeric group B adenovirus, administered intravenously in patients with metastatic epithelial tumors.** *Presenting Author: Emiliano Calvo, START Madrid, Centro Integral Oncológico Clara Campal, Hospital Universitario Norte Sanchinarro, Madrid, Spain*

**Background:** Enadenotucirev (E) is an Ad11/Ad3 group B adenovirus, selective for killing cancer cells with little or no activity expected in normal tissue. E shows a broad anti-tumor activity in preclinical models. **Methods:** Main objectives of this study were to evaluate safety, pharmacokinetics (PK), pharmacodynamics (PD) of E delivered intravenously (IV) on Day (D) 1, 3 and 5 as single cycle and to recommend a dose for phase 2 (DP2). Once determined, DP2 was confirmed with up to 4 repeat cycles. A ″3 + 3″ dose escalation design was employed in patients (pts) with epithelial tumors having no standard treatment options. **Results:** 34 pts were treated as shown in Table. Tumor origin included colorectal (26 pts), parotid (3 pts) and oropharynx, liver, stomach, gall bladder and breast (1 pt each). At a dose of 1e13 viral particles (vp) over 5 min, DLTs were observed in 2 pts, a reversible Grade (Gr) 3 acute lung injury and dyspnea with hypoxia, hence defining the Maximally Administered Dose. Adverse events (AEs) seen in ≥ 10% pts were pyrexia, chills, flu like illness, nausea, vomiting, diarrhea, anorexia, asthenia, musculoskeletal pain, thrombocytopenia and increased transaminase (incr transa) and gammaGT (GGT). Gr 3 AEs seen in 3 pts were asthenia, hypertension, neutropenia, lymphopenia, thrombocytopenia and incr alkaline phosphatase and transa; Gr 3 incr GGT occurred in 5 pts, Gr 4 incr transa was seen in 1 pt (already with a DLT). AEs were reversible and short lasting. Significant increase in cytokines (TNF, interferon gamma, IL6, IL12) occurred on D1 at ≥ 3 e12 vp but were attenuated with D3 and 5 dosing and with prolonged infusion duration. The proposed DP2 is 6e12 vp over 40 min, every three weeks. Preliminary PK and PD data suggest that E remains active in the blood and replicates in some pts when administered at the DP2. Antiviral antibody responses suggest that repeat cycles are feasible. **Conclusions:** E can be safely administered to cancer pts and a biologically relevant dose and schedule have been determined for Phase 2 study. Clinical trial information: NCT02028442, EUDRACT 2012-001067-79.

| Cohort | N | Dose (VP) | Infusion duration (min) |
|---|---|---|---|
| **1** | 3 | 1e10 | 5 |
| **2** | 3 | 1e11 | 5 |
| **3** | 3 | 1e12 | 5 |
| **4** | 4 | 1e13 | 5 |
| **5** | 3 | 3e12 | 5 |
| **6** | 3 | | 20 |
| **7** | 3 | 6e12 | 40 |
| **Expansion** | 9 | | |
| **Repeat cycles** | 6 | | |

**3104 General Poster Session (Board #171), Sun, 8:00 AM-11:45 AM**

**Oncolytic wild-type reovirus infection in brain tumors following intravenous administration in patients.** *Presenting Author: Adel Jebar, University of Leeds, Leeds, United Kingdom*

**Background:** Oncolytic viruses preferentially replicate in, and kill cancerous cells. Wild-type reovirus is a proprietary isolate of reovirus type 3 Dearing, a double-stranded RNA human reovirus. In two trials using intralesional administration in gliomas and recurrent brain tumours, wild-type reovirus has been well tolerated, with early signs of efficacy. A recently completed trial in Leeds, UK (Adair *et al.* 2012 *Sci Transl Med*) has proven that intravenous wild-type reovirus accesses colorectal cancer liver metastases. Intravenous delivery to brain tumours would be easier, cheaper and more acceptable to patients than intralesional administration. To date, no oncolytic virus has been shown to infect brain tumours following intravenous delivery. This trial aims to identify whether wild-type reovirus can cross the blood brain barrier and infect brain tumours following intravenous administration. **Methods:** This is an open-label, non-randomised, single centre study of intravenous wild-type reovirus administered to patients prior to planned surgery for recurrent high grade glioma or metastatic brain tumours. In total, 12 patients will be treated with a single infusion of $1x10^{10}$ $TCID_{50}$of wild-type reovirus. The primary objective is the presence of wild-type reovirus in the resected tumours as assessed by immunohistochemistry, RNA in-situ hybridization and retrieval of infectious virions. **Results:** Three patients have completed the study to date, including one glioblastoma multiforme, one grade 3 oligodendroglioma and one colorectal brain metastasis. Two of the 3 patients were taking high dose steroids. All 3 resected patient tumours contained wild-type reovirus RNA and protein. There was evidence for wild-type reovirus productive infection in 2 of the tumours. Grade 3-4 adverse reactions were neutropaenia in 1 patient and lymphopaenia in all 3 patients. **Conclusions:** We have shown for the first time that an oncolytic virus, wild-type reovirus, infects and replicates in brain tumours following intravenous administration. This trial will pave the way for phase I/II trials and combination studies using wild-type reovirus in patients with high grade gliomas and brain metastases. Clinical trial information: ISRCTN70443973.

**3105 General Poster Session (Board #172), Sun, 8:00 AM-11:45 AM**

**Oncolytic viral therapy for malignant gliomas using myxoma virus deleted for antiapoptotic M11L gene.** *Presenting Author: Peter A. J. Forsyth, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

**Background:** Malignant gliomas (MGs) remain largely incurable with a poor prognosis and an average survival of approximately 1 year. They are resistant to radiotherapy (RT) and temozolomide (TMZ). Clearly more effective treatments for MGs are needed. Oncolytic viruses are promising new agents used against experimental models of MGs and are now in several clinical trials. Myxoma virus is an excellent oncolytic virus because it is safe, selectively infecting and killing only cancer cells. We have shown that myxoma virus is efficacious in MGs and brain tumor initiating cells (BTICs) in vitro and in vivo, but the effect on survival in BTICs is not striking and only seen when combined with rapamycin. We think that manipulating myxoma virus will improve its therapeutic efficacy in MG, and hypothesize that genetic deletion of the anti-apoptotic gene M11L in Myxoma virus will enhance cell killing in MGs/BTICs and may be synergistic with TMZ and RT. **Methods:** We created the myxoma M11L knockout virus (M11L-KO) and tested its ability to kill MG cells and BTICs isolated from fresh human malignant gliomas. We have also examined the efficacy of M11L-KO virus on killing of BTICs when combined with TMZ and RT. **Results:** We found that M11L-KO is superior to WT-myxoma, produces a productive infection, and kills glioma cells and BTICs via apoptosis as shown by cleavage of PARP and caspase-3. As expected, the M11L protein in the WT virus does associate with the mitochondria, which is consistent with its role in inhibiting apoptosis. We have also found an additive effect of TMZ and RT with the M11L-KO virus compared to WT-myxoma. Finally, a microarray screen in BTICs showed several promising candidates in the intrinsic and extrinsic apoptosis pathways that are down- or up-regulated by M11L in WT-myxoma. Interestingly, our microarray data showed that TNFSF10 is up-regulated in BTICs infected with M11L-KO myxoma compared to cells infected with WT-myxoma, indicating its possible role in Myxv-M11L-KO-mediated killing of BTICs. **Conclusions:** These results will have clinical significance in the development of an experimental treatment in MGs patients.

**3106 General Poster Session (Board #173), Sun, 8:00 AM-11:45 AM**

**Activity of IMMU-130 anti-CEACAM5-SN-38 antibody-drug conjugate (ADC) on metastatic colorectal cancer (mCRC) having relapsed after CPT-11: Phase I study.** *Presenting Author: Efrat Dotan, Fox Chase Cancer Center, Philadelphia, PA*

**Background:** IMMU-130 is an ADC of the humanized anti-CEACAM5 antibody, labetuzumab, linked to the active metabolite of CPT-11, SN-38 (drug-antibody ratio=7.6). In an every other week dosing schedule, neutropenia was dose-limiting. Multiple doses of 12 mg/kg were tolerated with modest activity (1 PR). We are now examining a more frequent dose schedule. **Methods:** Patients with mCRC refractory to standard therapy, including CPT-11, with elevated blood CEA (>5 ng/mL) enrolled in this phase I trial. Two regimens are under evaluation: 1 x or 2 x weekly for 2 weeks in a 3-week cycle to assess safety and efficacy, and to determine a safe dose for multiple treatment cycles. **Results:** Thirteen patients were treated twice-weekly at 4, 6, 9, and 12 mg/kg/dose (n = 3, 6, 3, and 1, respectively). Neutropenia is dose-limiting (6 ≥ G2), with manageable G1-2 nausea (7), fatigue (6), vomiting (3), and diarrhea (2 G1-2, 1 G3) observed during treatment. At 12 or 9 mg/kg, dose reductions/delay were required due to ≥ G2 neutropenia. Two patients dosed at 9 mg/kg required dose reduction to 4.5 mg/kg, one completing 21 doses, with a 24% reduction in the target lesions and another with SD after 32 doses. Two of 6 pts in the 6 mg/kg cohort showed a treatment effect following dose reduction for toxicity; one with a 28% reduction in target lesions after 38 doses, and another with 63% reduction in the target lesions (RECIST1.1 PR) after continuing treatment at 3 mg/kg for 27 doses. A 4.0 mg/kg twice-weekly dose level is now under study. In the once-weekly schedule, 3 pts completed 1 cycle at 8 mg/kg, with 1 pt experiencing dose delay/reduction in the subsequent cycle due to Gr 4 neutropenia; 3 more pts are enrolled. CEA blood titers correlated with response. There have been no anti-antibody or anti-SN-38 antibody reactions based on ELISA tests. The Phase II will expand patients at optimal dosing and will assess PK and UGTA1A genotypes. **Conclusions:** These early results indicate therapeutic activity of IMMU-130 in advanced mCRC patients during Phase I extended dosing, even in patients who are relapsed/refractive to CPT-11, and with manageable neutropenia and GI toxicities. Clinical trial information: NCT1605318.

**3107 General Poster Session (Board #174), Sun, 8:00 AM-11:45 AM**

**Characterization of an anti-Trop-2-SN-38 antibody-drug conjugate (IMMU-132) with potent activity against solid cancers.** *Presenting Author: David M. Goldenberg, Immunomedics, Inc., Morris Plains, NJ*

**Background:** IMMU-132 is an antibody-drug conjugate (ADC) made from a humanized anti-Trop-2 mAb (hRS7) coupled through a linker to SN-38, the active metabolite of CPT-11. Trop-2 is found in a wide range of tumor, including gastric, pancreatic, triple-negative breast (TNBC), colonic, prostate, and lung. Current Phase I/II clinical trials confirm the anticancer activity of IMMU-132 in cancers expressing Trop-2. The current studies further characterize IMMU-132 in terms of conjugation, mechanism of action (MoA), and efficacy. **Methods:** SN-38 conjugation to hRS7 was analyzed by HIC, LC-MS, and HPLC. MoA was assessed by comparisons in binding, ADCC, and pro-apoptotic signaling pathways. Efficacy studies were performed in mice bearing human tumor xenografts. **Results:** IMMU-132 has a drug to antibody ratio of 7.6, <1% aggregation, and no loss in binding to cells or to a Trop-2 chip (cells: $K_D$ = 0.63 ± 0.26 nM *v* 0.54 ± 0.17 nM; BIACore: 0.26 ± 0.14 *v* 0.51 ± 0.04 nM, IMMU-132 and hRS7, respectively). Linkage chemistry should preserve the active lactone ring form; initial *in vivo* data suggest that conjugated SN-38 may not be glucuronidated until released. IMMU-132 retains binding to the neonatal receptor, but lost 65% of ADCC activity. Free SN-38 and IMMU-132 mediated the same signaling pathways in cells, with $p21^{WAF1/Cip1}$ up-regulation, cleavage of caspase 3 and 9, and poly-ADP-ribose polymerase cleavage. IMMU-132 treatment of gastric cancer xenografts (17.5 mg/kg; 2xwk x 4wks) result in significant anti-tumor effects compared to non-specific control ADC ($P$<0.0001). In tumors not typically treated with irinotecan as a single agent (pancreatic and TNBC), IMMU-132 provided significant tumor growth inhibition. Mice with a TNBC xenograft treated with 12.5 mg/kg IMMU-132 (q4dx4) resulted in 7/8 mice alive at study conclusion (day 105) *v* only 1/9 in saline-control group ($P$=0.001). Tumor regressions occur in mice bearing aggressive pancreatic tumor xenografts (untreated median survival = 11 d) when clinically relevant doses of IMMU-132 is given (HED=8 mg/kg; $P$=0.0003). **Conclusions:** Conjugation of SN-38 to hRS7 results in a potent ADC that retains characteristics of both the antibody and the drug.

**3108 General Poster Session (Board #175), Sun, 8:00 AM-11:45 AM**

**Activation of the human natural killer cells NK-92 with a lymphocyte-derived cytokine-rich supernatant.** *Presenting Author: Ioannis F. Voutsas, Department of Animal and Human Physiology, Faculty of Biology, University of Athens, Athens, Greece*

**Background:** *Ex vivo* activated NK cells adoptively transferred to cancer patients were among the first lymphocyte populations used in immunotherapeutic protocols. To enhance NK cell cytotoxicity, individual cytokines, as well as cytokine combinations have been tested. In an effort to achieve optimal cytokine combinations, conditioned media collected upon stimulation of immune cells have also been assessed. Human lymphocytes activated *in vitro* with anti-CD3 mAb secrete various immunomodulatory agents in their culture supernatant (ACD3S). We tested the *in vivo* efficacy of ACD3S-activated NK-92 cells in an adoptive cell transfer cancer immunotherapeutic model in mice. **Methods:** ACD3S was collected by stimulating normal peripheral blood mononuclear cells for 3 days with immobilized anti-CD3. IL-2-depleted NK-92 cells were *in vitro* reactivated with ACD3S for 24 hours and their cytotoxic activity was determined using standard $^{51}$Cr-release assay against K562, FM-3 and MCF-7 targets. Perforin production was assessed by FACS. SCID mice subcutaneously inoculated with human tumor cells (FM-3 and MCF-7) were intraperitoneally administered 3 doses of ACD3S-activated NK-92 cells. Tumor growth and overall survival of the animals were recorded. **Results:** IL-2-depleted NK-92 cells showed reduced cytotoxicity againstK562, FM-3 and MCF-7 target cells. Brief exposure of NK-92 cells to ACD3S resulted in a statistically significant enhancement of their lytic ability against the same targets and their intracellular perforin production was restored to levels comparable to standard NK-92 cells. When ACD3S-activated NK-92 cells were administered to FM-3 or MCF-7 tumor-bearing SCID mice, a statistically significant delay in tumor growth was recorded. Moreover, adoptive transfer of *ex vivo* ACD3S-activated NK-92 cells was well tolerated and prolonged the survival of mice. **Conclusions:** We propose an alternative method for the *in vitro* enhancement of NK-92 cell cytotoxicity, which is retained after their adoptive transfer in animals. The protocol used for NK-92 cell activation is brief, of low cost and of low risk for side-effects, and thus could eventually be considered for the treatment of solid tumors.

**3109 General Poster Session (Board #176), Sun, 8:00 AM-11:45 AM**

**The prognostic significance of ErbB-1 (EGFR), ErbB-2 (HER2), and c-MET overexpression in resectable gastric carcinoma (GC).** *Presenting Author: Aleksandra A. Paliga, The Ottawa Hospital, Ottawa, ON, Canada*

**Background:** This study investigates the prognostic value of overexpression of EGFR, HER2 and c-Met by immunohistochemistry (IHC) in Canadian patients with GC and correlates expression with clinicopathologic characteristics. **Methods:** Tissue microarrays (TMA) containing 4 cores/tumor were constructed from 120 consecutive GC resected between 2002-2008, stained for EGFR, HER2 and c-Met by IHC, and scored by 3 pathologists, from 0-3+, based on membranous and cytoplasmic staining intensity respectively. EGFR and c-Met score greater than 2 and HER2 3+ was considered overexpressed. Receptors' expression was compared with clinicopathological characteristics and survival. **Results:** Of 113 evaluable cases – median age 64 (range 29-94), 72% were male, histologic type: intestinal 76%, diffuse 14%, mixed 10%. We observed no correlation between T, N stage and EGFR, HER2 or c-Met overexpression. Differences were observed according to histologic type: intestinal type expressed more frequently HER 2 (10/12; p=0.26) and c-Met (51/65; p=0.02). EGFR and c-Met positive and HER2 negative trended to inferior overall survival (OS). As previously reported, the prognostic effect of c-Met overexpression was time-dependent, with OS curves separating after 26 months, trending to inferior OS in the c-Met + group. **Conclusions:** In our study, HER2 overexpression in GC trended to superior OS, while EGFR and/or c-Met overexpression trended to poor OS. However, only the group of EGFR+/c-Met+/HER2-, although quite small, reached statistical significance. Larger studies to confirm our findings are warranted, since targeted therapy may provide a major therapeutic advance.

| IHC expression | n/% | Median OS in months | | HR [95% CI], p-value |
|---|---|---|---|---|
| | | Present | Absent | |
| **EGFR overexpression** | 17/15 | 15 | 30 | 1.60 [0.89-2.87], p=0.11 |
| **HER2 overexpression** | 12/11 | 85 | 29 | 0.51 [0.22-1.18], p=0.11 |
| **c-Met overexpression** | 65/58 | 28 | 48 | 1.17 [ 0.74-1.87], p=0.49 |
| **EGFR+/c-Met+/HER2-** | 11/10 | 13 months | | 0.18 [0.02-1.43], p=0.04 |
| **EGFR-/c-Met-/HER2+** | 3/3 | not reached | | |

**3110 General Poster Session (Board #177), Sun, 8:00 AM-11:45 AM**

**Combining radiotherapy and immunotherapy in the treatment of advanced cancer: A limited meta-analysis.** *Presenting Author: Christine Zhou, Rochester Institute of Technology, Rochester, NY*

**Background:** A majority of patients with advanced cancer expire from uncontrolled disseminated disease due to lack of effective systemic treatment. Radiation (RT) serves a limited role as palliative therapy. Recently, a unique synergy between RT and immunotherapeutics (IT) has been noted. This study assesses currently published clinical data combining RT and IT (cRIT) to exam the effect of such combination treatment on patient survival and toxicity. **Methods:** Eligible studies were found through PubMed. Keywords included radiation, radiotherapy, metastasis, advanced cancer, immunotherapy, interleukin, interferon, dendritic cells, and NK cells. Criteria included clinical studies combining any RT and IT in patients with diagnosed advanced disease published since Jan 1, 1999, excluding studies that also combined chemotherapy. Patient survival and toxicity data was captured and analyzed. The primary endpoints included treatment response rates and median survivals. **Results:** Eleven studies were eligible with a total of 525 patients. Of those patients, 397 received cRIT; 110 and 41 patients received RT or IT alone, respectively. RT methods included conventional radiation, intensely modulated radiation therapy, and stereotactic radiotherapy. IT agents included interleukin 2, interferon $\alpha/\beta$, thalidomide, and dendritic cells. Pooled data from seven studies (309 patients) reported response rates of complete response as 21.4% (95% CI 0-49.4%), partial response as 19.5% (95% CI 0-39.9%), stable disease as 19.7% (95% CI 1.7-37.6%), and progressive disease as 30.0% (95% CI 10.7-49.4%). The disease-free survival in cRIT patients was 18.9 (90% CI 1.8-35.9) months and overall survival was 21.7 (95% CI 6.0-37.3) months. Most common toxicities included skin reactions (49.5%), esophagitis (81.2%), anemia (21.8%), anorexia (21.2%), and liver dysfunction (19.1%). Pooled data does not show any significant increase in toxicity level with combined therapy. **Conclusions:** Based on this limited pooled analysis, cRIT appeared to be effective and safe in certain patients with advanced cancers. Randomized trials are needed to further assess the value of this new treatment modality and the best combination of RT and IT.

**TPS3111 General Poster Session (Board #178A), Sun, 8:00 AM-11:45 AM**

**RANIDO: A phase III clinical trial of racotumomab-alum or nimotuzumab versus docetaxel in advanced non-small cell lung cancer patients.** *Presenting Author: Maurenis Hernandez, Center of Molecular Immunology, Havana, Cuba*

**Background:** Despite extensive research in NSCLC treatment, overall survival remains insufficient. Immunotherapy has become a viable treatment to help the immune system to control or eliminate cancer.Racotumomab-alum is an anti-idiotypic vaccine that induce an inmunological response against N-glycolilated gangliosides in NSCLC patients. Several studies have demonstrated its antitumoral effect and safety. Nimotuzumab is an anti-EGFR monoclonal antibody that has shown promising activity in NSCLC patients without skin toxicity. The aim of this study is to evaluate safety and efficacy of racotumomab-alum or nimotuzumab versus docetaxel as second line or switch maintenance therapy for advanced NSCLC. **Methods:** This phase III, randomized clinical trial will include 670 patients with histologically confirmed stage III-IV NSCLC, after first line therapy, with PS 0-2,aged>18 years, with written informed consent. The primary endpoint will be overall survival, and also we will assess quality of life, safety and immunological response. Patient will be randomized with 2:2:1 ratio to 3 arms: racotumomab-alum, nimotuzumab or docetaxel, in 2 strata: progressive patients that will receive the treatment as second line, and non-progressive patients that will receive it as switch maintenance. Racotumomab-alum treatment consists in 5 bi-weekly intradermal immunizations and re-immunizations every 4 weeks. Nimotuzumab arm will receive 6 weekly infusions followed by bi-weekly doses .Both drugs will be given until severe worsening of PS or toxicity. Treatment will not be interrupted at disease progression, even when other therapy line will be administered concomitantly. Docetaxel will be used at 75 mg/m$^2$ for six cycles, if no progressive disease after 3$^{rd}$ cycle. In the progressive setting racotumomab-alum and nimotuzumab will be considered as non-inferior to docetaxel if 1- year OS rate is 23.1% (HR 0.75) considering a 10 % non-inferiority margin. As switch maintenance therapy both drugs will be equivalent to docetaxel, if 1- year OS rate is 36% (HR 0.62) using a 15% non- inferiority margin. An interim analysis will be done when half the patients in each arm has completed 1 year follow-up.

**TPS3112 General Poster Session (Board #178B), Sun, 8:00 AM-11:45 AM**

**A phase 1 mechanism of action study of intratumoral or intravenous administration of enadenotucirev, an oncolytic Ad11/Ad3 chimeric group B adenovirus in colon cancer patients undergoing resection of primary tumor.** *Presenting Author: Rocio Garcia-Carbonero, Hospital Universitario Virgen del Rocio, Instituto de Biomedicina de Sevilla, Sevilla, Spain*

**Background:** To date convincing clinical success with oncolytic viruses tends to be associated with intra-tumoral (IT) administration and evidence for successful systemic delivery of viruses to tumor cells by intravenous (IV) infusion remains sparse. Enadenotucirev (E or ColoAd1) is a tumor selective Ad11/Ad3 group B adenovirus that has demonstrated preclinical activity in a metastatic model of colorectal cancer (CRC) and in human tumor biopsies ex-vivo [Kuhn et al, PLoS ONE 2008; 3 (6):e2409]. Serological studies suggest that the prevalence of neutralising antibodies against group B adenoviruses is low, which may permit systemic delivery [Holterman et al, J Virol. 2004 Dec; 78(23):13207-15]. CRC patients (Pts) scheduled for resection of primary tumor present a pre-surgical window of opportunity to evaluate IV and IT delivery to tumor, lymph nodes and normal margins in resected tissues. **Methods:** Pts with histologically confirmed CRC scheduled for surgical removal of primary tumor receive E delivered either IV on day (D) 1, 3 and 5 at a dose of 1e12 viral particles (vp) over 5 min (5 pts); or IT at a dose of 1e11 vp/mL with a variable volume injected based on the tumor surface area (5 pts). Surgery is performed 7 – 15 days post first dose of E. The primary objective is to assess the pattern and extent of E spread in the tumor, normal tissue and draining lymph nodes as visualised by IHC staining of E hexon protein. Evidence of immune modulation associated with virus activity is assessed by co-staining for markers including CD8, CD11b, CD57 and CD25. Additional staining includes the primary uptake receptors of E (CD46, DSG-2) and markers of endothelial cells (CD31) and myofibroblasts (SMA) that may influence viral delivery or spread. Additional analyses include electron microscopy and qPCR. Other objectives are assessment of safety, viral kinetics and immune response following IV and IT administration. Correlation with routine tumor biomarkers e.g. K-ras, BRAF, PI3K, PTEN, SPARC will also be evaluated. To date 3 pts have been treated, 1 IT and 2 IV, and 3 pts are scheduled for treatment. Clinical trial information: EUDRACT 2013-000562-11.

**TPS3113 General Poster Session (Board #179A), Sun, 8:00 AM-11:45 AM**

**Phase II study with immunotherapy with dendritic cells (DC) and intratumoral hiltonol in patients with advanced solid tumors.** *Presenting Author: José María López-Picazo, Department of Oncology, Clinica Universidad de Navarra, Pamplona, Spain*

**Background:** DC vaccines have proved efficacy in the treatment of cancer and combination strategies are expected to increase anti-tumor activity. Our study explores the efficacy of intratumoral Hiltonol, a potent TLR3 agonist in combination with an autologous vaccine of DC loaded with self-tumor lysates that we developed in a previous pilot trial (Alfaro C, J Immunology 2011) in patients with solid tumors. Hiltonol is an stabilized form of polyI:C, a nucleic acid that mimics viral RNA. It induces local release of cytokines that promote inflammation, induce type I interferon and favour traffic of leukocytes to infiltrate the tissue. Preclinical data indicates that intratumoral administration of Hiltonol triggers pro-inflammatory changes that increase the efficacy of DC vaccination. **Methods:** In this phase II study, 25 patients with advanced solid tumors non-amenable for conventional treatment are being treated with Hiltonol and DC vaccinations. The vaccination protocol includes the following strategies: (1) pretreatment with cyclophosphamide to decrease regulatory T cells; (2) maturation and activation of DC with TNF-alpha, interferon-alpha and *poly I:C*, a potent inducer of type I interferon; (3) use of autologous tumor as antigenic source to expose DC to antigens that are exclusive of tumor cells; and (4) daily intradermal doses vaccinations during four consecutive days in 2 cycles every 4 weeks. Two intratumoral ultrasound-guided injections of Hiltonol 0.25 mg are administered on alternate days the week following each DC cycle. Sample size has been calculated using a two-stage Simon´s Minimax design, with alpha error $\alpha = 0.05$ and beta-error=0.10 for $P_0=0.05$ and $P_1=0.25$. The main objective is response rate. Secondary objectives include assessment of toxicity, overall survival and immunologic response (in vitro lymphocyte responses against tumor antigens; delayed hypersensitivity reactions; and assessment of DC maturation by expression of pro-inflammatory cytokines). Clinical trial information: NCT01734564.

**TPS3114 General Poster Session (Board #179B), Sun, 8:00 AM-11:45 AM**

**Phase I/II, open-label study of nivolumab (anti-PD-1; BMS-936558, ONO-4538) as monotherapy or combined with ipilimumab in advanced or metastatic solid tumors.** *Presenting Author: Margaret K. Callahan, Department of Medicine at Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Nivolumab, a fully human IgG4 programmed death-1 (PD-1) immune checkpoint inhibitor antibody, and ipilimumab, a fully human IgG1 cytotoxic T-lymphocyte antigen-4 receptor (CTLA-4) blocking antibody, have shown antitumor activity and durable responses in patients (pts) with solid tumors including melanoma, renal cell cancer and non-small cell lung cancer. Preclinical and clinical data indicate that combined PD-1 and CTLA-4 blockade may improve antitumor activity. We hypothesize that nivolumab alone or combined with ipilimumab may have activity in additional solid tumor types. We describe a phase I/II signal detection, open-label study to analyze the safety and efficacy of these agents in locally advanced or metastatic triple-negative breast, small-cell lung, gastric or pancreatic cancer—areas of significant unmet medical need. **Methods:** The primary and secondary objectives of this study are objective response (OR) rate and safety, respectively. Exploratory objectives include progression-free survival, overall survival, immunogenicity, pt-reported global health outcomes, and analysis of pharmacodynamic activity of nivolumab alone or combined with ipilimumab in peripheral blood and tumor tissue. Additionally, evaluation of putative biomarkers such as PD-1 ligand (PD-L1) expression will be performed. The study uses a modified Simon 2-stage design. In stage 1, 36 pts for each tumor type will be assigned 1:1 to treatment with either nivolumab 3 mg/kg IV Q2W (arm N), or nivolumab 1 mg/kg + ipilimumab 3 mg/kg IV Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W (arm N+I), until progression or toxicity. Responses will be assessed using RECIST criteria at wks 6, 12, 18, 24 and then Q12W. Treatment arms will proceed independently into stage 2 if $\geq$2 pts in a given arm for each tumor type have an OR. In stage 2, an additional 22 pts per tumor type will be assigned to each arm (N or N+I) and receive the stage 1 dosing regimen. Key eligibility criteria include ECOG status $\leq$1, available fresh or archival tumor tissue, measurable disease by CT or MRI (RECIST 1.1), and adequate bone marrow, liver and renal function. Clinical trial information: NCT01928394.

**TPS3115 General Poster Session (Board #180A), Sun, 8:00 AM-11:45 AM**

**A phase I dose escalation and cohort expansion study of lirilumab (anti-KIR; BMS-986015) in combination with nivolumab (anti-PD-1; BMS-936558, ONO-4538) in advanced solid tumors.** *Presenting Author: Neil Howard Segal, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Killer cell immunoglobulin-like receptor (KIR) and programmed death-1 (PD-1) are immune receptors that downregulate natural killer (NK) cell and T-cell activity, respectively. Immune checkpoint blockade is emerging as a novel form of cancer immunotherapy. Lirilumab, an anti-KIR antibody, potentiates NK activity and innate immunity, with only modest side effects (mostly grade 1 or 2) in a phase I monotherapy trial. Nivolumab, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody, potentiates T-cell activity and adaptive immunity, and has shown durable activity in various solid tumors, including melanoma (MEL), kidney cancer and non-small cell lung cancer (NSCLC). We hypothesize that simultaneous KIR and PD-1 blockade will enhance innate and adaptive immunity, resulting in greater clinical activity than with either agent alone. We describe a phase I study of lirilumab and nivolumab in patients (pts) with advanced solid tumors, the first collaborative trial conducted by the International Immuno-Oncology Network. **Methods**: Approximately 150 pts will be treated across dose escalation and expansion. During dose escalation, pts with any solid tumor (excluding primary central nervous system tumors) will receive nivolumab 3 mg/kg IV Q2W plus lirilumab 0.1, 0.3, 1, or 3 mg/kg Q4W in 8-week cycles (max 12 cycles). During cohort expansion, pts with NSCLC (squamous/non-squamous), MEL, select gastrointestinal cancers, head and neck squamous cell carcinoma (SCCHN), and hepatocellular carcinoma will be enrolled at the maximum tolerated dose (MTD), or highest planned dose if no MTD is defined. The primary objectives are to determine the safety, tolerability, dose-limiting toxicities, and MTD of the combination. Secondary objectives are to assess preliminary antitumor activity, pharmacokinetics, and immunogenicity (all pts), and pharmacodynamic effect on tumor-infiltrating lymphocyte subsets (MEL and SCCHN pts). Exploratory objectives include an assessment of innate and adaptive immune responses in peripheral blood and/or tumor specimens and correlation with clinical outcome. Clinical trial information: NCT01714739.

**TPS3116 General Poster Session (Board #180B), Sun, 8:00 AM-11:45 AM**

**A multicohort trial of the safety and efficacy of the PD-1 inhibitor MK-3475 in patients with hematologic malignancies.** *Presenting Author: Guillermo Garcia-Manero, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Hematologic malignancies (HMs) are responsive to immunotherapy, but in some cases appear to usurp the PD-1 pathway for tumor immune escape. MK-3475 is a potent, highly selective, humanized IgG4/kappa isotype, anti-PD-1 monoclonal antibody designed to block PD-1 interaction with PD-L1 and PD-L2. In some patients with solid tumors, MK-3475 enhances anti-tumor immune activity and has demonstrated therapeutic activity. We are testing the safety and preliminary activity of MK-3475 in patients with HMs. **Methods:** This is a multicenter, nonrandomized, open-label phase 1b trial in patients with HMs, enrolling patients in 3 separate cohorts : hypomethylating agent failure myelodysplastic syndrome (MDS); relapsed/refractory (R/R) Hodgkin lymphoma (HL); and primary mediastinal large B cell lymphoma (MLBCL)/PD-L1 positive non-Hodgkin lymphoma (NHL). Approximately 78 pts will be enrolled. The primary objectives are to determine safety, tolerability, and objective response rate or complete remission rate of 10 mg/kg MK-3475 dosed every 2 weeks until disease progression or excessive toxicity. Secondary objectives include analysis of efficacy parameters (DOR/PFS/OS) for each indication, and association between PD-L1 expression and response. Exploratory objectives include PK and the relationship of candidate efficacy/resistance biomarkers and anti-tumor activity. Response will be evaluated using standard criteria. Patients receiving at least 1 dose will be included in the safety analysis. For the primary endpoint, the study provides ~80% power to detect a difference under the null hypothesis in a given cohort (20% difference in ORR for MDS; 20% difference in CRR for HL, 25% difference in ORR for MLBCL/NHL) with one-sided type I error rate of 5%. Clinical trial information: NCT01953692.

**TPS3117 General Poster Session (Board #181A), Sun, 8:00 AM-11:45 AM**

**A phase 1 (Ph1) trial of MK-3475 combined with lenalidomide (Len) and low-dose dexamethasone (Dex) in patients (pts) with relapsed/refractory multiple myeloma (RRMM).** *Presenting Author: David Samuel DiCapua Siegel, John Theurer Cancer Center, Hackensack, NJ*

**Background:** RRMM patients refractory to proteasome inhibitors and immunomodulatory drugs (IMiD) have a very poor outcome. PD-L1 expressed on most MM plasma cells is a potential mechanism of immune evasion. MK-3475 is a potent, highly selective, humanized IgG4/kappa isotype, anti-PD-1 monoclonal antibody designed to block PD-1 interaction with PD-L1 and PD-L2, enhancing lymphocytic activity, tumor regression and immune rejection. **Methods:** This is an open-label, Ph1 multicenter, non-randomized dose escalation trial of MK-3475 combined with Len/Low-dose Dex in RRMM patients failing two lines of prior therapy, including bortezomib and an IMiD, using a modified 3+3 design followed by a toxicity probability interval (TPI) for dose confirmation. Cohorts of 3-6 pts per dose level (DL) will be enrolled sequentially at escalating doses of MK-3475 (2, 5, 10 mg/kg) with Len (25mg) / Low-dose Dex (40mg) until a preliminary maximum tolerated dose (MTD) or maximum administered dose (MAD), is identified. Additional pts will be enrolled at the MTD/MAD in combination with Len/Low-dose Dex to confirm dose and evaluate safety and preliminary efficacy. Primary objectives of the trial are to establish a MTD/MAD and determine safety and tolerability of MK-3475 / Len / Dex in pts with RRMM. Secondary objectivesinclude analysis of efficacy (ORR/CR/sCR/TTP/DOR/PFS/OS), and PD-L1 expression and corresponding efficacy. Exploratory objectives are PK of MK-3475 with Len/Dex and the relationship of candidate efficacy/resistance biomarkers and anti-tumor activity. AEs as categorized in the NCI CTCAE v 4 will be summarized by DL for all pts receiving ≥1 dose. After the TPI, the dose-response relationship (% of subjects with ≥1 dose limiting toxicity (DLT) for each DL selected for confirmation), will be estimated by Bayesian pooling of adjacent violators analysis, using all DLT data. The dose-response profile, along with other tolerability data, will determine the recommended Ph2 dose for the combination. Efficacy endpoints (evaluated using established International Working Group response criteria) will be summarized for each DL using descriptive statistics. Clinical trial information: NCT02036502.

**TPS3118 General Poster Session (Board #181B), Sun, 8:00 AM-11:45 AM**

**A phase I study of adoptive T-cell therapy with or without dendritic cell vaccination in patients with metastatic melanoma.** *Presenting Author: Roger Tell, Department of Oncology-Pathology, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden*

**Background**: The addition of autologous dendritic cell vaccine (DCV) to adoptive T-cell therapy (ACT) may enhance the anti-tumor immune responses in melanoma. **Methods**: Study Population - Patients with advanced malignant melanoma who have tumor that is accessible for core biopsy or is resectable; confirmed progressing metastatic disease; refractory to standard therapy; not having had prior systemic cancer therapy within the past four weeks at the time of the start of the lymphodepletion regimen. Sample Size - 10 patients will be evaluated, 5 patients in each group. Study Desig - A phase I, nonrandomized, multicohort trial will be conducted to enroll patients at a single institution in a modified 5+5 design. Five patients will be assigned to each cohort (A or B) and receive adoptive transfer of in vitro expanded autologous tumor infiltrating lymphocytes (TIL) without (A) or with (B) autologous tumor lysate loaded DCV administered i.d. 3-5 times with weekly intervals. Prior to TIL transfer all patients will be pre-treated with a preconditioning regimen consisting of cyclophosphamide (60 mg/kg per day for 2 days) followed by fludarabine (25 mg/m(2) per day for 5 days). Administration of TIL will be followed by IL-2 administration (100,000 IU/kg intravenously three times a day to a maximum of 14 doses). All subjects will be monitored for 17 weeks. Outcome Measures - (1) The primary objective of the study is to investigate the safety of the T-cell therapy, with and without DCV, as evaluated according to the NCI CTCAE scale version 4.0. (2) The secondary objective is to measure time to disease progression according to RECIST 1.1. (3) TIL will be analyzed for anti-tumor reactivity as a possible predictive biomarker using an autologous melanoma cell line generated from the patient (when possible), or semi-allogeneic melanoma cell line that has at least one matched HLA-A allele, as targets. (4) In order to assess if the addition of DCV post TIL transfer has influenced TIL persistence, TIL and PBMC will be analysed by TCR sequencing. Clinical trial information: NCT01946373.

**TPS3119 General Poster Session (Board #182A), Sun, 8:00 AM-11:45 AM**

**A phase Ib multicohort study of MK-3475 in patients with advanced solid tumors.** *Presenting Author: Rita Nanda, The University of Chicago, Chicago, IL*

**Background:** Immune surveillance is one of the primary mechanisms to prevent neoplastic growth. The PD-1 receptor-ligand pathway can be used by tumors to evade immune surveillance. MK-3475 is a potent, highly selective, humanized IgG4/kappa isotype mAb designed to block PD-1 interaction with its ligands PD-L1 and PD-L2, and can reactivate the immune system to eradicate the host tumor. **Methods:** This is a multicenter, non-randomized, multi-cohort trial of single agent MK-3475 in over 130 patients diagnosed with locally recurrent and/or distant metastatic 1) triple negative breast cancer, 2) head and neck cancer (both HPV and non-HPV associated), 3) urinary tract cancer or 4) gastric cancer. All enrolled patients must express PD-L1 within their tumor microenvironment. MK-3475 is given intravenously at 10 mg/kg every 2 weeks. Primary objectives are to determine (1) safety and tolerability and (2) anti-tumor activity of MK-3475 in patients with PD-L1 positive, advanced solid tumors. Secondary objectives include progression-free survival, overall survival and response duration in treated patients. Radiographic imaging will be obtained every 8 weeks to assess clinical response defined by RECIST 1.1. Tumor biopsies will be available both pre-treatment and during treatment to allow investigation of candidate biomarkers which may predict clinical response to immune checkpoint blockade. Treatment continues for 24 months or until complete response, disease progression, unacceptable toxicity, physician decision, or patient's withdrawal of study consent. Retreatment for patients who progress after a complete response is allowed. AEs will be monitored and graded according to guidelines in the NCI CTCAE v. 4.0. Summary statistics for safety endpoints and the incidence rate of immune-related AEs and of Grade 3-5 AEs will be calculated. Efficacy will be evaluated in each cohort, in patients with baseline and with either ≥1 post-baseline evaluation or who discontinue the trial due to progressive disease or a drug-related AE. Overall response rate assessed by independent radiology review will be used as the primary endpoint for efficacy. Clinical trial information: NCT01848834.

**TPS3120^ General Poster Session (Board #182B), Sun, 8:00 AM-11:45 AM**

**A phase 1 study to evaluate the safety and tolerability of MEDI4736, an anti–PD-L1 antibody, in combination with tremelimumab in patients with advanced solid tumors.** *Presenting Author: Margaret K. Callahan, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** MEDI4736 (M) is a human IgG1 monoclonal antibody that binds specifically to programmed cell death ligand 1 (PD-L1), expressed on immune cells and tumor cells, preventing binding to PD-1 and CD80, expressed on T cells. Tremelimumab (T) is a human IgG2 monoclonal antibody directed against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Both PD-1 and CTLA-4 are regulators, or checkpoints, of T cell activation. The mechanisms of activation for these checkpoints are non-redundant, suggesting that targeting both pathways may have additive or synergistic activity. Data from mouse models of transplantable solid tumors support synergistic antitumor activity of combination immunotherapy. **Methods:** This open-label phase I study (NCT01975831) is designed to evaluate the safety of the combination of M and T in patients (pts) with advanced solid tumors. Eligible pts include those with histologically confirmed non-small cell lung, cervical, head and neck, colorectal, ovarian cancers, or renal cell carcinoma with adequate performance status and organ function who are not eligible for, have declined, or have failed standard treatment. The dose escalation phase uses a 3+3 design: M is administered at escalating doses starting at 0.3 mg/kg every 2 wks and T is administered at escalating doses starting at 3 mg/kg (up to 10 mg/kg) every 4 wks for the first 6 cycles, then every 12 wks. An expansion phase will evaluate the combination therapy at the maximum tolerated doses in each tumor type. Treatment may continue for up to 12 months or until progressive disease or unacceptable toxicity. The primary study end points are safety/tolerability and identification of the maximum tolerated dose of the combination. Secondary objectives include pharmacokinetics, immunogenicity, and clinical activity, as assessed by tumor response (RECIST v1.1 and Immune-related Response Criteria), progression-free survival, and overall survival. Exploratory objectives include the evaluation of tumor and serum PD-L1 levels, immune cell phenotypes, and tumor microenvironment. Recruitment is ongoing to a target enrollment of 102 pts. Clinical trial information: NCT01975831.

**TPS3121 General Poster Session (Board #183A), Sun, 8:00 AM-11:45 AM**

**First-in-human phase 1 study of the novel indoleamine-2,3-dioxygenase (IDO) inhibitor NLG-919.** *Presenting Author: Samir Khleif, GRU Cancer Center, Augusta, GA*

**Background:** IDO is an enzyme that catalyzes the initial and rate limiting step in the conversion of tryptophan to kynurenine. Tryptophan depletion enhances the number and function of the Treg (suppressive) arm of the immune system and inhibits the effector T cell (stimulatory) arm. In addition, it has been shown that kynurenine metabolites may augment the suppressive effects on inflammation and immune responses. The main function of IDO is the regulation of acquired local and peripheral immune tolerance in normal and pathological conditions. In cancer, IDO can either be expressed directly by the tumor cells themselves, or induced indirectly in host antigen presenting cells by the tumor. In these settings, IDO mediates an acquired immune tolerance towards tumors, allowing tumors to thwart immune responses by the host. Therefore, IDO is an attractive target in therapeutic interventions aimed at restoring the immune response towards the tumor. NLG-919 inhibits the enzymatic activity of IDO. Agents that inhibit the IDO pathway have been shown to act synergistically with each other as well as with chemotherapy and other checkpoint inhibitors such as anti-CTLA-4, anti-PD-1, and anti-PD-L1. We believe current SOC treatments that incorporate single or multiple IDO pathway inhibitors in combination with other checkpoint inhibitors may add significant benefit to an active immunotherapy regimen. **Methods:** This study is a Phase 1, dose escalation study of NLG-919 for patients with advanced solid tumor malignancies. Eligible patients have pathologically confirmed relapsed or refractory solid tumors for which no approved therapy exists. Up to 36 patients will be enrolled and the dose of NLG-919 will be escalated according to a standard 3+3 design. NLG-919 will be administered orally twice daily for the first 21 days of repeating 28 day cycles. Patients may receive drug until disease progression. Endpoints include safety, toxicity, and determination of a MTD or MBED that can be taken forward into phase 2 studies. Furthermore, additional immunological, pharmacokinetic, and pharmacodynamics tests are also planned. Clinical trial information: NCT02048709.

**TPS3122^ General Poster Session (Board #183B), Sun, 8:00 AM-11:45 AM**

**TREAT-ME 1: Treatment of advanced gastrointestinal cancer in a clinical phase I/II trial with genetically modified mesenchymal stem cells.** *Presenting Author: Jobst von Einem, Department for Hematology and Oncology, Klinikum Großhadern and Comprehensive Cancer Center, LMU Munich, Munich, Germany*

**Background:** Next generation somatic cell-based therapies are at the edge to add another therapeutic modality to clinical oncology particular for malignancies with still high medical need. Based on a vast number of preclinical data, we have initiated a phase I/II clinical trial for the treatment of advanced adenocarcinoma of the gastrointestinal tract applying genetically-modified mesenchymal stem cells (MSC) from the patients' own bone marrow (TREAT-ME 1). **Methods:** Autologous MSC have the capability to home to any (inflammatory) tumor site or metastasis to deliver therapeutic gene products in a highly effective way. Our pharmaceutical product (IND) is a genetically modified somatic cell suspension. The stable integration of the therapeutic gene (here HSV-TK) under the control of a tumor specific promoter (based on the molecular tumor tissue profile) is accomplished through the use of a gamma-retroviral, replication incompetent and self-inactivating (SIN) vector system. The manufactured MSC cell-suspension is applied intravenously for three consecutive weeks, followed by the administration of the prodrug which is activated only in the context of the tumor environment. The study has started to recruit (Oct 2013) and the first patient cohorts are designed to define the optimal cell dose and feasibility. Safety and tolerability will be evaluated and as secondary variables TTP and OS up to one year. Interim results of the phase I safety phase are expected in 2014. In this trial we have already demonstrated that the genetic modification of autologous MSCs from cancer patients and their manufacturing as an IND is feasible and does not alter the typical biological properties of MSCs. The therapeutic administration of genetically modified MSCs as a principle mechanism of a cell-based gene therapy respectively a gene product delivery tool holds promise for the clinical application of a patient-tailored combination of cell- and suicide gene therapy. We expect this innovative medicinal product will provide high local therapeutic activity and low (off-target) toxicity resulting in a positive safety profile.

**TPS3123 General Poster Session (Board #184A), Sun, 8:00 AM-11:45 AM**

**Active8: A randomized, double-blind, placebo-controlled study of chemotherapy plus cetuximab in combination with VTX-2337 in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN).** *Presenting Author: Ezra E.W. Cohen, Moores Cancer Center, University of California at San Diego, La Jolla, CA*

**Background:** The potential for synergy between cytotoxic and immunologic agents is an exciting area of exploration in oncology. Many chemotherapeutics like platinum and 5-FU can induce immunogenic antitumor effects. Natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity (ADCC) is an important mechanism of IgG1 monoclonal antibodies (MAb). VTX-2337 is a novel Toll-like receptor 8 (TLR8) agonist with preclinical data demonstrating synergistic effects with chemotherapy and increased ADCC with MAbs. For recurrent or metastatic SCCHN, the EXTREME regimen adding cetuximab to platinum and 5-FU improved median overall survival (OS) by 2.7 months. While a significant advance, further improvement is needed. Synergy with immunotherapy is one option. A phase Ib study of cetuximab and VTX-2337 in recurrent or metastatic SCCHN patients showed the combination to be tolerable and active. TLR8 activation and NK cell stimulation and mobilization provided a rationale to further assess this combination in SCCHN patients. **Methods:** This randomized, double-blind, placebo-controlled, phase 2 study evaluates the safety and efficacy of VTX-2337 with EXTREME vs. EXTREME alone for first-line treatment of recurrent or metastatic SCCHN. Patients must have a confirmed diagnosis with at least one measurable lesion and no previous systemic therapy for recurrence. Approximately 175 pts will be randomized 1:1 to receive VTX-2337 + EXTREME or placebo + EXTREME for 6 cycles (q3wk), followed by weekly cetuximab with biweekly VTX-2337/placebo. The primary objective is to compare progression-free survival (PFS) according to immune-related response evaluation criteria between the 2 treatment arms as determined by an independent review facility. Secondary objectives include comparisons of safety, OS, objective response rate, duration of best response, disease control rate, and duration of disease control of the two treatment groups. Pharmacodynamics and pharmacokinetics of VTX-2337 as well as translational medicine correlatives will also be evaluated. Enrollment began in October 2013.

**TPS3124 General Poster Session (Board #184B), Sun, 8:00 AM-11:45 AM**

**A phase 2 study of docetaxel in combination with indoximod in metastatic breast cancer.** *Presenting Author: Hatem Hussein Soliman, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

**Background:** Indoleamine 2,3 dioxygenase (IDO) is a tryptophan-catabolizing enzyme that tumors use to create a state of immunosuppression. Indoximod (D-1-methyltryptophan) is a broad IDO pathway inhibitor as it has been shown to potentially interfere with multiple targets within the IDO pathway. Preclinical studies in MMTV-neu mouse models have shown that indoximod combined with chemotherapy was more effective in causing tumor regressions than either agent alone. A phase 1 trial combining docetaxel and indoximod demonstrated safety and responses in metastatic breast cancer patients. Based on this data a phase 2 trial in metastatic breast cancer was initiated. **Methods:** The study is a 1:1 randomized, placebo controlled two arm phase 2 study. The study treatment is docetaxel 75mg/m2 IV D8 plus indoximod 1200mg PO BID D1-14 every 21 days or matching placebo. Primary endpoint is progression free survival. Secondary endpoints include overall survival, response rate per RECIST 1.1, and immune response correlative assays. Patients with measurable, histologically confirmed metastatic breast cancer, no prior chemotherapies for metastatic disease, ER+ or ER – HER2 -, ECOG PS 0-1, no active CNS disease, no active autoimmune disease are eligible. Target enrollment is 154 patients and it is currently enrolling patients in multiple clinical sites all around the US. Clinical trial information: NCT01792050.

**TPS3125 General Poster Session (Board #185A), Sun, 8:00 AM-11:45 AM**

**A phase 2 study of Ad.p53 DC vaccine in combination with indoximod in metastatic solid tumors.** *Presenting Author: Hatem Hussein Soliman, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

**Background:** Indoelamine 2,3 dioxygenase (IDO) is an inducible tryptophan-catabolizing enzyme that downregulates the immune system. Many tumor cell types overexpress IDO to avoid elimination by infiltrating cytotoxic T cells. Indoximod (1-methyl-D-tryptophan/ D1MT) is an IDO pathway inhibitor. Published preclinical data suggests that blockade of IDO with indoximod enhances the immunologic response to dendritic cell (DC) vaccines. Ad.p53 is an adenovirus used for generating DC vaccines directed against p53 epitopes. Ad.p53 when given to previously treated SCLC patients significantly increased their response rate to subsequent chemotherapy. Data showing a similar trend for enhanced response to subsequent chemotherapy was presented in breast cancer patients who were treated in the phase I trial using Ad.p53DC and indoximod. The primary endpoint in phase II is the response rate of indoximod +Ad.p53 in metastatic breast cancer patients. Secondary endpoints include safety, PFS, OS, and immunologic correlates. **Methods:** This Phase 2 study uses a single arm, Simon two stage design. Patients with measurable, metastatic breast cancer, <3 lines of prior chemotherapy in metastatic setting, p53 immunohistochemistry >5% in archival tumor specimen, ECOG 0-2, no autoimmune disease are eligible. Study treatment consists of 1600mg PO BID of indoximod given continuously along with up to 6 fixed doses of Ad.p53DC SQ vaccinations q2weeks. First stage of accrual is 12 patients with one response required for progression into the second stage of 25 additional patients. The study design is based on the alternative hypothesis of a 20% response rate, with 90% power to detect this level of activity with a significance of .09 (assuming a total of 4 responses out of 37 are observed). Accrual to the first stage of this trial is completed and the study remains open with some of the patients still undergoing study treatment. Clinical trial information: NCT01042535.

**TPS3126 General Poster Session (Board #185B), Sun, 8:00 AM-11:45 AM**

**A first-in-human study of pegylated recombinant human IL-10 (AM0010), daily administered for four months in selected advanced solid tumors.** *Presenting Author: Todd Michael Bauer, Sarah Cannon Research Institute/ Tennessee Oncology, PLLC, Nashville, TN*

**Background:** Cancer immunotherapy targets the activation of tumor infiltrating CD8 T cells. Tumor associated inflammation on the other hand is thought to both promote tumor growth and to inhibit the CD8 mediated immune responses. IL-10 directly induces Interferon gamma in tumor resident CD8+ T cells, stimulates the cytotoxic activity of CD8+ T cells, increases the immunoglobulin production of B cells and has strong anti-inflammatory activity. In preclinical studies, PEGylated IL-10 (PEG-IL-10) but not non-PEGylated-IL-10 induces the rejection of large syngeneic tumors and the development of immunological memory against the tumor cells. Maximal antitumor efficacy required daily subcutaneous injections of PEG-IL-10 for 2-4 weeks indicating the need for prolonged stimulation of the immune system. rHuIL-10 was used in previous clinical trials in inflammatory diseases but its short T1/2 prevented a meaningful clinical benefit. AM0010, a PEGylated human IL-10, is safe in preclinical species and a first in human study was started November 2013. **Methods:** This study will be performed in two parts and will enroll approximately 28 patients with advanced solid tumors in the escalation phase, followed by at least one expansion cohort of 15 patients. Patients with melanoma, non-small cell lung cancer, renal cell cancer, colorectal cancer, castrate resistant prostate cancer, ovarian cancer and pancreatic cancer will be enrolled during the dose escalation phase, followed by at least one disease specific expansion cohort. Patients will daily self-administrate subcutaneous doses of AM0010 for four cycles of 1 month without dosing holidays. The primary objectives are to establish the safety and tolerability, dose limiting toxicities, and MTD of AM0010. Secondary objectives are to assess preliminary anti-tumor activity, pharmacokinetics, and immunogenicity of AM0010. The pharmacodynamic effects of AM0010 on innate and adaptive immunity will be evaluated using serum cytokine measurements, immunohistochemistry of tumor infiltrating T cells and humoral and cellular tumor antigen specific responses in the blood of patients. Clinical trial information: NCT02009449.

**TPS3127 General Poster Session (Board #186A), Sun, 8:00 AM-11:45 AM**

**A phase 1b study to assess the safety of PLX3397, a CSF-1 receptor inhibitor, and paclitaxel in patients with advanced solid tumors.** *Presenting Author: Neelesh Sharma, University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH*

**Background:** Tumor-associated macrophages (TAMs) mediate resistance to chemotherapy and radiation therapy. Macrophages are regulated in part by colony stimulating factor -1 (CSF-1), which signals through the CSF-1 receptor (CSF-1R) expressed predominantly on TAMs. CSF-1 is expressed by several types of malignancies (including breast and prostate cancer, leiomyosarcoma and glioblastoma) and correlates with extent of TAM presence in tumor parenchyma. Preclinical studies demonstrated that tumor exposure to cytotoxic therapies such as paclitaxel, cisplatin or ionizing radiation lead to increased expression of CSF-1, IL-34 (the other ligand for CSF1R), and chemokines regulating TAM recruitments, CCL8/ MCP2. This is associated with an increased presence of TAMs in residual tumors, resulting in a tumor immune microenvironment favoring malignant cell proliferation and survival. PLX3397 is an orally available small molecule inhibitor of CSF-1R with IC50 of ~17 nM. *In vivo* studies in transgenic MMTV-PyMT mice with late-stage mammary cancer and lung metastases treated with paclitaxel and PLX3397 showed: reduced macrophage infiltration of primary tumor tissue; increased presence of tumor infiltrating $CD8^+$ and $CD4^+$ T-lymphocytes; and reduced tumor growth as well as pulmonary metastases compared to paclitaxel alone (DeNardo et al., 2011). These studies provide clinical rationale to study the combination of PLX3397 and paclitaxel in solid tumors. Safety, pharmacokinetics and pharmacodynamics data of single-agent PLX3397 have been previously presented (Anthony et al., 2011). **Methods:** In this phase Ib trial, patients with advanced solid tumors are treated with weekly paclitaxel and escalating doses of continuous dosing of oral PLX3397 to establish a RP2D of PLX3397. This will be followed by a dose expansion to a total of 15 patients, to further determine safety and preliminary efficacy of this combination. Exploratory objectives include correlating changes in serum CSF-1 levels and identifying novel biomarkers of clinical activity. This study will support further development of the PLX3397/paclitaxel combination in the I-SPY-2 neoadjuvant breast cancer trial. Clinical trial information: NCT01525602.

**TPS3128 General Poster Session (Board #186B), Sun, 8:00 AM-11:45 AM**

**Phase 2 study of programmed death-1 antibody (anti-PD-1, MK-3475) in patients with microsatellite unstable (MSI) tumors.** *Presenting Author: Dung T. Le, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

**Background:** We hypothesize that a correlation may exist between the number of somatic mutations in individual tumors and the response to immune checkpoint inhibitors since each protein-coding mutation has the potential to serve as a novel antigen for an immune response. This may explain why lung cancers and melanomas, which harbor hundreds of somatic tumors, respond so well to these agents. Microsatellite unstable (MSI) tumors are deficient in DNA mismatch repair which leads to hundreds to thousands of spontaneous mutations. Furthermore, similar to melanoma, MSI positive colon cancers, there is often prominent lymphocyte infiltration. PD-1 is upregulated on activated T cells and provides inhibitory signals to T cells undergoing activation. MK-3475 is a humanized monoclonal IgG4 antibody against PD-1 and is showing activity in multiple tumor types. This study aims to establish the treatment benefit and evaluate MSI as a predictive marker of response to anti-PD-1 blockade. **Methods:** This is an open-label, 2-stage, phase 2 study to evaluate the clinical activity of MK-3475 in 3 cohorts of patients: MSI positive colorectal cancer (CRC); MSI negative CRC; and MSI positive solid tumors but not CRC. MK-3475 will be administered at 10 mg/kg every 14 days. The co-primary endpoints for CRC cohorts are immune-related progression-free survival (irPFS) rate at 20 weeks and objective response rate assessed using immune related response criteria. The primary endpoint for the cohort with other solid tumors is irPFS at 20 weeks. Secondary endpoints include disease control rate, progression-free survival, overall survival and safety. Each MSI positive and MSI negative CRC cohort will evaluate up to 25 patients, and the cohort with MSI positive solid tumors but not CRC will enroll up to 21 patients. Results from exome sequencing and PD-L1 expression using IHC on tumor tissue will be correlated with response. Clinical trial information: NCT01876511.

**TPS3129 General Poster Session (Board #187A), Sun, 8:00 AM-11:45 AM**

**Randomized phase II study with dendritic cell (DC) immunotherapy in patients with resected hepatic metastasis of colorectal carcinoma.** *Presenting Author: Javier Rodriguez, Medical Oncology, Clinica Universidad de Navarra, Pamplona, Spain*

**Background:** Cellular immunotherapy with DC is a feasible strategy with proved activity in the treatment of cancer. Preclinical and clinical data indicate that efficacy of DC immunotherapy is improved when used in clinical settings of minimal residual disease, and Sipuleucel-T is the first approved treatment based in this approach. We are exploring the efficacy of an autologous vaccine of DC loaded with self-tumor antigens that we developed in a previous pilot trial (Alfaro, J Immunology 2011) in patients with colorectal cancer with completely resected hepatic metastasis following standard adjuvant treatment. **Methods:** In this randomized phase II study, patients with colorectal carcinoma with hepatic metastasis treated with complete surgical resection and standard adjuvant chemotherapy are randomized to receive DC vaccine or observation. The two-cycle vaccination protocol includes the following strategies: (1) pretreatment with cyclophosphamide to decrease regulatory T cells; (2) maturation and activation of DC with TNF-alpha, interferon-alpha and *poly I:C*, a potent inducer of type I interferon; (3) use of autologous tumor from resected liver metastasis as antigenic source to load antigens onto DC, including antigens that are exclusive of tumor cells; and (4) administration of daily intradermal vaccines during four consecutive days in 2 cycles every 4 weeks. The strategy is to replicate the immune response induced during an acute viral infection in terms of activation signals and persistence of antigens in lymph nodes. The main objective is progression-free survival. Thirty-six patients will be included, allowing to detect a HR=1.75 (alpha error=0.2, beta error=0.35). Secondary objectives include assessment of toxicity, overall survival and immunologic response (in vitro lymphocyte responses against tumor antigens; delayed hypersensitivity reactions; induction of tumor antibody responses; DC activation parameters including IL-12 and IL-6 production and expression of CD80, CD83, CD86, B7-H1, B7-H4 and B7-DC; assessment of DC maturation by expression of pro-inflammatory cytokines; and DC migration). Clinical trial information: NCT01348256.

**TPS3130 General Poster Session (Board #187B), Sun, 8:00 AM-11:45 AM**

**Safety and immunologic efficacy of personalized multiple HLA class I-restricted peptide vaccines for breast cancer patients in the adjuvant setting.** *Presenting Author: Uhi Toh, Department of Surgery, Kurume University Faculty of Medicine, Kurume, Japan*

**Background:** Despite several attempts to introduce immunotherapy in cancer treatments have been carried out mostly without achieving significant clinical effects for refractory cancer, HER-2+ breast cancer(BC) patients (pts) who received adjuvant trastuzumab(Tz) followed by vaccination with peptide vaccines(PVs) have a lower recurrence rate than adjuvant Tz therapy alone and suggested new adjuvant that can increase the efficacy of the novel immunotherapic strategies.(Sears AK, J Clin Oncol 29: 2011) We previously demonstrated safety, high immunogenicity and clinical benefit for pts with metastatic BC using selected personalized PVs (Toh U, 2013 SABCS), we further conducted a Phase II trial evaluating selected multiple PVs in the adjuvant setting to prevent BC recurrence. The primary endpoint of the study is to evaluate the safety and immunological response to selected multiple peptides vaccination carried out in pts who are in clinical disease free and have completed standard adjuvant chemotherapy, the secondary endpoints were recurrence free survival and overall survival. **Methods:** This single arm, multicentrePhase II trial enrolled each of HLA-A2, A24, A26 or A3 superfamily molecule postoperative BC patients. Pre-vaccination plasma was measured for their IgG levels reactive to each of the previously reported 31 candidate peptides followed by administration subcutaneously of the four peptides at maximum showing higher levels of IgG. Total sixteen vaccinations were given as weekly for initial eight administrations and as biweekly for further eight inoculations. The concurrent adjuvant endocrine therapy was available during vaccinations. Currently 22 pts have been accrued and 17 pts have completed treatment. Follow-up will be carried out for 24 months to register adverse events and to evaluate the immunological effects. Levels of IgG reactive to each peptide in the pre- and post-treatment plasma were measured using LUMNEX system as well as specific T-cell cytotoxicity assessed by Elispot in the pre- and post-treatment peripheral blood lymphocytes at every 6 times of vaccination. Correlation between survival and the immune activity was investigated. Clinical trial information: 000003081.

**TPS3131 General Poster Session (Board #188A), Sun, 8:00 AM-11:45 AM**

**A phase 1A/1B, two-stage study of a PSA/IL-2/GM-CSF vaccine for the treatment of PSA-recurrent prostate cancer in hormone-naive and hormone-independent patients.** *Presenting Author: Gregory A. Daniels, VA San Diego Healthcare System, San Diego, CA*

**Background:** Prostate cancer vaccines demonstrate clinical benefit in hormone refractory metastatic prostate cancer patients. The broader application to earlier disease stages remains both cost prohibitive and of unclear benefit. The aim of this trial evaluates the safety and tolerability of a simple recombinant PSA vaccine in men with either hormone naïve or hormone-independent prostate cancer without evidence of metastasis ("PSA-only"). Secondary aims include changes in PSA doubling time, time to measurable disease and vaccine-induced immunologic assessments. **Methods:** This is a Phase 1A/1B trial of PSA/IL-2/GM-CSF vaccine in recurrent prostate cancer in hormone-naïveand hormone-independent patients**.** Major inclusion criteria include adenocarcinoma of the prostate, rising serum PSA and no measurable disease. Phase 1A examines the rate of dose limiting adverse events (DLAEs) in an initial course of 6 vaccinations ("induction vaccination"). Phase 1B examines the rate of DLAEs with a continued coarse of an additional 6 vaccinations ("maintenance vaccine") in another 28 patients. There will be an interim analysis after the first 20 patients accrue. All patients will receive intradermal injections of the PSA/IL-2/GM-CSF vaccine at weeks 1, 2, 3, 7,11, and 15. Secondary endpoints including serum PSA and prostatic acid phosphatase (PAP) level measurements along withimmunological evaluations. All patients will be evaluated for diseaseprogression at Week 19. If the Phase 1A portion of the trial demonstrates safety of the induction vaccination, 28 additional patients will be enrolled in the Phase 1B portion of the trial. Patients will receive maintenance vaccine alternating every 4 weeks between IL-2 and the complete vaccine (PSA/IL-2/GM-CSF) starting at week 23 and until week 43 (6 injections total). To date, eight of twenty patients have received at least one vaccine injection in the phase IA portion without DLAEs. Enrollment continues in phase IA.

**TPS3132 General Poster Session (Board #188B), Sun, 8:00 AM-11:45 AM**

**A phase I study of BPX-201 vaccine plus AP1903 for chemo-naive metastatic castrate-resistant prostate cancer (mCRPC).** *Presenting Author: Guru Sonpavde, The University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL*

**Background:** We have reported promising activity, including one RECIST PR and potential synergy with chemotherapy, in a phase I trial of 18 men with mCRPC administered BPX-101 (Bellicum Pharmaceuticals), an autologous antigen presenting cell (APC)-based vaccine, pulsed with PSMA (prostate specific membrane antigen) and transduced with an adenovirus bearing iCD40, with each dose followed by *in vivo* activation by dimerizer drug AP1903 infusion (Slawin KM, Sonpavde G, et al, ASCO 2011). This provided a rationale for the study of our second-generation vaccine, BPX-201, manufactured with APCs transduced with an adenoviral vector bearing genes for iMyD88/CD40, which includes signaling elements from the "universal" adjuvant adapter, MyD88 (Narayanan, et al, JCI 2011), and PSMA, and followed by AP1903 activation. **Methods:** A 3+3 design Phase I dose escalation trial (NCT01823978) evaluating BPX-201 plus AP1903 is ongoing for men with chemo-naive mCRPC in 2 institutions: UAB (University of Alabama, Birmingham, AL) and Baylor Sammons Cancer Center (Dallas, TX). The primary objective is to determine the safety of BPX-201 in doses of 10, 20 and 40 million cells and AP1903 when administered to patients with chemo-naive mCRPC. Six patients will be enrolled per dose cohort (total accrual=18). Secondary objectives are to evaluate efficacy with vaccine and subsequent therapy, pharmacokinetics, and circulating tumor cells for up to 2 years. Extensive immune monitoring is performed during both the vaccination phase and during subsequent therapies. Patients undergo leukapheresis once at baseline followed by therapy with cryopreserved product after 2-3 weeks given intradermally q 2 weeks x 6 doses. AP1903 is administered intravenously 24 hours after each dose of the vaccine. Radiographic evaluation is performed q 3 months or earlier, if required. Post-vaccine systemic therapy is initiated for symptomatic or radiographic progression and not for PSA progression alone. Enrollment on the lowest dose cohort (n=6) is complete without dose limiting toxicities. Cohort 2 started enrolling in January 2014. Clinical trial information: NCT01823978.

**TPS3133 General Poster Session (Board #189A), Sun, 8:00 AM-11:45 AM**

**Local and systemic antitumor effects of activated autologous dendritic cells for intratumoral injection: A phase I/II trial.** *Presenting Author: Vivek Subbiah, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Dendritic cells (DC) are antigen presenting cells proficient in inducing de novo immune responses, and the presence of intratumoral DCs confers a survival advantage to patients, likely due to an improved balance between the immune system and the growing tumor lesion. We have initiated a Phase I/II clinical trial to exploit this finding, by using partially activated autologous DCs (aDC; DCVax-Direct) for intratumoral injection in inoperable tumors for which limited treatment options exist. These aDC retain antigen uptake and presentation capability and are conditioned to complete the maturation process following injection, resulting in initiation of a broad anti-tumor immune response. Preclinical animal data have demonstrated that these aDC can mobilize both local and systemic immune responses, and effectively clear both injected (local) and non-injected (distal) inoperable tumor lesions. **Methods:** The Phase I component of the trial aims to enroll 6 patients each in following indications: colorectal cancer, lung cancer, breast cancer with brain metastases, pancreatic cancer, melanoma and 'other'. Patients must have had at least one recent anti-tumor treatment other than active immune therapy prior to enrollment into the trial. A dose escalation across indications investigates the safety of 3 dose levels. The aDC are injected intratumorally, using imaging guidance, at days 0, 7 and 14, followed by injections at 8 and 16 weeks. Initial DLT assessments are done following the first three injections. Tumor biopsies are taken at the time of injections to assess local effects on the injection of aDC, and tumor response is assessed using both RECIST and Immune Related Response Criteria, starting 8 weeks after the first injection. The first dose cohort of the Phase I component has completed DLT assessments, and the second dose cohort's enrollment is nearly complete. In addition, the "other" cohort of multiple cancers has been fully enrolled. Correlative immune-biomarkers studies to evaluate response and/or resistance mechanisms are planned. The Phase II component will enroll 24 patients in a selected indication, based on the results obtained in Phase I. Clinical trial information: NCT01882946.

**TPS3134 General Poster Session (Board #189B), Sun, 8:00 AM-11:45 AM**

**Autologous dendritic cell vaccination (DCVAC/OvCa) added to standard of care therapy in three open-label randomized phase 2 studies in women with advanced stage ovarian cancer (OC).** *Presenting Author: Lukas Rob, Department of Gynecology and Obstetrics, Charles University and University Hospital Motol, Prague, Czech Republic*

**Background:** OC is the 5$^{th}$ most common type of cancer in women and the 4$^{th}$most common cause of cancer death in women. Immunotherapy, for induction of tumor cell specific immune responses destroying tumor cells, has emerged as a promising treatment modality in solid malignant tumors. Studies have shown that chemotherapy can be combined with vaccine without blunting the response to the vaccine. **Methods:** The approach tested in the reported trials is a patient specific active cellular immunotherapy using autologous dendritic cells differentiated from peripheral blood monocytes and presenting tumor antigens derived from killed OC cell lines (SK-OV-3, OV-90). A phase 1 trial of DCVAC/OvCa (EudraCT 2010-021462-30) was the basis for the phase 2 program. This includes 3 protocols designed for patients with 1$^{st}$line treatment, relapsed Pt-sensitive and relapsed Pt-resistant advanced stage OC. Immunotherapy is added to standard chemotherapy. *SOV01 (90 pts; EudraCT 2013-001322-26):* A randomized, open-label, three-arm, multi-center Phase II clinical trial evaluating effect of addition of DCVAC/OvCa to first line standard chemotherapy (carboplatin and paclitaxel) in women with newly diagnosed epithelial ovarian carcinoma. *SOV02 (60 pts; EudraCT 2013-001323-38):* A randomized, open-label, parallel group, multi-center Phase II clinical trial evaluating effect of addition of DCVAC/OvCa to standard chemotherapy (carboplatin and gemcitabine) in women with relapsed platinum sensitive epithelial ovarian carcinoma. *SOV03 (60 pts; EudraCT 2013-001325-24):* A randomized, open-label, parallel group, multi-center Phase II clinical trial evaluating effect of addition of DCVAC/OvCa to standard chemotherapy in women with relapsed platinum resistant epithelial ovarian carcinoma. The first patient in the phase 2 program was enrolled November 5, 2013, and all 3 trials are now recruiting patients. As of February 3, 10 patients had been screened and 7 had been randomized. Clinical trial information: EudraCT 2013-001322-26.

**3500 Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**Preoperative chemoradiotherapy and postoperative chemotherapy with 5-fluorouracil and oxaliplatin versus 5-fluorouracil alone in locally advanced rectal cancer: Results of the German CAO/ARO/AIO-04 randomized phase III trial.** *Presenting Author: Claus Rodel, University of Frankfurt, Frankfurt, Germany*

**Background:** The CAO/ARO/AIO-94 trial established preoperative chemoradiotherapy (CRT), total mesorectal excision (TME) surgery, and adjuvant chemotherapy with 5-FU as standard treatment for locally advanced rectal cancer. The goal of the CAO/ARO/AIO-04 trial was the integrating of more effective systemic treatment. First results of early secondary endpoints have been published (Rödel et al., Lancet Oncol 2012). Here we present the primary endpoint, disease-free survival (DFS) at 3 years. **Patients and Methods:** Patients with cT3/4 or cN+ rectal cancer were randomised into two arms: 1) preoperative 50.4 Gy plus infusional 5-FU 1 g/m$^2$ days 1-5 and 29-33, followed by TME-surgery and 4 cycles of bolus 5-FU 500 mg/m$^2$ for 5 days), and 2) preoperative 50.4 Gy plus infusional 5-FU (250 mg/m$^2$ days 1-14 and 22-35), oxaliplatin (50 mg/m$^2$ days 1, 8, 22, and 29), followed by TME and 8 cycles of adjuvant oxaliplatin (100 mg/m$^2$ day 1), leucovorin (400 mg/m$^2$ day 1) and infusional 5-FU (2,400 mg/m$^2$ day 1-2). The primary endpoint was DFS at 3 years defined as the interval from randomization to incomplete surgical resection, locoregional or metastatic recurrence or death, whichever occurred first. **Results:** A total of 637 patients were randomly assigned to arm 1 and 628 to arm 2. After a median follow-up time of 50 months, 198 patients in arm 1 had had a DFS-related event, as compared with 159 patients in arm 2 (HR 0.79, 95% confidence interval 0.64 to 0.98, P=0.03 by the mixed effects Cox model). The rate of DFS at three years was 71.2% (95% confidence interval, 67.6% to 74.9%) in arm 1 and 75.9% (95% confidence interval, 72.4% to 79.5%) in arm 2 (P=0.03 by the exact stratified log-rank test). Grade 3-4 late overall treatment-related toxicity occurred in 23% in arm 1 and 26% in arm 2 (P=0.14). The incidence of grade 3-4 sensory neuropathy in the oxaliplatin containing arm was 7% during treatment, decreasing to 3% at one year of follow-up. **Conclusions:** Adding oxaliplatin to 5-FU-based neoadjuvant CRT and adjuvant chemotherapy in locally advanced rectal cancer significantly improved DFS. Clinical trial information: NCT00349076.

**3501 Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: Disease-free survival results at interim analysis.** *Presenting Author: Hans-Joachim Schmoll, Martin Luther University Halle-Wittenberg, Halle, Germany*

**Background:** The PETACC-6 trial investigates whether the addition of oxaliplatin to preoperative oral fluoropyrimidine-based chemoradiation (CRT) followed by postoperative adjuvant fluoropyrimidine-based chemotherapy (CT) improves disease-free survival (DFS) in locally advanced rectal cancer. **Methods:** Between 11/2008 and 09/2011, patients with rectal adenocarcinoma within 12 cm from the anal verge, T3/4 and/or node-positive, with no evidence of metastatic disease and considered either resectable at the time of entry or expected to become resectable, were randomly assigned to receive 5 weeks of preoperative CRT with capecitabine, followed by 6 cycles of adjuvant CT with capecitabine with (arm 2) or without (arm 1) the addition of oxaliplatin before and after surgery. 440 DFS events were required to have 80% power to detect an improvement in 3-year DFS from 65% with capecitabine alone to 72% with capecitabine and oxaliplatin (HR=0.763) using a two-sided alpha of 5% and owing for an interim analysis for early efficacy at 200 events. The primary analysis was intent-to-treat and adjusted for stratification factors (clinical T category, nodal status, distance from the tumor to the anal verge and method of locoregional staging) except the center. **Results:** 1094 patients were randomized (547 in each arm). 543 eligible patients in arm 1 and 526 in arm 2 started their allocated treatment of whom 67.4% completed protocol treatment in arm 1 vs. 53.8% in arm 2. An independent data monitoring committee reviewed the interim data and recommended the early release of the results. At median follow-up of 31 months, respectively 124 and 121 DFS events were observed in arm 1 and 2 (adjusted HR=1.036, 95% CI: 0.806 -1.331, P=0.781). 3-year DFS was 74.5% (95% CI: 70.1% - 78.3%) in arm 1, which is higher than anticipated vs. 73.9% (95% CI: 69.5% - 77.8%) in arm 2. Conditional power under HR=0.763 is only 7%. **Conclusions:** Interim results indicate that the addition of oxaliplatin to capecitabine plus radiotherapy does not improve DFS. Careful follow-up should continue until the planned 440 events to document any late treatment difference. Clinical trial information: NCT00766155.

**3502 Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**Adjuvant chemotherapy with oxaliplatin/5-fluorouracil/leucovorin (FOLFOX) versus 5-fluorouracil/leucovorin (FL) for rectal cancer patients whose postoperative yp stage 2 or 3 after preoperative chemoradiotherapy: Updated results of 3-year disease-free survival from a randomized phase II study (The ADORE).** *Presenting Author: Yong Sang Hong, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

**Background:** To report the updated results of 5-fluorouracil (5-FU)/leucovorin (LV) (FL) with or without oxaliplatin (FOLFOX) in patients with curatively resected rectal cancer whose pathologic stages of ypII/III after preoperative chemoradiotherapy (CRT). **Methods:** This is a randomised phase II study accrued patients with curatively resected rectal cancer patients whose postoperative stage ypII (ypT3-4/ypN0) or III (any ypT/ypN1-2) after preoperative CRT with fluoropyrimidines alone. Patients were randomly assigned (1:1) to receive adjuvant chemotherapy either with FL (5-FU 380 mg/m$^2$, LV 20 mg/m$^2$ on days 1-5, every 4 weeks, 4 cycles) or FOLFOX (oxaliplatin 85 mg/m$^2$, LV 200 mg/m$^2$, 5-FU bolus 400 mg/m$^2$ on day 1, 5-FU infusion 2400 mg/m$^2$ for 46 hours, every 2 weeks, 8 cycles). Randomisation was centrally coordinated and stratified by the ypStage and participating sites. The primary endpoint was 3-year disease-free survival (DFS). **Results:** A total of 321 patients were randomly assigned between November 2008 and June 2012; 161 patients to FL and 160 to FOLFOX. The arms were balanced. At a median follow-up of 38.2 months (IQR, 26.4 – 50.6), 3-year DFS rate was 71.6% (95% CI, 64.6 – 78.6) in the FOLFOX arm and 62.9% (95% CI, 55.4 – 70.4) in the FL arm with a hazard ratio (HR) of 0.657 (95% CI, 0.434 – 0.994, $p$=0.047) by intention-to-treat analysis. After adjusting for stratification and prognostic variables, HR remained unchanged favoring FOLFOX (0.560; 95% CI 0.366 – 0.856; $p$=0.007) in terms of 3-year DFS. In the subgroup analysis, patients with ypStage III (HR 0.602 [0.371 – 0.977], $p$=0.040), ypN1b (HR 0.356 [0.132 – 0.960], $p$=0.041), ypN2 (HR 0.414 [0.181 – 0.946], $p$=0.037), and minimally regressed tumors (HR 0.395 [0.188 – 0.831, $p$=0.014] benefited more from FOLFOX than FL. Grade-3 or -4 adverse events were not statistically different between arms. **Conclusions:** Adjuvant FOLFOX demonstrated improved 3-year DFS in curatively resected rectal cancer patients whose postoperative stage of ypII/III after preoperative CRT. Clinical trial information: NCT00807911.

**3503^ Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**Maintenance strategy with fluoropyrimidines (FP) plus Bevacizumab (Bev), Bev alone, or no treatment, following a standard combination of FP, oxaliplatin (Ox), and Bev as first-line treatment for patients with metastatic colorectal cancer (mCRC): A phase III non-inferiority trial (AIO KRK 0207).** *Presenting Author: Dirk Arnold, Klinik für Tumorbiologie, Freiburg, Germany*

**Background**: The optimal maintenance strategy following combination chemotherapy plus Bev is still controversial. AIO KRK 0207 investigates whether after a 24-week standard induction with F//Ox/Bev, no continuation of therapy or continuation with Bev alone are non-inferior to FP plus Bev. **Methods:** Pts with mCRC and 'standard' eligibility criteria were enrolled. After 24 weeks of induction treatment with FP/Ox/Bev, pts without disease progression were randomized into one of the following arms: A) standard maintenance treatment with FP plus Bev; B) Bev alone; or C) no treatment. At first progression, re-induction of the initial treatment was planned. The primary endpoint was 'time to failure of strategy' (TFS), comprising maintenance *plus*re-induction after first progression. Sample size was calculated (one-sided alpha of 0.0125; power of 80%) to conclude non-inferiority compared with the FP plus Bev arm. Secondary endpoints included time to first progression (PFS1) and overall survival (OS). **Results:** 840 pts were enrolled, 473 randomized. Median follow-up is 27 months. After induction, 60% of pts had CR/PR, 40% SD. Median PFS1 in arms A, B, C were 6.2, 4.6 and 3.6 months (p< 0.0001; A vs C: HR 2.11, 95% CI 1.63-2.73; A vs B: HR 1.28, 95% CI 0.99-1.65; B vs C: HR 1.56, 95% CI 1.22-1.99), respectively. TFS favored arm A over arm C (HR 1.31, 95% CI 1.01-1.69, p=0.038) but without difference between arms A and B (HR 1.04,95% CI 0.81-1.36, p=0.74). However, upon first progression only 24% in arm A and 47 % in both arms B and C, received re-induction. After 200 documented events, preliminary OS is 23.4 months from randomization, without significant difference between treatment arms (p=0.69). **Conclusions:** Following 24 weeks of induction, active maintenance with both, FP plus Bev or Bev alone, show prolonged TFS over no treatment. Only a minority of patients received re-induction treatment as planned. With currently limited follow up, the different maintenance strategies had no impact on OS. Clinical trial information: NCT00973609.

**3504 Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**Final results and subgroup analyses of the phase 3 CAIRO3 study: Maintenance treatment with capecitabine + bevacizumab versus observation after induction treatment with chemotherapy + bevacizumab in metastatic colorectal cancer (mCRC).** *Presenting Author: Miriam Koopman, University Medical Center Utrecht, Utrecht, Netherlands*

**Background:** We investigated the efficacy of maintenance treatment with capecitabine (cap) + bev versus observation in mCRC patients (pts) not progressing during induction treatment with cap, oxaliplatin and bev (CAPOX-B). **Methods:** Previously untreated mCRC pts with stable disease or better after 6 cycles of CAPOX-B were randomized between observation (arm A) or maintenance treatment with cap 625 mg/m2 bid daily continuously + bev 7.5 mg/kg iv q 3 weeks (arm B). Upon first progression (PFS1), pts in both arms were to be treated with CAPOX-B until 2nd progression (PFS2, primary endpoint). Secondary endpoints were overall survival (OS) and time to 2nd progression (TTP2), which was defined as the time to progression on any treatment following PFS1, and quality of life (QoL). Preplanned subset analyses were performed. **Results:** A total of 558 pts were randomized. Upon PFS1, CAPOX-B was reintroduced in 61% of pts in arm A and 47% in arm B. There was a significant benefit for maintenance treatment for PFS1, TT2PD and PFS2 with a median of 8.5 m vs 11.7 m, respectively (HR 0.67, p < .0001). Multivariable analysis showed a significant interaction for treatment with OS. Subgroup analysis showed a significant interaction for treatment in pts with synchronous metastases with resected primary tumor (n=180): median OS 18.0 m (A) vs 25.0 m (B) (p <0.0001), and for pts with complete/ partial response to induction treatment before randomization (n=366) with median OS of 18.8 m (A) and 24.1 m (B; p < .0001). QoL was maintained during maintenance treatment, and was clinically not inferior compared to QoL in the observation arm. **Conclusions:** Final CAIRO3 results establish the benefit of maintenance treatment with cap + bev after first-line induction treatment in pts with mCRC. Multivariable analysis shows a significant interaction of treatment with OS. Our finding that the positive effect on survival for maintenance treatment is most pronounced in pts with synchronous disease and resected primary tumor and with PR/CR to induction treatment should be confirmed.

**3505 Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**Treatment outcome according to tumor *RAS* mutation status in OPUS study patients with metastatic colorectal cancer (mCRC) randomized to FOLFOX4 with/without cetuximab.** *Presenting Author: Carsten Bokemeyer, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

**Background:** The addition of cetuximab to FOLFOX4 significantly improved progression-free survival and response in the first-line treatment of patients (pts) with *KRAS* codon 12/13 (hereinafter exon 2) wild-type (wt) mCRC. Pts with *KRAS*exon 2 tumor mutations showed no such cetuximab benefit, with a trend for worse outcome. **Methods:** Available *KRAS* exon 2 wt tumors from OPUS study pts were screened for 26 mutations (new *RAS*) in 4 additional *KRAS* codons (exons 3 and 4) and 6 *NRAS* codons (exons 2, 3 and 4) using BEAMing technology (5% sensitivity cutoff selected for analysis). Outcome was assessed according to *RAS* mutation status (*KRAS* exon 2 + new *RAS*). **Results:** Mutation status was evaluable in 118/179 (66%) pts with *KRAS* exon 2 wt tumors. New *RAS* mutations were detected in 31/118 (26%) pts. In those with *RAS* wt tumors, response was significantly improved by the addition of cetuximab to FOLFOX4 (Table). The treatment effect for those with new *RAS* tumor mutations could not be definitively assessed due to low pt numbers. In pts with any tumor *RAS* mutation (*KRAS* exon 2 + new *RAS*), no benefit from the addition of cetuximab to FOLFOX4 was seen, with a clear trend for worse outcome. **Conclusions:** Pts with mCRC harboring any activating *RAS* mutation are unlikely to benefit from the addition of cetuximab to FOLFOX4. Restricting cetuximab administration to pts with tumors wt at all such loci might help further tailoring of therapy to maximize pt benefit. Clinical trial information: NCT00125034.

| | *RAS* wt* (all loci) | | New *RAS* mt* | | *RAS* mt† (any locus) | |
|---|---|---|---|---|---|---|
| Parameter | FOLFOX4 + cet N=38 | FOLFOX4 N=49 | FOLFOX4 + cet N=15 | FOLFOX4 N=16 | FOLFOX4 + cet N=92 | FOLFOX4 N=75 |
| Response rate, % | 57.9 | 28.6 | 53.3 | 43.8 | 37.0 | 50.7 |
| Odds ratio | 3.33 | | 1.50 | | 0.58 | |
| 95% CI | 1.36–8.17 | | 0.35–6.53 | | 0.31–1.08 | |
| P value‡ | 0.008 | | 0.60 | | 0.087 | |
| Median progression-free survival, months | 12.0 | 5.8 | 7.5 | 7.4 | 5.6 | 7.8 |
| HR | 0.53 | | 0.77 | | 1.54 | |
| 95% CI | 0.27–1.04 | | 0.28–2.08 | | 1.04–2.29 | |
| P value§ | 0.062 | | 0.60 | | 0.031 | |
| Median overall survival, months | 19.8 | 17.8 | 18.4 | 17.8 | 13.5 | 17.8 |
| HR | 0.94 | | 1.09 | | 1.29 | |
| 95% CI | 0.56–1.56 | | 0.44–2.68 | | 0.91–1.84 | |
| P value§ | 0.80 | | 0.86 | | 0.157 | |

Abbreviations: cet, cetuximab; HR, hazard ratio; mt, mutant; **RAS* evaluable population, N=118; †Subset of the OPUS *KRAS* evaluable population, N=315; ‡Cochran-Mantel-Haenszel; §log-rank.

**3506 Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**Treatment outcome according to tumor *RAS* mutation status in CRYSTAL study patients with metastatic colorectal cancer (mCRC) randomized to FOLFIRI with/without cetuximab.** *Presenting Author: Fortunato Ciardiello, Medical Oncology, Second University of Naples, Naples, Italy*

**Background:** The addition of cetuximab to FOLFIRI significantly improved progression-free survival, overall survival and response in the first-line treatment of patients (pts) with *KRAS* codon 12/13 (hereinafter exon 2) wild-type (wt) mCRC. Pts with *KRAS* exon 2 tumor mutations showed no cetuximab treatment benefit. **Methods:** Available *KRAS* exon 2 wt tumors from CRYSTAL study pts were screened for 26 mutations (new *RAS*) in 4 additional *KRAS* codons (exons 3 and 4) and 6 *NRAS* codons (exons 2, 3 and 4) using BEAMing technology (5% sensitivity cutoff selected for analysis). Outcome was assessed according to *RAS* mutation status (*KRAS* exon 2 + new *RAS*). **Results:** Mutation status was evaluable in 430/666 (65%) pts with *KRAS* exon 2 wt tumors. New *RAS* mutations were detected in 63/430 (15%) pts. In those with *RAS* wt tumors, a significant benefit across all endpoints was associated with the addition of cetuximab to FOLFIRI (Table). In pts with new *RAS* tumor mutations, no clear difference in efficacy outcomes between treatment groups was seen. In pts with any tumor *RAS* mutation (*KRAS* exon 2 + new *RAS*), no benefit from the addition of cetuximab to FOLFIRI was apparent. **Conclusions:** In the first-line treatment of mCRC, pts with *RAS* wt tumors derived a marked benefit from the addition of cetuximab to FOLFIRI; pts with *RAS* tumor mutations did not benefit. This finding may allow the further tailoring of cetuximab therapy to maximize pt benefit. Clinical trial information: NCT00154102.

| | *RAS* wt* (all loci) | | New *RAS* mt* | | *RAS* mt† (any locus) | |
|---|---|---|---|---|---|---|
| Parameter | FOLFIRI + cet N=178 | FOLFIRI N=189 | FOLFIRI + cet N=32 | FOLFIRI N=31 | FOLFIRI + cet N=246 | FOLFIRI N=214 |
| Response rate, % | 66.3 | 38.6 | 34.4 | 35.5 | 31.7 | 36.0 |
| Odds ratio | 3.11 | | 1.02 | | 0.85 | |
| 95% CI | 2.03–4.78 | | 0.33–3.15 | | 0.58–1.25 | |
| P value‡ | <0.0001 | | 0.97 | | 0.40 | |
| Median progression-free survival, months | 11.4 | 8.4 | 7.2 | 6.9 | 7.4 | 7.5 |
| HR | 0.56 | | 0.81 | | 1.10 | |
| 95% CI | 0.41–0.76 | | 0.39–1.67 | | 0.85–1.42 | |
| P value§ | 0.0002 | | 0.56 | | 0.47 | |
| Median overall survival, months | 28.4 | 20.2 | 18.2 | 20.7 | 16.4 | 17.7 |
| HR | 0.69 | | 1.22 | | 1.05 | |
| 95% CI | 0.54–0.88 | | 0.69–2.16 | | 0.86–1.28 | |
| P value§ | 0.0024 | | 0.50 | | 0.64 | |

Abbreviations: cet, cetuximab; HR, hazard ratio; mt, mutant; **RAS* evaluable population, N=430; †Subset of CRYSTAL *KRAS* evaluable population, N=1063; ‡Cochran-Mantel-Haenszel; §log-rank.

**3507 Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**Prognostic impact of deficient mismatch repair (dMMR) in 7,803 stage II/III colon cancer (CC) patients (pts): A pooled individual pt data analysis of 17 adjuvant trials in the ACCENT database.** *Presenting Author: Daniel J. Sargent, Mayo Clinic, Rochester, MN*

**Background:** MMR status has been established as an important prognostic factor in CC pts. We determined the association of dMMR status with clinical/pathological features and prognosis using the ACCENT database. **Methods:** Microsatellite instability (MSI, 14 studies) or immunohistochemical analysis (1 study) for MLH1/MSH2/MLH6 proteins was performed on 7,803 stage II/III pts enrolled in 17 trials; 2 studies tested both. 571 pts received surgery alone; 3,878 5FU monotherapy (mrx); 2,299 5FU+oxaliplatin (oxal); and 1,055 5-FU+irinotecan (iri). Tumors with MSI-high or an absent protein were classified as dMMR; remainder were MMR-proficient (pMMR). Median follow-up was 7 years. Outcomes included overall survival (OS) and time to recurrence (TTR). Correlation analyses included all pts; prognostic analyses were limited to pts receiving surgery alone or 5FU mrx excluding pts receiving oxal/iri. **Results:** 524 (23.1%) of 2,270 stage II and 823 (14.9%) of 5,533 stage III pts exhibited dMMR. MMR status was associated with female sex (dMMR, 19% F v 16% M, p=0.004), higher T stage (dMMR, 11% T1/2 v 18% T3 v 21% T4, p < 0.001), and right-sided tumor location (dMMR, left 9% v right 27%, p < 0.001). Compared to pMMR, dMMR was strongly associated with improved OS (HR=0.27, p=0.01) and TTR (HR=0.27, p=0.01) in stage II pts treated with surgery alone (Table). Association of MMR was prognostic although of attenuated impact in 5FU treated stage II and in stage III pts , with significance confined to 5FU-mrx treated stage III pts (HR=0.80, p =0.02 for TTR; HR=0.79, p=0.02 for OS). **Conclusions:** Our study confirms prognostic utility of MMR status in stage II CCs. MMR also impacts outcome in stage III patients, but does not currently alter pt management.

| | TTR | | | | | OS | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 5-yr recurrence-free rate | | HR | 95% CI | p | 5-yr survival rate | | HR | 95% CI | p |
| Treatment | dMMR | pMMR | | | | dMMR | pMMR | | | |
| **Stage II** | | | | | | | | | | |
| Surgery alone (n=307) | 89% | 74% | 0.27 | 0.10 -0.75 | .012 | 90% | 78% | 0.27 | 0.10 - 0.74 | .011 |
| 5FU-mrx (n=1155) | 88% | 83% | 0.81 | 0.55 – 1.19 | .285 | 88% | 87% | 0.87 | 0.61 – 1.26 | .469 |
| **Stage III** | | | | | | | | | | |
| Surgery alone (n=264) | 60% | 47% | 0.59 | 0.28 – 1.23 | .162 | 59% | 54% | 0.69 | 0.35 – 1.36 | .283 |
| 5FU-mrx (n=2723) | 72% | 64% | 0.80 | 0.66 - 0.97 | .025 | 77% | 71% | 0.79 | 0.65 - 0.97 | .023 |

**3508 Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**Impact of adjuvant chemotherapy with 5-FU or FOLFOX in colon cancers with microsatellite instability: An AGEO multicenter study.** *Presenting Author: David Tougeron, Department of Gastroenterology, Poitiers University Hospital, Poitiers, France*

**Background:** Microsatellite instability (MSI) is found in 12% of colon cancers (CC) and associated with a low recurrence rate after curative surgery. Adjuvant chemotherapy with 5-FU seems ineffective, but small studies recently suggest that adjuvant chemotherapy with FOLFOX could be effective (Zaanan et al.). The aim of this study was to analyze efficacy of adjuvant chemotherapy with 5-FU or FOLFOX in relapse-free survival (RFS) of MSI CC. **Methods:** This multicenter retrospective study included patients with stage II or III MSI CC with curative surgery between 2000 and 2012. High-risk stage II CC were defined by one of these criteria: stage T4, bowel obstruction, tumoral perforation, vascular emboli, lymphatic invasion, perinervous invasion, or a number of lymph nodes examined inferior to 10. Prognostic factors of RFS were analyzed in univariate and multivariate analysis using Cox model. **Results:** A total of 433 MSI CC patients were analyzed, including 57% and 43% stage II and III, respectively. Median follow-up was 35 months. Mean age was 70 $\pm$ 17 years. Overall, 61%, 27%, 12% patients had a surgery alone (n=263), adjuvant FOLFOX (n=119) or 5-FU (n=51) respectively. Adjuvant chemotherapy was administered in 17% of stage II (n=41) and 70% of stage III (n=129). Recurrence rates were 6% (n=14) for stage II and 21% (n=39) for stage III. Adjuvant chemotherapy was associated with better RFS in univariate analysis, but only for FOLFOX (HR=0.46, 95%CI 0.23-0.79) and not for 5-FU (HR=1.02, 95%CI 0.60-1.73). Three-years RFS was 75% for surgery alone, 66% for 5-FU and 84% for FOLFOX (p=0.02). In multivariate analysis taking account the other prognosis factors, adjuvant chemotherapy with oxaliplatin remains significantly associated with better RFS (HR=0.29, 95%CI 0.13-0.65 ; p=0.003). In the subgroup analyses, benefit of FOLFOX, as compared to 5-FU and surgery alone, was significant in stage III (HR=0.38, 95%CI 0.21-0.69 ; p=0.0014) and a trend was observed for high-risk stage II (HR=0.141 95%CI 0.02-1.04 ; p=0.0549). **Conclusions:** This multicenter study confirms that adding oxaliplatin to 5-FU can restore the chemosensitivity of MSI CC.

**3509 Clinical Science Symposium, Tue, 9:45 AM-11:15 AM**

**Mutation and copy number discordance in primary versus metastatic colorectal cancer (mCRC).** *Presenting Author: Scott Kopetz, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Molecular profiling for CRC commonly utilizes formalin-fixed tissue of convenience, which may include tissue obtained from primary or metastatic tumors. While the alterations in *KRAS*have been shown to have a high degree of concordance, a detailed survey of other commonly mutated genes, copy number variations, and the influence of intervening treatment in CRC has not been conducted. **Methods:** Primary and metastatic tissue underwent sequencing on a 46 or 50-gene hotspot AmpliSeq panel (IonTorrent) in a CLIA-compliant setting. For a subset of patients, targeted resequencing of a panel of 202 genes by HiSeq 2000 (Illumina) to an average depth of 800 was performed by the MDACC Institute of Personalized Cancer Therapeutics, with single nucleotide variations and copy number called by in-house algorithms. **Results:** Sequencing was successfully completed on 115 pairs of primary and metastatic tumors (N=107 for 46/50-gene, and N=17 for 202-gene). Forty-six high level amplifications (>4 copies) were found in 28 genes in 11 of 17 pairs, with discordant results in all cases, including discordance in potentially clinically relevant amplifications: *HER2, NOTCH1, FLT3*, and *AURKA*. Overall concordance rate for mutations on the 46/50-gene panel was 78%, but varied substantially by gene. *APC, TP53, NRAS,* and *BRAF* demonstrated concordance similar to *KRAS* (89% concordance), while *PIK3CA* demonstrated a 6.8-fold higher odds of discordance between primary and metastatic site (95% CI of odds ratio (OR) of 2.1 to 22.6, P<0.001). Genes with low prevalence (<10%) such as *FGFR3, STK11*, and *FBXW7* likewise had high levels of discordance (OR 4.4, 95% CI: 1.4 to 14.1, P=0.008). Intervening chemotherapy treatment was associated with a 3.5 fold higher odds of discordance across all genes compared to patients that did not receive therapy between resection of primary and metastatic tumors (95% CI 1.26 to 10.4, P=0.008), including *KRAS, TP53,* and *PIK3CA*(OR of 5.2, 3.5, and 3.3 respectively). **Conclusions:** Rates of discordance between primary and metastases mutations vary substantially by gene and prior treatment in mCRC. Prospective efforts to enrich for biomarkers need to account for tumor site and treatment variability on a gene-by-gene basis.

**3510 Clinical Science Symposium, Tue, 9:45 AM-11:15 AM**

**Analysis of clonal evolution in colorectal cancer.** *Presenting Author: Donna M. Graham, Princess Margaret Cancer Centre/Ontario Cancer Institute, Toronto, ON, Canada*

**Background:** Comparisons of primary tumor and metastases (met) from the same individual patients (pts) highlight intratumor heterogeneity and clonal evolution with treatment. Results of genomic mutation analysis may guide treatment decisions in colorectal cancer (CRC). **Methods:** Ultra-deep (mean 35,000x coverage) amplicon sequencing was performed for hotspot regions of *TP53*, *APC*, *KRAS*, *NRAS, PIK3CA*, and *BRAF* on 36 DNA samples isolated from metachronous FFPE tumor specimens from 15 pts with CRC. The cohort included 10 pts with tissue from the primary and $\geq$1 met, four pts with pairs of mets, and one pt with a recurrent tumor at the primary site. One sample from each pt had prior analysis with a customized 23-gene panel for Sequenom. Samples were compared for presence of mutation and variant allele frequency (all-freq). **Results:** All *KRAS, NRAS, PIK3CA,* and *BRAF* mutations identified using Sequenom were confirmed by ultra-deep sequencing. Analysis for the six pts with *KRAS* codon 12 mutation, three pts with *TP53* mutation, and one pt with *NRAS* mutation confirmed mutation persistence from primary to met. Seven of the 15 pts had interval treatment with chemotherapy +/- bevacizumab. *KRAS* all-freq differed between primary and met based on interval treatment. Elevated all-freq (2.4 fold) between primary and met was found for three pts who received interval chemotherapy compared with a 0.6 fold average change in all-freq for three pts with no interval treatment ($p$=0.05 by Mann-Whitney U test). All-freq of *TP53* R273H mutation also increased (4.2 fold change) between primary and met in one treated pt. No low-frequency *KRAS* mutations or other mutations were identified in either sample of 3 pts previously found to be wild-type for KRAS; none had received anti-epidermal growth factor receptor therapy. One pt with anastomotic recurrence at 5 years had discordant *TP53*, *PIK3CA,* and *BRAF* mutation status from the primary suggesting the possibility of new CRC primary. **Conclusions:** Ultra-deep sequencing confirmed persistent clinically-relevant mutations between CRC primary and met. *KRAS* mutated subclones may be enriched in metastases following systemic chemotherapy. Targeted deep sequencing of driver mutations provides a powerful tool to monitor tumor behavior, and to identify recurrent lesions that are molecularly distinct from primary tumors.

**3511 Clinical Science Symposium, Tue, 9:45 AM-11:15 AM**

**Colorectal Cancer Subtyping Consortium (CRCSC) identification of a consensus of molecular subtypes.** *Presenting Author: Rodrigo Dienstmann, Sage Bionetworks, Seattle, WA*

**Background:** Recently, a number of independent groups reported novel molecular subtypes in colorectal cancer (CRC). A formal comparison across these classifiers is needed to reconcile findings and accelerate clinical translation. The CRCSC was formed to identify a consensus among the subtyping systems through large scale data sharing and meta-analysis. **Methods:** The CRCSC consists of 6 groups (15+ institutions) that analyzed more than 30 patient cohorts with gene expression data, spanning multiple platforms and sample preparation methods. Each of the 6 classifiers (with 3-6 subtypes) was applied to the collection of public and proprietary datasets encompassing over 4,000 samples, mostly stage II-III CRC. Concordance of subtype calls and associations with clinical, molecular and pathway features were assessed centrally by an independent team. **Results:** Despite heterogeneities in cohorts and methods, subtype concordance analysis readily yielded a clear consensus on 4 CRC molecular subtypes (CMS1-4), with significant interconnectivity among the calls from the participating groups. The remaining 16% of samples did not have a consensus assignment, which may be partly explained by an additional mixed subtype with variable epithelial-mesenchymal activation; further refinement is needed. **Conclusions:** This is the first example of a large-scale, community based comparison of cancer subtypes. Within the largest collection of CRC samples we identified recurrent signals of 4 biologically distinct subtype classes enriched for key clinical, pathway and molecular traits. Ongoing efforts are attempting to improve the granularity of these subtypes.

| | | |
|---|---|---|
| **CMS1** | 14% | MSI, immune pathway activation/expression, right-side tumors, older age at diagnosis, females, hypermutation, *BRAF* mut, intermediate survival |
| **CMS2** | 41% | High CIN, MSS, strong WNT/MYC pathway activation, left-side tumors, *TP53* mut, *EGFR* amplification/overexpression, better survival |
| **CMS3** | 8% | Low CIN, moderate WNT/MYC pathway activation, *KRAS* mut, *PIK3CA* mut, IGFBP2 overexpression, intermediate survival |
| **CMS4** | 20% | CIN/MSI heterogeneous, mesenchymal/TGF-beta activation, younger age at diagnosis, NOTCH3/VEGFR2 overexpression, worse survival |

**3512 Clinical Science Symposium, Tue, 9:45 AM-11:15 AM**

**Molecular subtyping of colon cancers and distinct prognostic groups [NCCTG N0147 (Alliance)].** *Presenting Author: Frank A. Sinicrope, Mayo Clinic, Rochester, MN*

**Background:** Categorization of colon cancers (CCs) into subtypes based upon pathways of tumorigenesis may improve prognostication. CCs were studied from a randomized trial of adjuvant FOLFOX ± cetuximab. **Methods:** Stage III CCs (N=3,018) were prospectively analyzed for *BRAF*$^{V600E}$ and *KRAS* (codons 12, 13) mutations by a PCR-based assay. DNA mismatch repair (MMR) proteins (MLH1, MSH2, MSH6) were analyzed; loss of any indicated deficient (dMMR) *vs* proficient MMR (pMMR). Sequencing-based methylation of *MLH1*was performed. Association with 5 yr disease-free survival (DFS) was evaluated using Cox models. **Results:** CCs were categorized into 5 subtypes (Table): Traditional (49%), Alternate (35%), Serrated (6.9%), Serrated dMMR (6.8%) or Familial dMMR (2.6%). Traditional *vs* alternate or serrated pMMR CCs were more likely left-sided (67% *vs* 42% or 24%; p<.0001) and from men (58% *vs* 51% or 41%; p< .0001). Alternate and serrated *vs* traditional pMMR tumors were frequently right-sided [58% and 76% *vs* 33%, p<.0001] and from women (p< .001). Serrated *vs* traditional pMMR CCs had more high grade histology (44% *vs* 19%, p < .0001) and N2 stage (59% *vs* 41%, p<.0001). Serrated *vs* familial dMMR CCs were older and more likely female (p <.0001). Alternate or serrated pMMR (*vs*traditional) tumors showed worse DFS (Table). Compared to alternate CCs, traditional [HR= 0.68 (0.58 -0.79), p<.001], serrated dMMR [HR=0.73 (0.54-.99), p=.042], and familial dMMR [HR=0.51 (0.30-.87), p=.0130] CCs showed favorable DFS. DFS of dMMR and traditional subtypes were similar. **Conclusions:** Subtype categorization of CCs reveals distinct clinical features and prognoses. Alternate and serrated pMMR subtypes show poor DFS whereas more prevalent traditional CCs have favorable DFS that is similar to dMMR CCs.

| Subtype | HR (95% CI) for DFS | P value[a] |
|---|---|---|
| Traditional (pMMR; wild-type *BRAF* and *KRAS*) | Ref | |
| Alternate (pMMR; wild-type *BRAF*, mutant *KRAS* | 1.48 (1.27-1.74) | <.001 |
| Serrated pMMR (mutant *BRAF*$^{V600E}$, wild-type *KRAS*) | 1.43 (1.11-1.85) | .007 |
| Serrated dMMR (mutant *BRAF*$^{V600E}$, wild-type *KRAS*, hypermethylated *MLH1*) | 1.09 (0.80-1.48) | .59 |
| Familial dMMR (wild-type *BRAF*, any *KRAS*, unmethylated *MLH1* | 0.76 (0.45-1.29) | .31 |

[a]Adjusted for age, sex, T, N stage, grade, site, # LNs, treatment.

**3513 Poster Highlights Session (Board #1), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Antitumor effects of dabrafenib, trametinib, and panitumumab as single agents and in combination in *BRAF*-mutant colorectal carcinoma (CRC) models.** *Presenting Author: LI Liu, GlaxoSmithKline, Oncology, Collegeville, PA*

**Background:** In contrast to *BRAF*-mutant melanoma, the inhibition of *BRAF* or *BRAF*/MEK has been relatively ineffective in the treatment of *BRAF*-mutant CRC, possibly due to EGFR-dependent resistance mechanisms. This study aimed to determine the anti-tumor activities for *BRAF*/MEK inhibition with or without EGFR inhibition in *BRAF*$^{V600E}$ CRC models and to identify biomarkers of response/resistance. **Methods:** We assessed cell growth inhibition, apoptosis and cell signaling changes by inhibitors of *BRAF* (dabrafenib, D), MEK (trametinib, T), and EGFR (panitumumab, P, cetuximab, and erlotinib) dosed as monotherapies and in combination in five *BRAF*$^{V600E}$ human CRC lines (Colo205, HT29, RKO, SW1417 and LS411N). Further, these inhibitors were evaluated for their anti-tumor effects either alone or in combination in two *BRAF*$^{V600E}$ CRC patient derived tumor xenografts (PDXs) established in female nude mice. One patient-derived xenograft (PDX) harbored the PIK3CA$^{H1047R}$ mutation (Co-018) and the other (Co-012) was wildtype for PIK3CA. **Results:** In three out of five lines, all three EGFR inhibitors enhanced cell growth inhibition by D and the combination of D/T. Adding P to D or to the combination of D/T led to sustained suppression of pERK. The triple combination of P/D/T most effectively inhibited both pERK and pS6, and increased PARP cleavage in HT29 cells. P significantly improved the efficacy of either D or D/T in the Co-012 and Co-018 models. The triple combination of P/D/T was highly efficacious in both PDXs, and more effectively delayed tumor growth than the combination of P/D or D/T in Co-018 model, while D and P alone showed little or no activity. Pharmacodynamic changes and baseline characterization including expression levels of EGFR and EGFR ligands are under evaluation, and will be tested in clinical samples. **Conclusions:** While inhibition of MAPK or EGFR signaling has limited activity in *BRAF*-mutant CRC, the combined inhibition of MAPK signaling and EGFR has significant anti-tumor activity, with the triple combination being the most efficacious in preclinical models of *BRAF*$^{V600E}$ CRC. The results support ongoing clinical trials of D/T/P combinations in subjects with V600E BRAF-mutation positive CRC.

**3514 Poster Highlights Session (Board #2), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Phase I study of the selective BRAF$^{V600}$ inhibitor encorafenib (LGX818) combined with cetuximab and with or without the $\alpha$-specific PI3K inhibitor BYL719 in patients with advanced *BRAF*-mutant colorectal cancer.** *Presenting Author: Robin Van Geel, The Netherlands Cancer Institute, Amsterdam, Netherlands*

**Background:** In contrast to *BRAF*$^{V600}$ mutated (*BRAF*m) advanced melanoma, *BRAF*m colorectal carcinoma (CRC) does not respond to BRAF inhibitors due to strong feedback activation of the epidermal growth factor receptor (EGFR) upon *BRAF* inhibition. However, combining a *BRAF* and an EGFR inhibitor resulted in strong synergistic activity with complete inhibition of tumor growth in vitro and in vivo. The addition of a phosphatidylinositol 3-kinase (PI3K) inhibitor increased synergy. **Methods:** This is a phase I study evaluating safety, tolerability and anti-tumor activity of encorafenib (LGX818), a highly selective *BRAF*$^{V600}$ inhibitor, the EGFR mAb cetuximab, ± the $\alpha$-specificPI3K inhibitor BYL719 in patients (pts) with advanced *BRAF*m/*KRAS* wild-type CRC. Cohorts of pts were treated with escalating doses of oral encorafenib once daily in combination with IV cetuximab (400 mg/m$^2$ loading dose, 250 mg/m$^2$weekly) (dual arm), or with escalating doses of oral encorafenib and oral BYL719 once daily in combination with cetuximab (triple arm). **Results:** By November 08, 2013, 18 pts were enrolled across four dual combination dose levels: 100 (n = 2), 200 (n = 4), 400 (n = 9) and 450 mg (n = 3) encorafenib. Three pts were enrolled in the triple arm at 200 mg encorafenib, 100 mg BYL719 and cetuximab. Dose escalation has been completed in the dual arm where a phase 2 dose has been identified; dose finding is ongoing in the triple arm. In the dual arm, 2 dose-limiting toxicities, vomiting grade 3 (400 mg) and QTc prolongation grade 3 (450 mg), were observed, and fatigue (33%) and vomiting (28%) were the most frequently observed treatment-related adverse events. Three partial responses, including one in the triple arm, have been observed and prolonged disease stabilization was frequently achieved including two pts that have remained on treatment for one year. Decrease in carcinoembryonic antigen (CEA) has also been observed. Updated data from the triple arm will be presented. **Conclusions:** These results indicate that combination treatment of encorafenib and cetuximab ± BYL719 is well tolerated with promising antitumor activity in pts with advanced *BRAF*m CRC who failed standard treatment. Clinical trial information: NCT01719380.

**3515 Poster Highlights Session (Board #3), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Efficacy and tolerability in an open-label phase I/II study of MEK inhibitor trametinib (T), BRAF inhibitor dabrafenib (D), and anti-EGFR antibody panitumumab (P) in combination in patients (pts) with BRAF V600E mutated colorectal cancer (CRC).** *Presenting Author: Johanna C. Bendell, Sarah Cannon Research Institute, Nashville, TN*

**Background:** BRAF V600 mutations occur in 5–10% of CRC and confer poor prognosis. Unlike in BRAF mutant (BRAFm) melanoma, BRAF and MEK inhibitors show limited activity in BRAFm CRC. Preclinical data suggest that EGFR can mediate resistance in BRAFm CRC, which can be overcome by combined inhibition of BRAF and EGFR. Therefore, combined inhibition of the BRAF pathway (with D or D + T and with anti-EGFR agent P) to prevent EGFR-mediated resistance is a rational and promising approach to treat BRAFm CRC. **Methods:** Eligible pts with BRAFm CRC enrolled in Parts 1 and 2 of the ongoing 3-part study, dose escalation (DE; Part 1), cohort expansion (CE; Part 2) and a planned randomized comparison (Part 3), received either the doublet (D + P) or triplet (D + P + T) combination. **Results:** 19 pts received D + P ± T in DE or CE. Doublet: 6 pts received the full doublet dose (D 150 mg twice daily [BID] + P 6 mg/kg every 2 weeks [Q2W]) in Cohort 1 DE and 3 pts received the doublet in Part 2 CE. Triplet: 3 pts received the lowest combination dose of the triplet (D 150 mg BID + P 4.8 mg/kg Q2W + T 1.5 mg once daily [QD]) in Cohort 2. DE Cohorts 3A (D 150 mg BID + P 4.8 mg/kg Q2W + T 2 mg QD), n = 4 and 3B (D 150 mg BID + P 6 mg/kg Q2W + T 1.5 mg QD), n = 3 were opened simultaneously. No dose-limiting toxicities have been seen in any cohorts. Most common drug-related adverse event (AE) was dermatitis acneiform for doublet (5/9 pts, all Grade [Gr] 1) and triplet (5/10 pts, 3 Gr 1 and 2 Gr 2) pts. In the doublet group, no possibly drug-related Gr > 3 events were reported. In the triplet group, Gr > 3 events at least possibly drug-related, included vomiting (n = 1), rash (n = 1) and skin fissures (n = 1). In preliminary efficacy data, partial responses have been seen in 4/6 evaluable pts on the triplet dose (3/4 ongoing, 1 > 7 months) with 2 pts with stable disease (SD; 1 ongoing and 1 discontinued due to AE). Of the 8 evaluable pts on the doublet dose, 7/8 achieved SD (lasting 6–26 weeks; 2 pts ongoing) as the best overall response. Updated results will be presented. **Conclusions:** P can be safely combined with D or D/T. Encouraging evidence of clinical activity has been seen. Clinical trial information: NCT01750918.

**3516 Poster Highlights Session (Board #4), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Phase 1B study of vemurafenib in combination with irinotecan and cetuximab in patients with *BRAF*-mutated advanced cancers and metastatic colorectal cancer.** *Presenting Author: David S. Hong, Department of Investigational Cancer Therapeutics (Phase I Program), University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** *BRAF V600* mutations, present in 5-10% of patients (pts) with metastatic colorectal cancer (mCRC), are considered poor prognostic markers, and <10% of *BRAF*-mutated mCRC pts respond to a combination of cetuximab (C) and irinotecan (I). Vemurafenib (V), an oral kinase inhibitor to the mutated V600 isoform of BRAF, demonstrated a 5% response rate in a phase I trial with *BRAF*-mutated mCRC. In vitro data in CRC cell lines has shown that blockade of mutated BRAF by vemurafenib triggers compensatory activation of EGFR. Inhibition of EGFR combined with vemurafenib results in synergistic cytotoxicity in preclinical models, further augmented by irinotecan. The safety and efficacy of the combination in pts with *BRAF*-mutated advanced malignancies have not been studied. **Methods:** In this 3+3 phase I study, pts with refractory *BRAF*-mutated cancer received escalating doses of vemurafenib in combination with cetuximab and irinotecan over a 14-day cycle. Radiographic responses were evaluated every 4 cycles by RECIST 1.1. Adverse events (AEs) were assessed by CTCAE 4.0. **Results:** Through 1/2014, 10 pts have been enrolled: 7 at dose level 1(DL) (V- 480mg PO BID, C-250 mg/m2 weekly and I- 180mg/m2 every 14 days) and three at DL 2 (increased to V-720mg PO BID). One dose-limiting toxicity was observed at DL1 (grade 3 arthralgia) and resolved with dose reduction. The most common AEs were rash, nausea, and diarrhea. Of the 6 evaluable pts treated at DL 1, 5 had mCRC and 1 had appendiceal adenocarcinoma. Four of the 5 mCRC pts (80%) achieved a partial response. For the 5 mCRC pts, median best response was a reduction of -44% (range, 0% to -70%) with duration of responses of 5, 5+, 8+, 12+, and 14+ cycles. The appendiceal carcinoma pt had disease progression. PK and PD analysis is planned. **Conclusions:** The combination of vemurafenib with irinotecan and cetuximab seems well tolerated in pts with *BRAF*-mutated mCRC. Even with a low vemurafenib dose, PRs were seen in 4 of 5 evaluable mCRC pts in the first cohort. Additional pts continue to be enrolled at higher dose levels of vemurafenib. A US cooperative group randomized phase II trial of this combination in BRAF-mutated mCRC (SWOG1406) is planned. Clinical trial information: NCT01787500.

**3517 Poster Highlights Session (Board #5), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Phase 1-2 trial of the BRAF inhibitor dabrafenib (D) plus MEK inhibitor trametinib (T) in BRAF V600 mutant colorectal cancer (CRC): Updated efficacy and biomarker analysis.** *Presenting Author: Ryan Bruce Corcoran, Massachusetts General Hospital, Boston, MA*

**Background:** *BRAF V600* mutations occur in 5-15% of metastatic CRC and predict poor prognosis. Although highly effective in *BRAF* mutant melanoma, BRAF inhibitor monotherapy has shown poor efficacy in *BRAF* mutant CRC. Preclinical data suggest that improved MAPK pathway suppression with combined inhibition of BRAF and MEK may improve efficacy. **Methods:** 43 patients (pts) with *BRAF V600* mutant stage IV CRC were treated with D (150mg BID) and T (2mg QD), 17 of whom were enrolled in a pharmacodynamic cohort with tumor biopsies pre-treatment and after 2 weeks of therapy. Archival tissues were analyzed for microsatellite instability (MSI), PTEN loss, and 487-gene sequencing (Illumina). **Results:** Of 43 pts, 5 (12%) achieved partial response (PR) or better (with or without confirmation), including 1 (2%) pt with complete response (CR) ongoing >22 months. An additional 22 (51%) pts achieved stable disease (SD) at first restaging, of which 11 (26%) pts had a minor response (10% to 30% tumor reduction). 10 (23%) pts remained on study >6 months. All 9 evaluable post-dose biopsies had reduced levels of phospho-ERK relative to pre-dose (average decrease 47% ±24), however, the % pERK inhibition and response did not correlate proportionally. Mutational analysis of 15 subjects has been completed to date. The pt with CR and 2 of 3 evaluable pts with PR had PIK3CA mutation. Neither PTEN loss nor MSI correlated with efficacy. **Conclusions:** The combination of D + T has activity in a subset of *BRAF V600* mutant CRC pts, with several PRs and a durable CR. MAPK signaling was inhibited in all pts evaluated, but to a lesser degree than observed in *BRAF* mutant melanoma with D as a single agent. PIK3CA mutations were identified in responding patients and thus do not preclude response to this regimen, but a definitive correlation between PIK3CA mutations and efficacy cannot be established given the limited pt sample. Biomarker refinement and additional therapeutic combinations may improve clinical activity. Clinical trial information: IND No: 113,557.

**3518^ Poster Highlights Session (Board #6), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**VE-BASKET, a Simon 2-stage adaptive design, phase II, histology-independent study in nonmelanoma solid tumors harboring BRAF V600 mutations (V600m): Activity of vemurafenib (VEM) with or without cetuximab (CTX) in colorectal cancer (CRC).** *Presenting Author: Josep Tabernero, Vall d'Hebron University Hospital, Barcelona, Spain*

**Background:** Low prevalence of V600m in non-melanoma cancers requires novel trial designs to assess the activity of BRAF inhibitors. Based on preclinical models that V600m positive (+) CRC upregulates the EGFR pathway and sensitizes to EGFR inhibitors in response to VEM (Prahallad et al Nature 2012), we investigated the activity of VEM in V600m+ CRC with or without CTX. Here we present preliminary efficacy and safety data for the VEM cohort and VEM + CTX dose-finding cohorts. **Methods:** This multicohort, Simon 2-stage adaptive design, single-proportion study included adult patients (pts) with V600m+ cancers refractory to standard therapy or for whom standard/curative therapy is not available. Pretreated CRC pts received either VEM (960 mg bid) without (cohort 3a) or with CTX (cohort 3b, 3+3 dose escalation) until investigator (INV)-assessed disease progression or unacceptable toxicity. Primary objective was INV-assessed response rate at wk 8 (RECIST v1.1). Maximum tolerated dose (MTD) and recommended dose (RD) were to be determined for the VEM + CTX cohort. **Results:** Median (range) treatment duration was: cohort 3a, 77 (24-225) d; 3b, 114 (36-279) d. At stage I, no responses were observed in cohort 3a (n=10). In cohort 3b, 14 pts have been enrolled for determination of MTD/RD. No dose-limiting toxicities (DLT) have been observed in dose level (DL) 1 (VEM 720 mg bid/CTX 200 mg/m$^2$/wk) and DL 2 (VEM 720 mg bid/CTX 250 mg/m$^2$/wk); 1 pt experienced a DLT (asymptomatic amylase grade 3 and lipase grade 4 elevation) in DL 3 (VEM 960 mg bid/CTX 250 mg/m$^2$/wk). Preliminary response data are in table. DL 3 was selected as the RD. There were no unexpected safety findings in either cohort. **Conclusions:** VEM + CTX show early signs of activity in V600m+ CRC; a formal evaluation of efficacy and safety results will be provided at the meeting. VEM monotherapy is not effective in V600m+ CRC. Clinical trial information: NCT01524978.

| | Week 8 | | | Week 16 | | | Week 24 | |
|---|---|---|---|---|---|---|---|---|
| n | DL 1 | DL2 | DL 3 | DL 1 | DL 2 | DL 3 | DL 1 | DL 2 |
| Pts with tumor assessment | 3 | 2 | 5 | 3 | 1 | 3 | 2 | 1 |
| Complete response | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Partial response | 1 | 1 | 0 | 1 | 0 | 0 | 1 | 0 |
| Stable disease | 2 | 1 | 3 | 1 | 1 | 2 | 1 | 1 |
| Progressive disease | 0 | 0 | 2 | 1 | 0 | 1 | 0 | 0 |
| Clinical benefit | 3 | 2 | 3 | 2 | 1 | 2 | 2 | 1 |

**3519 Poster Highlights Session (Board #7), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Subgroup analyses in *RAS* mutant, *BRAF* mutant and all-wt mCRC pts treated with FOLFOXIRI plus bevacizumab (bev) or FOLFIRI plus bev in the TRIBE study.** *Presenting Author: Fotios Loupakis, U.O. Oncologia Medica 2, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy*

**Background:** Phase III TRIBE trial demonstrated that first-line FOLFOXIRI plus bev improved PFS and RECIST response and, at adjusted analyses, OS as compared to FOLFIRI plus bev. The prognostic and/or predictive effect to anti-EGFRs of *RAS* and *BRAF*mutation is well established. We conducted this post-hoc analysis in the TRIBE study in order to describe the predictive and prognostic effect of each molecular cathegory. **Methods:** Mutational analyses were centralized at the Coordinating Center. Mutations within *KRAS* and *NRAS* codon 12, 13 and 61 and *BRAF* codon 600 were analyzed by means of pyrosequencing in tumoral DNA extracted from primaries or metastases. Pts not bearing *RAS* or *BRAF*mutations were defined as "all wt". **Results:** Molecular results are available for 375 out of 508 randomized pts (73.8%). *KRAS*, *NRAS* and *BRAF* were found mutated (mut) in 198 (52.8%), 20 (5.3%) and 28 (7.5%) cases, respectively. All wt pts were 129 (34.4%). Predictive analyses: see table. No significant interaction between *RAS* or *BRAF* status and treatment effect was reported in PFS or OS. All wt pts treated with upfront FOLFOXIRI plus bev achieved median PFS and OS of 13.3 and 41.7 mos, respectively. Prognostic analyses: as compared to all wt pts, *BRAF* mut had significantly shorter PFS (HR: 2.29 [1.49-3.52], p=0.0002) and OS (HR: 3.31 [2.03-5.39], p<0.0001) while for *RAS*mut no difference in PFS was detected (HR: 1.15 [0.91-1.45], p=0.256), but OS was significantly shorter (HR: 1.48 [1.09-2.00], p=0.012). **Conclusions:** Benefit from FOLFOXIRI plus bev was independent of *RAS* and *BRAF* mutational status, with a trend toward a larger benefit in *BRAF* mut limited by small subgroup size. All wt pts treated with FOLFOXIRI plus bev achieved impressive PFS and OS results. Independently from the treatment received *RAS* or *BRAF*mut pts had shorter long-term survival. Clinical trial information: NCT00719797.

| | FOLFIRI+bev | | FOLFOXIRI+bev | | HR (95%CI) | |
|---|---|---|---|---|---|---|
| | mPFS | mOS | mPFS | mOS | *PFS* | OS |
| All wt (N=129) | 11.3 | 34.4 | 13.3 | 41.7 | 0.77 (0.52-1.12) | 0.84 (0.51-1.38) |
| *RAS mut* (N=218) | 9.5 | 23.1 | 12.0 | 28.6 | 0.82 (0.62-1.09) | 0.86 (0.61-1.23) |
| *BRAF* mut (N=28) | 5.5 | 10.8 | 7.5 | 19.1 | 0.56 (0.20-1.14) | 0.55 (0.24-1.23) |

**3520 Poster Highlights Session (Board #8), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Combined epiregulin (EREG) and amphiregulin (AREG) expression levels as a biomarker of prognosis and panitumumab benefit in *RAS*-wt advanced colorectal cancer (aCRC).** *Presenting Author: Jenny F. Seligmann, University of Leeds, Leeds, United Kingdom*

**Background:** RNA expression of epiregulin (EREG) ligands EREG and/or amphiregulin (AREG) has shown correlation with the efficacy of EGFR-targeted therapy in advanced colorectal cancer (aCRC). This finding requires validation, and interaction with MEK-AKT pathway mutations clarified. We examined both ligands and mutations in patients (pts) in a large randomised trial of panitumumab. The *a priori* hypothesis was that high expression of either AREG or EREG, in *RAS*-wild type (wt) pts, would predict panitumumab benefit. **Methods:** AREG and EREG expression and *RAS (KRAS* and *NRAS*) and *BRAF* mutations were assessed in archival tumor from 323 pts randomised to irinotecan (Ir) or irinotecan/panitumumab (IrPan) as second-line treatment of aCRC (PICCOLO trial, Lancet Oncol 14: 749-759). A predefined dichotomous model classified ligand expression as "high" (either EREG or AREG in top tertile for mRNA level) or "low" (neither EREG nor AREG in top tertile). Prognostic effect was assessed, then predictive effect by testing interaction with drug impact. The primary population was *RAS*-wt (n=220); primary endpoint was progression-free survival (PFS). **Results:** High ligand expression was not a significant prognostic marker for PFS (HR 0.93, 95% CI 0.68-1.27, p=0.64) or overall survival (OS) (HR 0.79, 95% CI, 0.58-1.09, p=0.15). However, it was significantly predictive. For *RAS*-wt pts with high ligand expression, median PFS was 8.3 months (IrPan) vs 4.4 months (Ir) (HR=0.62, 95%CI 0.49-0.78, p<0.001). Conversely, *RAS*-wt pts with low expression gained no benefit: 3.2 months (IrPan) vs. 4 months (Ir) (HR=0.97, 95%CI 0.8-1.17, p=0.73). The ligand-treatment interaction was p=0.01. Less effect was seen on the secondary endpoints response rates (interaction p=0.09) and overall survival (interaction p=0.11). Ligand expression was markedly lower in *BRAF*-mutated than all-wt tumours (p<0.001), however ligand expression remained predictive of panitumumab effect following adjustment for *BRAF*. **Conclusions:** The hypothesis was confirmed: high ligand expression predicts panitumumab benefit on PFS in *RAS*-wt pts; there was no evidence of benefit with low ligand expression. Optimisation of the ligand model for clinical use is needed, however this work confirms that EREG and AREG are potentially useful biomarkers for anti-EGFR therapy.

**3521 Poster Highlights Session (Board #9), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Amphiregulin (AREG) SNP rs161511 to predict cetuximab efficacy independent of AREG mRNA levels: Data from FIRE3 (AIO KRK-0306).** *Presenting Author: Sebastian Stintzing, USC Norris Comprehensive Cancer Center, Los Angeles, CA*

**Background:** Anti-bodies targeting the epidermal growth factor receptor (EGFR) have shown efficacy in metastatic colorectal cancer (mCRC). The extended RAS analysis has further defined EGFR dependent tumors that are more sensitive to EGFR inhibition. Beyond RAS mutations, expression of EGFR ligands (amphiregulin (AREG) and epiregulin (EREG)) have shown predictive values. The challenge to move these biomarkers into clinic are the standardization of quantitative intra-tumor measurements. If germline single nucleotide polymorphisms (SNPs) in AREG and/or EREG would be predictive this could easily used in clinical practice. We have previously shown that rs1615111 associated with time-to-recurrence in gastric cancer. Aim of this study was to test the predictive value of rs1615111 in cetuximab treated mCRC patients. **Methods:** Genomic DNA was isolated from tissue samples of 299 patients (median age 64 years, male 67.2%) treated in first-line with either FOLFIRI cetuximab (n=139) or FOLFIRI bevacizumab (n=160) from the FIRE-3 trial (NCT00433927). In 174 samples, tumor cells were micro-dissected for mRNA extraction. rtPCR was carried out using LightCycler technology. All patients were *KRAS*/*NRAS* wild-type. The bevacizumab arm served as negative control arm. **Results:** The minor allele A of rs1615111 was associated with decreased tumor response (37% vs. 78.4%, two-sided Fisher's p=0.02) shorter progression free survival (5.9 months vs. 10.6 months, logrank p=0.001 HR 3.46) and OS (11.4 months vs. 33.1 months, logrank p=0.001, HR 3.87) in FOLFIRI plus cetuximab treated patients. Low AREG mRNA expression was associated with short OS (3.2 months vs. 33.1 months logrank p<0.001, HR 0.08) but no association with rs1615111 could be established. In FOLFIRI plus bevacizumab treated patients rs1615111 did not have any predictive value. **Conclusions:** AREG SNP rs1615111 is *predictive* for cetuximab treatment. No prognostic value could be established. Biological function of rs1615111 remains unknown as it was not associated with mRNA expression. Beyond RAS mutations and EGFR ligand expression SNPs in AREG are new promising predictive marker for EGFR inhibitors. Prospective studies to validate and confirm these data are warranted.

**3522 Poster Highlights Session (Board #10), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Influence of mRNA expression of *epiregulin (EREG)* and of *amphiregulin (AREG)* and *RAS* mutations on outcome of patients with metastatic colorectal cancer treated with 5-FU/LV plus irinotecan or irinotecan plus oxaliplatin as first-line treatment (FIRE 1-trial).** *Presenting Author: Arndt Stahler, Department of Pathology, University of Munich, Germany, Munich, Germany*

**Background:** Our aim was to investigate the impact of *EREG/AREG* expression and *RAS (KRAS/NRAS)* mutations in patients with metastatic colorectal cancer (mCRC) receiving systemic treatment without monoclonal antibodies. **Methods:** In total, 208 (of 479) patients with mCRC of a randomized trial receiving 5-FU/LV plus irinotecan (FUFIRI) or irinotecan plus oxaliplatin (mIROX) as first-line treatment were included in this analysis. Median progression-free-survival (PFS) and overall survival (OS) of the subset were well comparable to the whole study population. *RAS* mutation detection was performed by pyrosequencing of exons 2-4 of the *KRAS*- and *NRAS*- gene (codons 12, 13, 61 and 146). mRNA expression was quantified by RT-qPCR. To discriminate high and low expression, a ROC analysis resulted in a cut-off value using the maxima of sensitivity and specificity for overall response rate. *RAS* mutation and mRNA expression of *AREG* and *EREG* were correlated with response, PFS and OS. **Results:** In 107 of 208 patients (51.4%) a *RAS* mutation could be detected. mRNA expression was analysed in 192 patients, concerning *AREG* (low: 161 vs high: 31) and *EREG* (low: 103 vs high: 89). *RAS* wild-type tumors were not associated with better PFS (8.7 vs 8.2 months, HR: 0.93, p=0.62) and OS (21.9 vs 18.6 months, HR: 0.88, p=0.41). High compared to low *AREG* expression did not influence outcome concerning PFS (10.0 vs 8.2 months, HR: 0.68, p=0.07) and OS (24.6 vs 18.7 months, HR: 0.72, p=0.11). High compared to low *EREG* expression correlated with prolonged PFS (9.7 vs 7.0 months, HR: 0.58, p<0.01) and OS (25.8 vs 15.5 months, HR: 0.48, p<0.01). The favourable prognostic effect of high *EREG* expression was evident independently of *RAS* mutation (OS: HR wild-type: 0.50, HR mutated: 0.44; p<0.01), and treatment (OS: HR FUFIRI-arm: 0.42, HR mIROX-arm: 0.53; p<0.01). **Conclusions:** *EREG* expression appears as powerful prognostic marker in patients with mCRC receiving systemic therapy without monoclonal antibodies. Neither *RAS* mutations nor *AREG* expression showed a significant correlation with outcome in the FIRE1-trial.

**3523 Poster Highlights Session (Board #11), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Mir-31-3p as a predictive biomarker of cetuximab effects in a post hoc analysis of new EPOC phase III trial.** *Presenting Author: Pierre Laurent-Puig, UMR-S775 Bases Moléculaires de la Réponse aux Xénobiotiques, Paris, France*

**Background:** miR31-3p expression level has been associated with progression free survival (PFS) in *KRAS* wild type metastatic colorectal cancer (mCRC) patients treated with anti-epidermal growth factor receptors (EGFRs). In this study we evaluated its predictive value on PFS in the new EPOC trial by measuring its expression in primary tumors and liver metastases. **Methods:** miR31-3p expression was determined by RT-QPCR in 125 formalin-fixed and paraffin-embedded (FFPE) primary tumor samples from patients. There were 63 patients (control arm) who received oxaliplatin or irinotecan-based chemotherapy and 62 received the above plus cetuximab. Correlations between miRNA expression and survival were performed using an adjusted Cox model. Liver metastasis were available for 58 of the 125 patients and comparison was done using a Pearson correlation on log2 transformed miR31-3p expression value. **Results:** A significant association was found between PFS and miR31-3p expression in the cetuximab arm (p=0.035; HR=1.2, CI95% CI [0.98 – 1.48]), and not in the control arm (p=0.36; HR=0.96, CI95% [0.75 – 1.23]).A predictive model was developed dichotomizing patients with high or low risk of progression. In the cetuximab arm PFS was significantly shorter in patients with high expression than in patients with low expression (p=0.033). In all patients with high miR31-3p expression, PFS was significantly shorter in the cetuximab treated arm than in the control arm (p=0.0177, median PFS: 49.6 and 64.9 weeks respectively), in all patients with low miR31-3p expression, PFS was not different between cetuximab and control arm. Study of miR-31-3p expression in primary tumor and matching metastasis showed a correlation in the control arm (p=0.00004) but not in the cetuximab arm (p=0.55). **Conclusions:** We demonstrated for the first time that miR31-3p expression is predictive of cetuximab effects and replicated association of its expression with PFS in patients receiving cetuximab. Furthermore miR31-3p allowed identification of a subgroup of patients in which cetuximab with chemotherapy had a detrimental effect on PFS. Eventually the correlation of miR31-3p expression in metastases and primary tumors in the control arm, but not in the cetuximab arm, suggests cetuximab has an effect on miR31-3p expression, supporting its involvement in the EGFR pathway.

**3524 Poster Highlights Session (Board #12), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Phase II study of single-agent cetuximab in *KRAS* G13D mutant metastatic colorectal cancer (mCRC).** *Presenting Author: Marta Schirripa, U.O. Oncologia Medica 2, Azienda Ospedaliero-Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy*

**Background:** *RAS* mutant metastatic colorectal cancer (mCRC) patients (pts) are excluded from treatment with anti-EGFR monoclonal antibodies. Nevertheless, retrospective data from large phase III trials led to hypothesize a potential benefit from cetuximab in *KRAS* G13D mutant pts both in first and advanced lines of treatment (De Roock *JAMA* 2010, Tejpar *JCO* 2012). In the refractory setting, *KRAS* G13D mutant pts achieved a superior progression free survival (PFS) (4.0 vs. 1.9 months, HR=0.51, p=0.004) and overall survival (OS) (7.6 vs. 5.7 months, HR=0.50, p=0.005) compared to pts with other *KRAS* mutations. We conducted the present trial in order to prospectively confirm those findings and to evaluate the clinical relevance of single agent cetuximab in *KRAS* G13D mutant mCRC pts. **Methods:** According to previously reported results, using a phase 2 Fleming single-stage design, with 90% power and alpha 0.05, setting p0=10% and p1=50%, the study required the inclusion of 12 pts. The alternative hypothesis would have been rejected if 3 or less pts would have been progression-free at four months after treatment start. We prospectively enrolled mCRC patients to receive treatment with cetuximab monotherapy (500 mg/mq bi-weekly). Main eligibility criteria were the following: *KRAS* G13D mutant, measurable metastatic disease, progression after treatment with fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab or no other valid therapeutic option. Pts were re-evaluated according to RECIST 1.1 criteria. **Results:** Twelve consecutive *KRAS* G13D mutant eligible pts were enrolled. Main pts' characteristics were the following: Male/Female, 6/6; median age, 74 years (range 26-79); Eastern Cooperative Oncology Group performance status 0/1-2, 6/6; synchronous/metachronous disease, 8/4; median number of previous CT lines, 2 (range 0-5). Three patients (25%) showed disease stabilization at four months after treatment start and no RECIST responses were observed. Disease control rate at six months was 0%. Median PFS and OS were 1.9 and 7.2 months, respectively. Grade 3 rash was observed in two (17%) patients and no unexpected toxicities occurred. **Conclusions:** The hypothesis of a clinically relevant benefit with cetuximab monotherapy in *KRAS* G13D mutant mCRC pts was rejected. *KRAS* G13D mutant mCRC pts should not be treated with cetuximab and alternative strategies should be adopted.

**3525 Poster Highlights Session (Board #14), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Overall survival result and outcomes by *KRAS*, *BRAF*, and DNA mismatch repair in relation to primary tumor site in colon cancers from a randomized trial of adjuvant chemotherapy: NCCTG (Alliance) N0147.** *Presenting Author: Frank A. Sinicrope, Mayo Clinic, Rochester, MN*

**Background:** We report mature overall survival (OS) data in stage III colon cancers from a phase III trial of adjuvant mFOLFOX6 ± cetuximab. Biomarkers were analyzed in relation to primary tumor site and OS, and include additional non randomized patients (pts) with *KRAS*mutant tumors. **Methods:** Cancers (N= 3,018) were analyzed prospectively for $BRAF^{V600E}$ (exon 15) and *KRAS* (exon 2;codons 12, 13) mutations, and expression of DNA mismatch repair (MMR) proteins (MLH1, MSH2, and MSH6). Loss of an MMR protein indicated deficient (d) MMR. Tumor site was categorized as proximal *vs*distal (inclusive of the splenic flexure). Median follow-up was 4.9 yrs. Cox proportional hazards models were adjusted for covariates including treatment. **Results:** Consistent with our previously reported DFS data, the addition of cetuximab was associated with worse OS in pts with wild type *KRAS* (p=.0073). Activating $BRAF^{V600E}$ or KRAS mutations were detected in 346/2831 (12.2%) and 1042/2905 (35.9%) tumors, respectively; dMMR was found in 329/2906 (11.3%). dMMR or mutations in $BRAF^{V600E}$ or *KRAS* were more likely to occur in proximal *vs* distal tumors [all p<.0001]. $BRAF^{V600E}$ mutations were associated with older age, female sex, high grade histology, dMMR, and higher T and N stage (all p< 0.01). A tumor site interaction was observed for OS with *KRAS* (p=.0435) and MMR (p=.0097), but not *BRAF*. *KRAS* mutations [HR 1.98 (1.49-2.63); p<.0001] and dMMR [HR 1.85 (0.99-3.46); p=.054] were each associated with worse OS in distal (*vs* proximal) cancers. dMMR predicted favorable OS in proximal tumors [HR 0.71 (0.53-0.97); p=.030]. Tumors with wild type copies of both *BRAF* and *KRAS* showed better OS within proximal [HR 0.74 (0.59-0.93); p=.009] and distal [HR 0.51 (0.39-0.67); p<.0001] cancers compared to those with a $BRAF^{V600E}$ or *KRAS*mutation. **Conclusions:** The addition of cetuximab to mFOLFOX6 resulted in significantly poorer OS. The prognostic impact of biomarkers on OS differed significantly by tumor site. Novel findings include poor OS of *KRAS* mutant tumors that was restricted to the distal colon, and a divergent prognosis for dMMR by primary tumor site. Clinical trial information: NCT00079274.

**3526 Poster Highlights Session (Board #15), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Evolution of heterogeneous mechanisms of acquired resistance to cetuximab-based therapy in colorectal cancer.** *Presenting Author: Clara Montagut, University Hospital del Mar - IMIM, Barcelona, Spain*

**Background:** Anti-EGFR drug resistance is a major challenge in metastatic colorectal cancer (mCRC). The aim of this study was to elucidate molecular mechanisms of acquired resistance in mCRC patients treated with cetuximab-based therapy. **Methods:** 37 mCRC patients with acquired resistance to cetuximab-based therapy with paired tumor samples (prior and at progression to treatment) were prospectively included. In three patients, multiple biopsies were obtained over the course of the disease. Mutations in *EGFR*, *KRAS, NRAS*, *BRAF* and *PIK3CA* genes were evaluated by next-generation pyrosequencing. Gene amplification was evaluated by FISH. Mutations were also assessed in plasma in 7 representative cases. **Results:** Eighty-one percent of patients harbored a molecular event (comprising mutations and amplifications) in post-treatment biopsies. In one third of patients, multiple molecular events (range 2-5) coexisted in the same sample. *RAS* mutations were the most frequent event (40% of patients) and mostly affected exons 3 and 4, followed by mutations in *PIK3CA (19%), BRAF (11%), EGFR* S492R (8%) and novel mutations in *EGFR* ectodomain (5%). Of note, in 9 patients the mutations were already detected at diagnosis by next-generation sequencing. Multiple repeat biopsies revealed that the percentage of mutant alleles increased under drug pressure and became undetectable following drug withdrawal. Mutations were detected in plasma samples in 62% of tested cases. **Conclusions:** We provide comprehensive evidence for the evolution of multiple mechanisms of acquired resistance to cetuximab-based therapy in mCRC. This data establishes the need of routine molecular studies at disease progression to individualize further therapeutic decisions.

**3527 Poster Highlights Session (Board #16), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Surgical resection of primary tumors (SRPT) in asymptomatic patients with stage IV colorectal cancer (CRC): A Canadian province experience.** *Presenting Author: Shahid Ahmed, Department of Medical Oncology, Saskatoon Cancer Centre, Saskatchewan Cancer Agency, University of Saskatchewan, Saskatoon, SK, Canada*

**Background:** Surgical resection of primary tumors (SRPT) in asymptomatic stage IV colorectal cancer (CRC) patients remains controversial. Reported survival benefit in literature has been attributed to selection of younger healthier patients with good performance status (PS). We have shown that SRPT improves survival independent of age, PS, and comorbid illness (JCO 30: 2013;456). This study was conducted to validate prognostic role of SRPT in asymptomatic patients with stage IV CRC. **Methods:** A cohort of newly diagnosed asymptomatic patients with stage IV CRC during 1992-2005, in Saskatchewan, was evaluated. Kaplan-Meier method was used to determine survival. Log-Rank test was done to compare survival. Cox proportional hazard model was performed to determine prognostic importance of SPRT. **Results:** There were834 patients with median age of 70 years (22-93) and male to female ratio of 58:42 were identified. Twenty six percent had Eastern Cooperative Oncology Group (ECOG) PS of >1 and 62% had a comorbid illness. There were 521 (63%) patients who underwent SRPT and 43.3% received chemotherapy. Median overall survival (OS) of patients who received chemotherapy was 16 (95% CI: 13.8-18.2) months. Patients who underwent SRPT had median OS of 19.7 (16.9-22.6) months vs. 8.4 (6.9-10.0) months without surgery (p<0.0001). Patients who received second generation therapy and underwent SRPT had median OS of 29.4 months (24.2-34.5) vs. 16.0 (13.2-18.9) months if they received older regimen. On multivariate analysis 5FU-based chemotherapy (HR 0.43; 95% CI: 0.36-0.53), SRPT (0.47; 0.39-0.57), metastesectomy (0.48; 0.38-0.62), and second line chemotherapy (0.72; 0.58-0.92) were correlated with superior survival whereas, elevated bilirubin (1.48; 1.11-1.62), low albumin (1.48; 1.25-1.75), ECOG PS >1 (1.36; 1.15-1.62), high grade tumor (1.34; 1.06-1.58), leukocytosis (1.30; 1.06-1.58), anemia (1.28;1.09-1.49), and age ≥ 65 years (1.20; 1.02-1.42) were correlated with poor survival. Test for interaction between ≥ 1 metastatic sites and SRPT was significant (p=0.03) suggesting larger benefit of SRPT in stage IVA disease. **Conclusions:** This first large population based cohort study confirmss that SRPT, improves survival independent of chemotherapy, age, functional status and comorbid illness, in asymptomatic patients with stage IV CRC .

**3528 Poster Highlights Session (Board #17), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Surgical outcome for pulmonary metastasis of colorectal cancer in the modern chemotherapy era: Results of a retrospective Japanese multicenter study.** *Presenting Author: Tomoyuki Hishida, Department of Thoracic Surgery, National Cancer Hospital East, Chiba, Japan*

**Background:** There have been few reports of surgical outcome for pulmonary metastasis (PM) of colorectal cancer (CRC) (CRC-PM) in the era of modern effective chemotherapy including oxaliplatin. **Methods:** Clinical and survival data of patients undergoing first metastasectomy for CRC-PM between 2004 and 2008 were collected from 46 institutions. Data cut-off date was August 31, 2013. **Results:** A total of 1,237 patients' (pts') data were collected. After exclusion of ineligible cases including non-R0, 898 pts' data were analyzed. Of these, 161 (18%) pts had synchronous PM with primary tumor. Median number of resected PMs was 1 (range, 1–10) and 124 (14%) had bilateral PMs. The five-year overall survival (OS) and disease-free survival (DFS) were 65.7% (95% CI, 62.3–69.2) and 35.3 % (32.1–38.8) after median follow-up period of 61 months, respectively. According to the status of pre or postoperative adjuvant chemotherapy (Pre-/ Post-C), pts were classified into four groups: A (-/-, n=417), B (-/+, n=368), C (+/-, n=55), and D (+/+, n=58). There were substantial differences in background among four groups. Independent prognostic factors for OS and DFS were elevated carcinoembryonic antigen (CEA) level at the time of lung resection (OS: HR=2.03, 95% CI, 1.61–2.57; DFS: 1.58, 1.32–1.88), and the number of resected PMs (OS: 1.20, 1.10–1.30; DFS: 1.21, 1.13–1.29). The five-year OS and DFS after surgery alone (group A) were 66.8% (62.1–72.0), and 39.3% (34.6–44.6), respectively. After adjusting by above prognostic and background factors among four groups, overall perioperative use of chemotherapy (B+C+D vs. A) was not statistically associated with prolonged OS (HR=0.95, 0.66–1.35) and DFS (0.93, 0.71–1.20). HR of Pre-C (group C vs. A) was 2.26 (95% CI, 1.06–4.81) for OS and 2.26 (1.28–3.98) for DFS. On the other hand, HR of Post-C (B vs. A) was 0.81 (0.55–1.19) for OS and 0.87 (0.66–1.14) for DFS. **Conclusions:** Modern surgical resection for CRC-PM demonstrated favorable prognosis. This retrospective study did not reveal a relevant effect of perioperative chemotherapy on survival. However, HR of Post-C prompted further investigation for adjuvant chemotherapy after resection of CRC-PM.

**3529 Poster Highlights Session (Board #18), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**A comparison of survival by site of metastatic resection (MR) in metastatic colorectal cancer (mCRC).** *Presenting Author: Brandon David Bernard, British Columbia Cancer Agency, Vancouver, BC, Canada*

**Background:** MR of liver limited disease is an effective therapy for patients (pts) with mCRC. Despite limited data, this approach has been expanded to include MR in other sites. We compared survival for mCRC pts undergoing MR of liver metastasis vs MR in other sites. **Methods:** Pts with mCRC who underwent MR in British Columbia over 5 time cohorts between 1995 and 2010 were reviewed. Pts without data on the site of MR or survival were excluded. Overall survival (OS) was defined as the time from diagnosis of metastasis to death. Kaplan Meier methodology and log-rank tests were used to compare the impact of site of MR on OS. Multivariate Cox regression was performed to assess for the impact of MR on OS, adjusting for known prognostic factors. **Results:** 2,082 pts with mCRC were identified; 1,197 men (57.5%) and 885 women (42.5%); 236 (1995-96), 206 (2000), 351 (2003-4), 546 (2006), 743 (2009-10). Median age at diagnosis of mCRC was 69 (14-94). 544 pts (30.0%) received a MR: 207 liver (38.1%), 57 lung (10.5%), 11 liver and lung (2.0%), 98 peritoneal (18.0%), 50 ovarian (9.2%), 34 brain (6.3%) and 87 other (16.0%). Pts that did not undergo MR had an OS of 13.4 months (ms) vs 41.8 ms for those that had MR of liver, lung or ovary (HR 0.31 (0.27-0.36); p<0.0001). By MR subgroup, OS was 46.2 ms for liver, 43.0 for lung, 41.2 for liver and lung, 13.4 for peritoneum, 21.8 for ovary, and 15.8 for brain. When compared to MR of liver, no significant difference in OS was observed for MR in lung (p=0.61) or liver and lung (p=0.26). Multivariate OS data are shown in the Table. **Conclusions:** MR of lung and liver and lung appears to confer a comparable survival advantage to MR of liver limited disease. Additional investigation is needed to further select pts most likely to benefit from MR.

| Multivariate analysis for OS | HR | p-value |
|---|---|---|
| MR (liver, lung, or ovar)y | 0.36 (0.31-0.42) | <0.0001 |
| Age (< 65 vs ≥ 65) | 0.89 (0.63-1.27) | 0.54 |
| Sex (M vs F) | 1.03 (0.94-1.13) | 0.51 |
| Primary (colon vs rectum) | 1.11 (1.00-1.20) | 0.03 |
| M1 at presentation (N vs Y) | 0.85 (0.77-0.95) | 0.0016 |
| ChemoTx (Y vs N) | 0.48 (0.24-0.82) | 0.009 |
| Primary resection (Y vs N) | 0.57 (0.49-0.65) | <0.0001 |
| 2000 vs 1995-96 | 1.40 (1.10-1.60) | 0.0012 |
| 2003-4 vs 1995-96 | 1.30 (1.10-1.60) | 0.005 |
| 2006 vs 1995-96 | 1.30 (1.10-1.60) | 0.0006 |
| 2009-10 vs 1995-96 | 1.40 (1.20-1.60) | 0.0001 |

**3530 Poster Highlights Session (Board #19), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Complete neoadjuvant therapy in rectal cancer (CONTRE): A Brown University Oncology Research Group phase II study.** *Presenting Author: Kimberly Perez, Brown University Oncology Research Group, Providence, RI*

**Background:** After preoperative chemoradiation and surgery, many patients (pts) with clinical stage II-III rectal cancer are unable to tolerate adjuvant FOLFOX chemotherapy, which may compromise disease-free and overall survival (DFS/OS). This study was designed to assess treatment delivery, toxicity and impact on pathologic response of administering chemotherapy prior to chemoradiation and surgery. **Methods:** Pts with clinical T3-4 and/or N1-2 rectal cancer, staged by endorectal ultrasound (ERUS) and pelvic MRI, received modified (m) FOLFOX6 every two weeks x eight cycles, followed by 50.4 Gy IMRT with concurrent capecitabine 825mg/m$^2$ BID, 5 days per week, followed by surgery 4-8 weeks later. **Results:** There were 39 pts enrolled between August 2010 and June 2012; median age was 61 (30-79); clinical stage II n=7, stage III n=32. Distance from the anal verge: <3cm n=5; 3-5cm n=5; >5cm n=29. There were four pts presented with lumen obstruction preventing advancement of the endoscope and 31 with rectal bleeding. There were 36 pts (92%) completed eight cycles of mFOLFOX6. Grade 3 toxicities during chemotherapy included diarrhea (n=2), neutropenia (n=6), and renal dysfunction (n=1). There was one pt with a cardiovascular disease had a TIA (grade 4). There was one pt had grade 4 neutropenia. All pts had resolution of bleeding and improvement of obstructive symptoms, with no complications requiring surgical intervention. There as two pts declined radiation after completing chemotherapy, and one withdrew due to grade 3 diarrhea. At surgery, pathologic complete response (ypT0N0) (pCR) was confirmed in 13 pts (33%; 95% CI 18.24%-47.76%), residual stage I in 10 (26%), stage II in seven (18%), and stage III in eight (20%); one pt did not undergo surgery. There was two pts with microsatellite unstable tumors had no evidence of response to treatment. **Conclusions:** Over 90%of pts wereable to complete mFOLFOX6 when administered prior to chemoradiation and surgery. The pCR rate was higher than typically seen with chemoradiation alone. A randomized study would be required to determine if improved delivery of chemotherapy using this approach improves DFS/OS, but CONTRE represents a well-tolerated alternative to the current standard treatment sequence and could serve as a platform for clinical trials in rectal cancer. Clinical trial information: NCT01363843.

**3531 Poster Highlights Session (Board #20), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Neoadjuvant radiotherapy (RT) combined with capecitabine (Cape) and sorafenib (Sor) in patients (pts) with locally advanced, k-ras-mutated rectal cancer (LARC): A phase I/II trial SAKK 41/08.** *Presenting Author: Roger Von Moos, Kantonsspital Graubünden, Chur, Switzerland*

**Background:** K-ras mutation is found in up to 40% of LARC. Sor is a multitarget tyrosine kinase inhibitor including raf and VEGFR and has demonstrated radiosensitizing effects. Sor might improve outcome of standard preoperative radio-chemotherapy in patients with k-ras mutated LARC. **Methods:** Pts with k-ras mutated T3-4 and/or N+, M0 disease by MRI were included. Recommended doses from phase I part consisted of RT 1.8 Gy/day x25 with Cape 825mg/m$^2$bid x 33 in combination with Sor 400mg/d. The primary endpoint for the phase II part was pathological complete response (pCR) prospectively defined as grade 3 (near complete regression) or 4 (complete regression) in the histological grading system according to Dworak (DC). A pCR rate of 8% or lower was considered uninteresting and of 22% or higher was promising. Secondary endpoints included sphincter preservation, R0 resection, downstaging and safety. **Results:** 54 pts were treated in 18 centers in Switzerland und Hungary, 40 pts were included into the single arm phase II part. Median dose intensity per day was 100.0% for RT, 98.6% for Cape and 100.0% for Sor respectively. pCR rate was 60.0% (95%CI: 43.3%, 75.1%) by central independent pathological review (15.0% DC grade 4; 45.0% DC grade 3). Sphincter preservation was achieved in 89.5%, R0 resection in 94.7% and downstaging in 81.6% of the pts. The most common grade 3 toxicities included diarrhea (15.0%), skin toxicity outside of the RT field (12.5%), pain (7.5%), skin toxicity in RT field, proctitis, fatigue and cardiac ischemia (each 5.0%). Laboratory AEs grade 3/4 were neutropenia (1 pt grade 4; 1 grade 3), creatinine elevation (1 pt grade 3). **Conclusions:** The combination of Sor to standard RCT with Cape in k-ras mutated LARC tumors is highly active with acceptable toxicity and deserves further investigation. Clinical trial information: NCT00869570.

**3532 Poster Highlights Session (Board #21), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**External validation of the neoadjuvant rectal (NAR) score and Valentini prediction nomogram (VPN): A multicenter study.** *Presenting Author: Soundouss Raissouni, Tom Baker Cancer Centre, Calgary, AB, Canada*

**Background:** The VPN [JCO 2011;29(23)] is a tool used for individualized prognostication in rectal cancer, and the recently described NAR score [Yothers et al. JCO 32, 2014 abst: 38] has been suggested as a surrogate endpoint for overall survival (OS) in clinical trials. However, these tools have not been validated outside of the clinical trial setting. We assessed these models in a retrospective multi-institution database, to determine their predictive ability for outcome in patients with rectal cancer treated with neoadjuvant chemoradiation (nCRT). **Methods:** Data from patients with locally advanced rectal cancer who received nCRT and had curative intent surgery from 2005 to 2012 were collected from Tom Baker Cancer Center, Cross Cancer Institute, BC Cancer Agency, Ottawa Hospital Cancer Centre and Dr. H. Bliss Murphy Cancer Centre. The NAR score was compared with pathologic complete response (pCR) status for OS and with the VPN for local control (LC), distant control (DC) and OS using Akaike's information criterion (AIC – a tool for comparing models in a dataset). C-index was evaluated for VPN and NAR for OS. **Results:** 1,172 patients were included; pCR was achieved in 16.6%.The median NAR score was 17.36; NAR risk groups included low (22.6%), intermediate (42.6%), and high (34.9%). The 5-year OS in the NAR risk groups were 88.1% (low), 82% (intermediate – HR 1.89, 95% CI 1.13 – 3.1), 59.5% (high – HR 5.05, 95% CI 3.1 – 8.2), and 89.9% for pCR (HR 0.25, 95% CI 0.14 – 0.45) versus 73.1 % for no pCR (log rank p-value $<0.0001$ for both). AIC favoured NAR compared with pCR for OS (2,549.6 v 2,824.0).VPN as a continuous variable predicted LC (HR 0.97, 95% CI 0.95-0.99, p=0.015), DC (HR 0.98, 95% CI 0.98-0.99, $p<0.0001$) and OS (HR 0.96, 95% CI 0.95-0.96, $p<0.0001$). The AIC favoured VPN over NAR for LC (851.2 v 856.5), DC (2,154.5 v 2,160.6) and OS (2,455.3 v 2,549.6). C-index also favoured VPN over NAR for OS (0.697 v 0.66). **Conclusions:** Similar to recent clinical trial data, NAR outperformed pCR in predicting OS, and the VPN was significantly associated with LC, DC and OS in the non-clinical trial setting. VPN appeared to better predict LC, DC, and OS compared with the NAR score and is favoured for individual patient prognostication.

**3533 Poster Highlights Session (Board #22), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Neoadjuvant rectal cancer (RC) score to predict survival: Potential surrogate endpoint for early phase trials.** *Presenting Author: Greg Yothers, National Surgical Adjuvant Breast and Bowel Project Biostatistical Center, and University of Pittsburgh Graduate School of Public Health, Department of Biostatistics, Pittsburgh, PA*

**Background:** Valentini, et al. (J Clin Oncol 29: 2011, 3163-72) developed nomograms for predicting overall survival (OS) based on clinical factors available after neoadjuvant therapy (tx). Pathologic T-stage (pT), N-stage (pN), and clinical T (cT) were the most important independent predictors of OS. We developed a neoadjuvant RC score (NAR score) using pN and downstaging of T (cT – pT) based on relative weights suggested by the nomograms. NSABP's R-04 trial presents an opportunity for independent validation of the NAR score. **Methods:** Pts with clinical stage II/III RC undergoing preoperative RT (4,500cGy in 25 fractions over 5 wks + boost of 540-1080cGy in 3-6 daily fractions) were randomized to one of four regimens in a 2x2 design: CVI 5-FU (225mg/m$^2$ 5 days/wk), with or without oxaliplatin (Ox) (50mg/m$^2$ /wk x 5) or oral capecitabine (825 mg/m$^2$ BID 5 days/wk), with or without Ox. The NAR score is computed as [5 pN – 3 (cT – pT) + 12]$^2$ / 9.61 where: cT in {1, 2, 3, 4}, pT in {0, 1, 2, 3, 4}, and pN in {0, 1, 2}. The NAR score takes values from 0 to 100; higher scores indicate poorer prognosis. Analyses based on the score should be stratified by cT. NAR score is compared to pathologic complete response (ypCR) by Akaike's information criterion (AIC) to determine the better predictor of OS. **Results:** 1,479 pts had data for the NAR score and follow-up for OS. Continuous NAR score was significantly associated with OS (HR/unit 1.04 95% CI 1.03-1.05, $p<0.0001$). Pts were grouped into low, intermediate, and high risk of death categories based on tertiles of the NAR score. Categories were significantly associated with OS ($p<0.0001$) with 5yr OS values of 92, 89, and 68%, respectively. ypCR was also significantly associated with OS (HR 0.37 95% CI 0.24-0.58, $p<0.0001$). Continuous NAR score had a much lower AIC (2902.49) than ypCR (2987.08) suggesting stronger association with OS. **Conclusions:** The NAR score has been validated as a predictor of OS after neoadjuvant tx for RC. AIC of the continuous NAR score suggests it is a better predictor of OS than dichotomous ypCR. NAR score could be used in place of ypCR as a surrogate endpoint for OS in early phase neoadjuvant rectal trials. Support:U10-CA-12027, U10-CA-37377, U10-CA-69651, U-10-CA-69974; Sanofi; Roche. Clinical trial information: NCT00058474.

**3534 Poster Highlights Session (Board #23), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**A randomized phase III trial of mFOLFOX6 plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment for metastatic colorectal cancer: West Japan Oncology Group study 4407G (WJOG4407G).** *Presenting Author: Kentaro Yamazaki, Divison of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan*

**Background:** FOLFIRI and FOLFOX showed equivalent efficacy for metastatic colorectal cancer (mCRC), however their combination with bevacizumab (Bev) have not been directly compared. **Methods:** The WJOG4407G study was a randomized, open-label, phase III trial. Patients (pts) with previously untreated mCRC were randomized to receive either mFOLFOX6+Bev (group A; oxaliplatin 85mg/m$^2$, l-leucovorin 200mg/m$^2$, bolus 5-FU 400mg/m$^2$, infusional 5-FU 2,400mg/m$^2$, and Bev 5mg/kg; q2w) or FOLFIRI+Bev (group B; irinotecan 150mg/m$^2$instead of oxaliplatin), stratified by institution, adjuvant chemotherapy, and liver limited disease. The primary objective was to investigate non-inferiority of B to A in progression free survival (PFS) assessed in the full analysis population (all randomized pts without major violation of eligibility criteria); non-inferiority margin of hazard ratio (HR) 1.25 based on the assumption of median PFS 10/11 months in A/B (power 0.85, 1-sided alpha 0.025). The secondary endpoints were response rate, overall survival (OS), safety, and quality of life (QOL). **Results:** From September 2008 to January 2012, 395 (A/B 198/197) of 402 enrolled pts were eligible for efficacy analysis. Data cut-off date was July 2013. Median PFS in A/B were 10.7/12.0 months (HR 0.905, 95% CI 0.723-1.133; p=0.003 for non-inferiority and p=0.427 for superiority; events in 78% pts). There was no interaction effect between the treatment and *KRAS*(codon12, 13) mutation status. Subsequent treatments were performed in 168/157 pts after A/B. Median OS in A/B were 28.9/31.8 months (HR 0.901, 95% CI 0.683-1.189; events in 50% pts), and response rates were 62.2/63.8%. The common grade 3 or 4 adverse events in A/B were leukopenia 4.5/11.3%, neutropenia 35.4/45.6%, diarrhea 5.1/8.7%, febrile neutropenia 1.5/5.1%, peripheral neuropathy 21.7/0%, and venous thromboembolism 1.5/6.2%. The QOL assessed by FACT-C (TOI-PFC) and FACT/GOG-Ntx were favorable for B throughout 18 months. **Conclusions:** FOLFIRI+Bev was non-inferior to mFOLFOX6+Bev with respect to PFS as 1st-line treatment for mCRC, and showed better trend in QOL. Clinical trial information: UMIN000001396.

**3535 Poster Highlights Session (Board #24), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Metformin (M), diabetes (DM), and colorectal cancer (CRC) survival among U.S. veterans.** *Presenting Author: Jessica K Paulus, Tufts Clinical and Translational Science Institute, Boston, MA*

**Background:** Although diabetes (DM) is associated with a worse colorectal cancer (CRC) prognosis, metformin (M) use has been associated with improved overall and CRC-specific survival in several prior studies. We examined the impact of M use on overall survival (OS) in patients with type 2 DM and CRC among US veterans while adjusting for treatment, stage and diabetic severity, offering the largest cohort study examining this issue to date. **Methods:** There were 21,352 patients with CRC were diagnosed between 2001 and 2008 in the US Veterans Health Administration. OS was compared across four groups: patients without DM (n=16,355); patients with DM on M (n= 2,038); patients with DM on anti-DM medications other than M (n=2,136); and patients with DM not on anti-DM medication (n=823). Multivariate Cox proportional hazards models were used to estimate the association between M use, DM and OS while adjusting for age, race, stage, body mass index, HbA1C, comorbidity index, and cancer treatment. **Results:** Median survival was 61 months in non-diabetics, 67 months in metformin users, 45 months in users of other diabetic medications, and 51 months in diabetics not on anti-DM medication. HbA1C levels were 6.9%, 6.8%, and 6.2% in patients with DM on metformin, other, or no anti-DM medication, respectively. In the subset of CRC patients with DM, those patients taking M had a 21% decrease in the risk of death compared to patients with diabetes taking anti-DM medications other than M ($HR_{adj}$ 0.79; 95% CI 0.73-0.86, $p=<0.001$), while diabetic patients not on any anti-DM medications had a 13% decrease in risk of death ($HR_{adj}$ 0.87; 95% CI 0.78-0.97, p=0.02). No interaction between M and BMI was observed (p=0.86). In the entire cohort, patients with DM on anti-DM medications other than M had a statistically significant increase in risk of death compared to non-diabetics ($HR_{adj}$ 1.26; 95% CI 1.19-1.33, $p=<0.0001$). However, patients with DM on M had similar OS as compared to non-diabetics ($HR_{adj}$ 1.05; 95% CI 0.99-1.12, p=0.11), as did patients with DM not on anti-diabetic medication ($HR_{adj}$1.08; 95% CI 0.99-1.18, p=0.07). **Conclusions:** Among diabetics with CRC, M use is associated with improved survival as compared to the use of other medications. Metformin may reduce the survival disadvantage associated with DM among CRC patients.

**3536 Poster Highlights Session (Board #25), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Racial differences in *KRAS*/*BRAF* mutation rates and survival in colon cancer (NCCTG N0147 [Alliance]).** *Presenting Author: Harry H. Yoon, Mayo Clinic, Rochester, MN*

**Background:** It is unknown if racial disparities in colon cancer outcomes persist after controlling for clinicopathologic variables and treatment. Molecular characterization of colon cancers in a North American population that includes Asians has not been reported. **Methods:** *KRAS*/*BRAF* mutation (mt) was determined in stage III colon cancer patients (pts, N = 3305) in the North American phase 3 adjuvant trial N0147. Race categories included Asian (149), black (240), or white (2916). Outcomes were analyzed in 2931 pts randomized to FOLFOX +/- cetuximab. Given a lack of interaction between race and treatment, arms were pooled. Cox models were used to estimate disease-free survival (DFS). **Results:** *BRAF* mt frequency in tumors from whites was twice that of tumors from Asians or blacks; *KRAS* mt rates were highest in tumors from blacks; *KRAS/BRAF* wildtype (wt) rates were highest in tumors from Asians (all $P<.005$; Table). Compared to whites, tumors from blacks were more likely to be N1 (*vs* N2) or low-grade (*vs* high), and tumors from Asians were more likely to be distal (*vs* proximal) (all $P<.003$). Blacks were younger than whites ($P<.001$). Notably, the prognostic impact of race differed based on N stage ($P_{interaction}=.0049$) and age ($P_{interaction}=.012$). Thus, DFS was analyzed by N stage (Table) and age. Blacks had shorter DFS than whites among N1 pts, and Asians had longer DFS among N2 pts, independent of covariates including *KRAS/BRAF* (Table). Among age <50, blacks had shorter DFS than whites (multivariate HR 2.8; 95% CI 1.7-4.6; $P<.0001$). Findings were consistent using time to recurrence as the outcome. **Conclusions:** These data, to our knowledge, are the first to show that Asians have a significantly lower rate of *KRAS/BRAF* mutations than blacks or whites. We also report a novel interaction of race with N stage and age, showing that racial disparities in survival persist despite uniform stage and enrollment in a phase 3 trial.

| | Mt rates | | | | DFS[a] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | $N_1$ subset | | | $N_2$ subset | | |
| Race | BRAF mt | KRAS mt | *WT* for both | $P_{overall}$ | HR | 95% CI | P | HR | 95% CI | P |
| Asian | 6% | 28% | 67% | <.0001 | .94 | .43, 2.02 | .87 | .50 | .25, .99 | .045 |
| Black | 6% | 44% | 50% | | 1.54 | 1.04, 2.29 | .032 | .96 | .60, 1.52 | .85 |
| White | 14% | 35% | 51% | | | ref | | | ref | |

[a] Adjusted for *KRAS/BRAF*, mismatch repair, T stage, grade, tumor site, age, body mass index, smoking.

**3537 Poster Highlights Session (Board #26), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Body mass index (BMI) as prognostic in metastatic colorectal cancer (mCRC): A pooled analysis of 21 first-line trials in the ARCAD database.** *Presenting Author: Lindsay A. Renfro, Mayo Clinic, Rochester, MN*

**Background:** Recent retrospective analyses in early CRC showed low and high BMI associated with worse outcomes; limited data exist on BMI as a prognostic or predictive factor in mCRC. **Methods:** Data from 18,564 pts enrolled to 21 first line mCRC trials from 1997-2009 were pooled. BMI was studied as possibly non-linear in Cox models for overall survival (OS) and progression-free survival (PFS); both prognostic and predictive effects were tested. Adjustments for and interactions with age, sex, and performance status (PS) were considered. Subgroup analyses within anti-EGFR vs. anti-angiogenesis were performed. Clinically relevant effects with $p<0.05$ were deemed significant. **Results:** BMI was prognostic for OS ($p<0.0001$) and PFS ($p<0.0001$) with "L" shape risk; i.e., risk of progression and/or death was greatest near BMI = 15, risk decreased as BMI increased to approximately BMI = 28, then plateaued. Relative to obese pts, low BMI pts had 46% increased risk of a PFS event and 85% increased risk of death. Low BMI was associated with poorer survival for males than females (interaction $p=0.0003$); high BMI was associated with worse survival for patients with PS 2+ but not lower PS (interaction $p=0.003$); other interactions and predictive tests were not significant. The BMI effect was similar in anti-EGFR and anti-angiogenesis therapy. **Conclusions:** Low BMI was associated with higher risk of progression or death among the mCRC trial pts studied, with decreased risk for higher BMI, opposite of reports in the adjuvant setting. Possible explanations include cancer cachexia in low BMI pts and increased dose or selection bias in high BMI pts, who may have comorbidities making them ineligible for clinical trials. Further study to understand the mechanisms of this association are warranted.

**3538 General Poster Session (Board #1), Sat, 8:00 AM-11:45 AM**

**Early predictors of prolonged overall survival (OS) in patients (pts) on first-line chemotherapy (CT) for metastatic colorectal cancer (mCRC): An ARCAD study with individual patient data (IPD) on 10,962 pts.** *Presenting Author: Dirkje Willemien Sommeijer, NHMRC Clinical Trials Centre, Sydney; Flevohospital, Almere; Academic Medical Centre, Amsterdam, Netherlands*

**Background:** To expedite drug development and improve treatment (trt) decisions, early indicators of trt efficacy are needed. We evaluated the pt-level association between early tumor shrinkage (ETS; ≥ 20% decrease from baseline), early objective tumor response (EOTR; CR/PR by RECIST), and early nonprogression status (EnPD;CR/PR/SD by RECIST) at 6, 8/9, or 12 weeks (wks) with OS, and compared these with standard endpoints (best overall response [BOR] and confirmed response [ConfR]) in pts treated with 1st-line CT. **Methods:** 16 phase III trials, including 10,962 pts on 5FU-LV/capecitabine alone or with oxaliplatin/irinotecan, from the ARCAD database were analyzed. Associations between early endpoints and OS were tested by stratified Cox models with a landmark approach. Prediction performance was compared by the C-index (c), a measure of relative accuracy to distinguish those at high versus low risk of death (higher value indicates better risk discrimination). **Results:** ETS and EOTR were significant predictors of OS with similar hazard ratios (HRs) to BOR and ConfR ($p<0.0001$; see Table). Pts without early progression (non-PD) showed the largest risk reduction (HRs ~ 0.3). Adjusting for age, performance status, number of metastases, and prior trt, significance remained. C-indices were similar across early endpoints, and similar to those for BOR and ConfR. **Conclusions:** Early responses are significantly associated with prolonged OS in mCRC pts on 1st-line chemotherapy. Early PD strongly correlates with an increased hazard of death. The pt-level prediction accuracy is as strong as for standard endpoints with the advantage of earlier tumor evaluation. Similar performance of ConfR implies the lack of utility for response confirmation. Formal surrogacy testing at trial level is ongoing.

| | EOTR | ETS | EnPD | BOR | ConfR |
|---|---|---|---|---|---|
| Weeks | HR (95% CI) [c] | HR (95% CI) [c] | HR (95% CI) [c] | HR (95% CI) [c] | HR (95% CI) [c] |
| 6 | .61 (.54-.69) [.55] | .61 (.55-.67) [.57] | .31 (.27-.36) [.56] | .59 (.56-.63) [.58] | .65 (.59-.70) [.55] |
| 8/9 | .60 (.62-.69) [.58] | .64 (.57-.71) [.57] | .24 (.19-.30) [.56] | | |
| 12 | .61 (.56-.65) [.58] | .63 (.58-.67) [.57] | .35 (.32-.39) [.57] | | |

**3539^ General Poster Session (Board #2), Sat, 8:00 AM-11:45 AM**

**Correlation of *PI3KCA* and extended *RAS* gene mutation status with outcomes from the phase III AGITG MAX involving capecitabine (C) alone or in combination with bevacizumab (B) with or without mitomycin C (M) in advanced colorectal cancer (CRC).** *Presenting Author: Timothy Jay Price, The Queen Elizabeth Hospital and University of Adelaide, Woodville, Australia*

**Background:** Mutations affecting *RAS* genes are now established predictive markers of non-response to anti-epidermal growth factor receptor (EGFR) antibodies in advanced colorectal cancer (CRC). *PI3KCA* (and *BRAF*) may also be predictive. A previous analysis restricted to *KRAS* exon 2 has not revealed any role for mutation status as a predictive marker for bevacizumab therapy. This analysis assessed the prognostic and predictive impact of extended *RAS and PI3KCA* gene mutation status in patients receiving C +/- B +/- M in the randomised phase III MAX study. **Methods:** DNA was macrodissected from archival formalin fixed paraffin embedded tumor tissue. Mutation status was determined using pyrosequencing and confirmed with Sanger sequencing (for equivocal *RAS*). Mutation status (Wild type/WT v Mutated/MT) was correlated with efficacy outcomes (RR, PFS & OS). Predictive analyses were undertaken using a test for interaction involving both C vs CB + CBM **Results:** Patient demographics and clinical outcomes were comparable between the tissue study population (n=281/60%) and the intention to treat population (n=471). MT in K*RAS* exons 2, 3, 4 and *NRAS* 2, 3, 4 as follows; 32.4%, 4.3%, 3.9%, 1.4%, 0.7% & 0. There were five patients who had more than one *RAS* MT (four with *KRAS* exon 2&4, one *KRAS* exon 2&3*).* The total proportion with any *RAS* MT is 40.9%. *PI3K* MT rate was 7.5% exon 9, and 3.6% exon 20. All *RAS* gene mutation status (WT v MT) had no prognostic impact for PFS, HR 0.92 (0.72-1.17) or OS HR 0.97(0.73-1.27). Using the comparison of C v CB + CBM, *RAS* gene mutation status was not predictive of the effectiveness of B for PFS, HR 0.56 (0.37-0.84) for *RAS* MT and HR 0.69 (0.49-0.97) for *RAS* WT, p for interaction 0.51. RR with *RAS* MT was higher without Bev (C 50% v CB/CBM 37.3%), but RR improved with Bev in the WT group (C 27.3% v CB/CBM 42.3%), p for interaction 0.01. *PI3KCA* mutation was neither predictive for bevacizumab effect nor prognostic. **Conclusions:** An additional 12.6% of MAX study patients who were *KRAS* exon 2 WT had additional RAS mutations. Neither all *RAS* gene mutation status nor *PI3KCA* mutation status was prognostic for progression-free survival or overal survival, or predictive of bevacizumab outcome in patients with advanced CRC. Clinical trial information: NCT00294359.

**3540 General Poster Session (Board #3), Sat, 8:00 AM-11:45 AM**

**Survival outcomes for patients with metastatic colorectal cancer (mCRC) based on primary site, right (R) colon versus left (L) colon versus rectal (Rec) primary: Results from the South Australian Registry of mCRC.** *Presenting Author: Yoko Tomita, The Queen Elizabeth Hospital, Adelaide, Australia*

**Background:** Previous reports have described differences in biology and outcome based on R or L sided primary bowel cancer. Possible differences in response to biological agents have also been reported. **Methods:** We explored the SA mCRC registry to assess differences in patient characteristics, treatment received, and outcomes based on if the primary was R colon (caecum to transverse colon), L colon (splenic flexure to sigmoid), or rectal. KM was used for survival outcomes and Cox proportional hazards regression modeling was used to assess defined prognostic markers. **Results:** 3,121 patients were analysed. 33.5% had R colon, 35.3% L colon and 26.7% rectal primary. Major differences between the groups are shown in the Table. There was no major difference between L and Rec. There were statistically significant differences between both R v L and R v Rec; R occurred more in females and older age, and had more poorly differentiated pathology. Biological agent use, chemotherapy (CT) use, and metastatectomy were all less common in R. KRAS MT rates were greater in R v L (p=0.007). Analysis of systemic therapy revealed similar rates of 1st line therapy, but different 2nd line; R 47% v L 60% v Rec 60% respectively. The mOS for the entire group R v L v Rec was 9.8 v 19.2 v 17.8 months. For the group who had active therapy defined as CT (+/- metastatectomy), mOS was R 15.5 v L 26.2 v Rec 26.3 months. For those (n=168) who underwent liver resection (+/- chemotherapy) 5 year survival was R 55%, L 58% Rec 55%. In patients treated with only CT, mOS was R 10.3 v L 15.1 v Rectal 15 months. **Conclusions:** There were no major differences noted between L colon and Rectal primary. Patients with R primary had more negative prognostic factors and indeed had inferior outcomes when compared to those with L or Rectal primary. Patients who were suitable for hepatic surgery had no difference in outcome.

| | Right | Left | Rectum |
|---|---|---|---|
| Female | 51.2% | 41.4% | 34.9% |
| Median age (years) | 76 | 71.4 | 69.3 |
| Synchronous | 68.1% | 64.6% | 55.2% |
| Poorly diff path | 34.9% | 21.8% | 19.8% |
| Liver/lung only | 35.2%/4.2% | 40.6%/7.4% | 36.3%/12.8% |
| KRAS exon 2 WT | 52.2% | 64.3% | 60.4% |
| Liver surgery +/- CT | 6.8% | 10.4% | 4.7% |
| CT +/- metastatectomy | 51.4% | 60.7% | 64.6% |

**3541 General Poster Session (Board #4), Sat, 8:00 AM-11:45 AM**

**Survival of high-grade neuroendocrine carcinomas (HGNEC) of the colon and rectum: Analysis of the Surveillance, Epidemiology, and End Results (SEER) database.** *Presenting Author: Hammad Shafqat, Memorial Hospital of Rhode Island, Pawtucket, RI*

**Background**: HGNECs are rare, aggressive colorectal tumors, biologically similar to small cell lung cancer. Their optimal management is unclear and based on case series. Our study sought to compare survival outcomes and the role of surgery in HGNECs and high-grade adenocarcinomas (AC) using the population-based SEER registry. **Methods**: We obtained data on patients (pts) with colorectal HGNEC or AC diagnosed between 1998 and 2011. Relative survival (RS) was the primary endpoint. Trends in incidence and survival were calculated as annual percent change (APC). Associations with prognostic factors and treatment were analyzed in multivariate proportional hazard models, accounting for immortal time bias, and reporting hazard ratios (HR) with 95% confidence intervals (CI). **Results**: Compared with AC ($N$=392,854), HGNECs ($N$=1,455) were more often metastatic (18% *vs.* 54%, respectively) and more commonly located in the cecum or rectum, but rarely in the sigmoid ($P$<.0001). The incidence of HGNEC increased during the study period (APC 2.5%, $P$=.015), while the incidence of AC decreased (APC -3%, $P$<.0001). Survival was significantly worse for HGNECs than for high-grade AC at every stage (Table). No improvement over time in survival of HGNEC was seen (APC, 0.1%, $P$=.88), unlike in AC (APC, 0.9%, $P$<.0001). Stage I-III HGNECs were less likely to undergo resection (84% vs. 91% for AC, $P$<.0001), although the survival benefit (HR 0.50, 95% CI 0.34-0.74) was the same as for AC ($P$ for interaction=.88). Compared with high-grade AC, resected HGNECs were more often node-positive (68% vs. 53%) or >5 cm in size (59% vs. 50%). The number of metastatic nodes was prognostic in HGNEC (HR for N2 vs. N1, 1.94, 95%CI 1.41-2.66). **Conclusions**: The prognosis of HGNEC has not improved over the past decade, despite advances in therapy of AC. HGNECs benefit from surgery similarly to ACs. Pts with stage I-II HGNECs have similar 5-year RS of 51%, warranting studies of adjuvant systemic therapy.

| | High-grade AC | | HGNEC | |
|---|---|---|---|---|
| | 5-year RS, % | 95% CI | 5-year RS, % | 95% CI |
| All pts | 50.3 | 49.8-50.9 | 17.4 | 14.7-20.3 |
| Stage | | | | |
| I | 87.8 | 86.0-89.4 | 50.5 | 32.0-66.4 |
| II | 77.8 | 76.5-78.9 | 51.4 | 34.8-66.0 |
| III | 53.3 | 52.5-54.2 | 28.6 | 22.4-35.1 |
| IV | 7.2 | 6.7-7.7 | 3.7 | 2.4-5.5 |

**3542 General Poster Session (Board #5), Sat, 8:00 AM-11:45 AM**

**The effect of chemotherapy delivered until progression versus complete stop on the overall survival of patients with metastatic colorectal cancer: A meta-analysis of randomized trials.** *Presenting Author: Allan Andresson Lima Pereira, Instituto do Câncer do Estado de São Paulo - ICESP/FMUSP, São Paulo, Brazil*

**Background:** The impact of the duration of chemotherapy on the overall survival (OS) of patients with metastatic colorectal cancer (mCRC) is controversial. We performed a systematic review and meta-analysis of randomized controlled trials (RCT) that compared chemotherapy continuously administered until progression versus complete treatment interruption after first line therapy for patients with mCRC **Methods:** We searched medical literature databases and oncology conferences proceedings for RCTs that compared the OS of mCRC patients who received first line chemotherapy until progression with those who were offered complete treatment stop after a fixed number of cycles. RCT that evaluated the role of any kind of maintenance therapy were excluded. A meta-analysis of reported Hazard Ratios for OS, with respective 95% confidence intervals, was performed using the fixed-effect models. **Results:** Our search retrieved 106 trials, of which sox were eligible (N=2373). The meta-analysis (N=2,334) showed a statistically significant OS benefit in favor of chemotherapy delivered until progression (*HR= 0.89, 95%CI= 0.82 to 0.98; p= 0.01; $I^2$ 0%*). The range of chemotherapy-free interval in the complete-stop group across trials was 3.7 – 4.3 months. Only three trials reported quality of life (QoL) data. Chemotherapy administered until progression was associated with more adverse effects and impaired QoL. **Conclusions:** Chemotherapy administered continuously until progression for mCRC patients is associated with a modest but significant improvement in OS. However mCRC is a heterogeneous disease and identification of molecular biomarkers could help clinicians to predict which patients would benefit from continuous or intermittent cancer-directed therapies.

**3543 General Poster Session (Board #6), Sat, 8:00 AM-11:45 AM**

**An internally and externally validated nomogram to predict severe neutropenia in Japanese patients (pts) with advanced colorectal cancer (aCRC) treated with irinotecan (IRI)-based regimens.** *Presenting Author: Wataru Ichikawa, Showa University, Tokyo, Japan*

**Background:** Irinotecan (IRI)-based regimens are one of the standard treatments for advanced colorectal cancer (aCRC). In Asians, *UGT1A1*6* and *UGT1A1*28* are associated with IRI-related severe neutropenia. We conducted a prospective observational study to examine the correlation between *UGT1A1*genotypes and the clinical outcome of IRI-based regimens in Japanese patients (pts) with aCRC (NCT 01039506). We presented the data of the interim safety analysis at the 2013 ASCO annual meeting (Abstract No. 3535) and the European Control Conference (ECC) 2013 (Abstract No. 2364). We developed a final nomogram that predicts severe neutropenia, based on the data from 1,312 pts enrolled into the study, and externally validated it using independent data from 350 pts. **Methods:** From October 2009 to March 2012, pts with histologically confirmed aCRC treated with IRI-based regimens were enrolled into the study. *UGT1A1* genotypes were categorized into three groups: wild (**1/*1*), hetero (**1/*6*, **1/*28*), and homo (**6/*6*, **6/*28*, **28/*28*). Detailed toxicities in the first three months of treatment were prospectively recorded. A nomogram for predicting severe neutropenia was developed using multiple logistic regression that included *UGT1A1*genotypes and non-genetic factors. The nomogram was internally validated using bootstrap resampling, and externally validated using independent cohorts from six sites. **Results:** The final nomogram was developed using the safety data from 1,312 of the 1,376 enrolled pts. The frequencies of *UGT1A1* polymorphisms were 48%, 41%, and 11% for the wild, hetero, and homo groups, respectively. Severe neutropenia was observed in 31% of all pts: 25%, 34%, and 49% for the three groups, respectively. The nomogram integrates important factors such as regimen, initial doses of IRI, age, sex, performance status, *UGT1A1* genotype, pre-treatment neutrophil count, and total bilirubin. The concordance index (c-index) was 0.693, which was higher than that of 0.593 for a model that used just the *UGT1A1*genotype. The nomogram was externally validated with a c-index of 0.702, using independent data from 350 pts. **Conclusions:** This nomogram can be used to accurately predict IRI-related severe neutropenia in Japanese pts with aCRC.

**3544 General Poster Session (Board #7), Sat, 8:00 AM-11:45 AM**

**A phase II trial of combined chemotherapy with oral S-1 and 24-hour infusions of irinotecan plus bevacizumab in patients with metastatic colorectal cancer.** *Presenting Author: Sotaro Sadahiro, Department of Gastroentelogical Surgery, Tokai University School of Medicine, Isehara, Japan*

**Background:** Irinotecan causes S-phase-specific cell killing. Its active metabolite, SN-38, is catalyzed by carboxylesterases. Prolonged exposure to low concentrations of irinotecan is associated with less carboxylesterase saturation, thereby enhancing therapeutic effectiveness (Houghton PJ, 1995, Rothenberg ML, 1998). We previously reported that combined chemotherapy with oral UFT/leucovorin or S-1 plus 24-hour infusions of irinotecan is very effective. We examined the effectiveness and safety of combined chemotherapy with S-1 and 24-hour infusions of irinotecan plus bevacizumab in patients with metastatic colorectal cancer (mCRC). **Methods:** Patients who had mCRC, an age of ≥ 20 years, and an ECOG PS of 0-1 were eligible. S-1 (40 mg/m$^2$) was given orally twice daily on days 1 to 14. Irinotecan was given as continuous 24-hour intravenous infusion on days 1 and 15. On the basis of the results of a previous phase I study, patients who were homozygous for the UGT1A1*28 allele received 100 mg/m$^2$ of irinotecan, and those with other genotypes received 125 mg/m$^2$of irinotecan. Bevacizumab (5 mg/kg) was given intravenously on days 1 and 15, followed by a two-week rest. This four-week regimen was regarded as one cycle and was repeated. The primary endpoint was overall response (OR). The secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. **Results:** 79 patients were enrolled; median age, 68 years (range, 38-85); 42% female; ECOG PS 0/1, 58%/42%; and first line/second line therapy, 58%/42% (adjuvant chemotherapy, 16%). Three patients (4%) were homozygous for the UGT1A1*28 allele. Median follow-up time was 18.1 months. The median number of treatment cycles was seven. The OR rate was 77.2% (95% confidence interval, 66.4-85.9; first line, 80.4%; second line, 72.7%). Median PFS was 15.7 months (first line, 16.4 months; second line, 16.5 months). Median OS were not reached. Grade 3 or higher adverse events that occurred at an incidence of ≥ 10% were neutropenia (43.0%), leukopenia (20.3%), anorexia (19.0%), and diarrhea (10.1%). **Conclusions:** This regimen appears to be highly active and well tolerated, both as first-line and second-line chemotherapy for mCRC. Clinical trial information: 10R-121.

**3545 General Poster Session (Board #8), Sat, 8:00 AM-11:45 AM**

**Asia-Pacific colorectal screening score and colorectal cancer screening in asymptomatic Asian population.** *Presenting Author: Joseph JY Sung, Institute of Digestive Disease, The Chinese University of Hong Kong, Hong Kong, Hong Kong*

**Background:** There has been a rapid rise in colorectal cancer (CRC) incidence in recent decades in many Asian countries. Age, gender, smoking, and family history are the significant risk factors of CRC. This study would like to develop an Asia-Pacific Colorectal Screening (APCS) score to identify subjects with high-risk for colorectal advanced neoplasia (AN) in Asia. **Methods:** A multicentre study was in 11 Asian cities. A total of 7,463 asymptomatic subjects underwent screening colonoscopy. The first 2,000 subjects were used as a derivation cohort. AN was defined as advanced adenoma and CRC. A multiple logistic regression was applied to the derivation cohort identifying significant risk factors for AN; odds ratios of significant risk factors were then utilized to develop APCS score ranging from 0-6, including age (0=40-49, 1=50-59, 2=60+), gender (0=female, 1=male), family history (0=absent, 1=present), smoking (0=no, 1=current or past), and Body Mass Index (BMI) (0= <23kg/m$^2$, 1= >23kg/m$^2$). Three tiers of risk were defined: 0 'average risk' (AR); 1-3 'moderate risk' (MR); and 4–6 'high risk' (HR). The APCS score was applied to the validation cohort as performance assessment. **Results:** The baseline prevalence of AN were 4.9% and 5.4% in the derivation and validation cohorts. In the validation cohort, 110 subjects (2.0%) were in AR, 4,148 subjects (75.9%) in MR, and 1,205 (22.1%) subjects in HR. Prevalence of AN in AR, MR and HR were 0.9%, 4.1% and 10.5% respectively. Compared with AR, subjects in MR and HR had 4.5-fold and 11.5-fold increased prevalence of AN. **Conclusions:** The APCS score based on age, gender, family history, smoking and BMI is a useful tool in stratifying asymptomatic Asians for priority of CRC screening.

**3546 General Poster Session (Board #9), Sat, 8:00 AM-11:45 AM**

**MLN0264, an investigational antiguanylyl cyclase C (GCC) antibody-drug conjugate (ADC), in patients (pts) with advanced gastrointestinal (GI) malignancies: Phase I study.** *Presenting Author: Cristina Cruz Zambrano, Vall d'Hebron University Hospital, Barcelona, Spain*

**Background:** This first-in-human study (NCT01577758) assessed the safety and tolerability, dose limiting toxicities (DLTs), maximum tolerated dose (MTD), pharmacokinetics, and preliminary antitumor activity of MLN0264 in adult patients (pts) with advanced gastrointestianl (GI) malignancies expressing the surface antigen guanylyl cyclase C (GCC). Preclinical studies have shown antitumor activity in GI tumor animal models, including GCC-expressing human colorectal cancer (CRC) xenografts. **Methods:** Pts received MLN0264 by IV infusion on day 1 of 21-day cycles. Dose escalation proceeded via a Bayesian continual reassessment method in pts with GI malignancies. At the MTD, pts with metastatic CRC were enrolled to an expansion cohort (including ≥ 6 with high GCC expression). **Results:** As of November 27, 2013, 36 pts have received MLN0264, 19 at 0.3–2.4 mg/kg in the dose-escalation cohorts and 20 (including 3 from dose escalation) in the MTD expansion cohort. Median age was 60 years (30–78); 69% were male; 30 had CRC, two had pancreatic, two had esophageal, one had gastric cancer, and one had small intestine carcinoma. Median time from diagnosis was 37.6 mos. DLTs were seen in four pts: grade 4 neutropenia in two of four pts at 2.1 and the one pt at 2.4 mg/kg (all >MTD), and grade 4 febrile neutropenia in 1 of 6 pts at the MTD of 1.8 mg/kg. Pts received a median of 2 (1–8) cycles. Adverse events (AE) (NCI-CTCAE v4.03) were reported in 86% of pts. Common AEs (all grades) included fatigue (42%), nausea (42%), diarrhea (36%), and decreased appetite (31%); 56% of pts had grade ≥3 AEs, including neutropenia (19%), hypokalemia (11%), diarrhea (8%), and anemia (8%). Four pts discontinued due to AEs. MLN0264 concentration was detectable in all pts in a dose-dependent manner. Antibody drug conjugates (ADC) was detectable in serum at the pre-infusion time of the next cycle (day 21) for pts dosed at ≥1.2 mg/kg. The drug in the ADC, monomethyl auristatin E, was detectable in a dose-dependent manner, with peak concentration occurring approximately 2–3 days after each infusion. One pt (gastric carcinoma, 1.8 mg/kg) had a PR (RECIST 1.1); 13 pts had SD, including three treated for ≥ four cycles. **Conclusions:** The MTD of MLN0264 was determined as 1.8 mg/kg every three weeks. MLN0264 appeared generally well tolerated; preliminary antitumor activity was seen. Further investigation is warranted. Clinical trial information: NCT01577758.

**3547 General Poster Session (Board #10), Sat, 8:00 AM-11:45 AM**

**The 12-gene colon cancer assay validation and utility: Summary of clinical evidence.** *Presenting Author: Emily Burke, Genomic Health, Inc., Redwood City, CA*

**Background:** The 12-gene colon cancer assay is the first commercially available molecular assay to predict the risk of recurrence in stage II/III colon and rectal cancer. Rigorous evidence for clinical validity and utility of an assay is imperative since the result is used for treatment decision-making. This summary outlines the studies that meet an established definition of clinical validation and additional studies that support the utility of the assay. **Methods:** Prospectively designed studies using archival tissue with pre-specified methods, clinical outcomes, and analysis plan were considered clinical validation studies (Simon et al. JNCI 2009). Additional studies that demonstrated the utility of the assay in a clinical setting were considered supportive. **Results:** The assay has been clinically validated in four independent studies with 3,315 patients (2,390 stage II/628 stage III colon and 130 stage II/167 stage III rectal). All four studies demonstrated a significant association ($p<0.05$) between the result and outcome (e.g. recurrence risk and cancer specific survival). The score was examined in the context of other variables, including T and N stage, mismatch repair status, number of nodes examined, lymphovascular invasion, and tumor grade; across all studies, the result consistently contributed to risk stratification beyond these variables. Three clinical utility studies with 502 patients showed that 29-45% of initial treatment recommendations in stage IIA colon cancer were changed, with a net reduction in use of adjuvant chemotherapy. **Conclusions:** Clinical validation of the 12-gene assay followed a now-standard approach of using archived tissue from multiple large, prospectively-designed studies with documented long-term outcomes; the 12-gene colon assay meets level IB evidence criteria. Subsequent studies showed the assay has impact on clinical practice. The underlying tumor biology assessed by the score is relevant in both colon (stage II and III) and rectal cancer, providing information beyond conventional features, and can help guide treatment decisions regarding adjuvant chemotherapy.

**3548 General Poster Session (Board #11), Sat, 8:00 AM-11:45 AM**

**A phase 1b study of VEGFR inhibitor fruquintinib in patients with pretreated advanced colorectal cancer.** *Presenting Author: Jin Li, Fudan University Cancer Hospital, Shanghai, China*

**Background:** Fruquintinib is a novel oral small molecule compound selectively inhibits vascular endothelial growth factor receptors (VEGFR) 1, 2, and 3 with potent inhibitory effects on multiple human tumor xenografts. In the first-in-human phase I study, fruquintinib demonstrated good tolerability and impressive antitumor activity (ORR=38.2% and DCR=82.4%) in patients (pts) with various heavily pre-treated solid tumors including colorectal cancer (CRC) (ASCO 2012 Abs#3038). **Methods:** This phase Ib study was designed to evaluate the safety, pharmacokinetics , and efficacy of two fruquintinib regimens: 4mg once daily continuously (QD) or 5mg once daily for three weeks followed with one week break (3/1 wk), as treatment for pts with advanced CRC who had failed at least two prior systemic therapies. The study consists of two stages: a two-arm 1:1 randomization stage including both QD and 3/1 wk regimens, and an expansion stage with the selected regimen. Tumor response was assessed per RECIST1.1. **Results:** Forty pts were enrolled in the randomization phase, with 20 pts in each QD or 3/1 wk group. Patient characteristics at baseline were similar between the two groups. The median treatment duration was 90 (7-280) days for QD regimen and 119 (14-364) days for 3/1 wk regimen. The most common treatment-related toxicities were hand-foot syndrome (HFS), hoarseness, proteinuria, hypertension and fatigue. The 3/1 wk group had less Grade 3/4 AEs than the QD group, particularly HFS (5% vs. 30%). Thirty-five pts were evaluable for response, 17 in QD and 18 in 3/1 wk. In QD group: DCR=76.2% (2 partial responses or PRs and 2 minor responses or MRs who achieved a 20-30% tumor reduction), 16-wk progression free survival (PFS)=40.0%, and 9-month survival=41.2%. In 3/1 wk group: DCR=83.3% (1 PR and 3 MRs), 16-wk PFS=65.0%, and 9-month survival=53.8%. 5mg 3/1 wk regimen was selected as the recommended regimen and additional 22 CRC pts were enrolled in the expansion stage. **Conclusions:** Fruquintinib administered at 5mg once daily in cycles of three weeks on and one week off was well tolerated and demonstrated encouraging preliminary clinical efficacy in pts with advanced CRC. Further clinical studies are warranted. Clinical trial information: NCT01975077.

**3549 General Poster Session (Board #12), Sat, 8:00 AM-11:45 AM**

**Prognostic value of *KRAS* exon 2 gene mutations in stage III colon cancer: Post hoc analyses of the PETACC8 trial.** *Presenting Author: Julien Taïeb, APHP and Paris Descartes University, Paris, France*

**Background:** Prognostic value of *KRAS* mutations in resected colon adenocarcinoma remains debated. We examined the prognostic impact of *KRAS* exon 2 mutations in stage III patients receiving adjuvant FOLFOX + /-cetuximab patients from the PETACC8 Phase III trial. **Methods:** *KRAS* exon 2 mutations in codon 12 (p.G12V, p.G12R, p.G12S, p.G12A, p.G12C, p.G12D) and codon 13 (p.G13D) were examined in all patients with available material and signed translational research informed consent enrolled in the PETACC8 trial. Analyses were restricted to *BRAF* wild type tumors, since the prognostic impact of BRAFV600E in this population has already been described. Because no benefit or deleterious effect from adjuvant cetuximab was reported in this trial, tumors from both study arms were pooled for analysis. Association between time to recurrence (TTR) and disease-free survival (DFS) and type of *KRAS* mutation was evaluated using Cox proportional hazard model. **Results:** *KRAS* mutations were found in 638/1657 tumors, including 502 codon 12 and 136 codon 13 alterations. *KRAS* mutations in codon 12 (HR: 1.67; 95% confidence interval [CI] [1.35-2.04]; P<0.001) but not in codon 13 (HR: 1.23; 95% confidence interval [CI] [0.85-1.79]; P=0.26) were significantly associated with shorter TTR as compared to patients with *KRAS*/*BRAF* wild-type tumors, independently of other covariates. Similar results were found for DFS. When anatomic sites were taken into account, the impact of *KRAS* mutations on TTR was only found for distal tumors (n=1043) with an increased risk of relapse (HR: 1.96; 95% confidence interval [CI] [1.51-2.56]; P<0.0001) for *KRAS*codon 12 mutated tumors and a trend for codon 13 (HR: 1.59; 95% confidence interval [CI] [1.00-2.56]; P=0.051), as compared to *KRAS/BRAF*wild type patients. Similar results were found for DFS. **Conclusions:** *KRAS* exon 2 mutations are independent predictors of TTR or DFS for patients with stage III distal colon cancer receiving adjuvant therapy. Future clinical trials in the adjuvant setting should consider tumor location and type of *KRAS* mutation as important stratification factors.

**3550^ General Poster Session (Board #13), Sat, 8:00 AM-11:45 AM**

**Survival outcomes in patients (pts) with *KRAS/NRAS* (*RAS*) wild-type (WT) metastatic colorectal cancer (mCRC) and non-liver-limited disease (non-LLD): Data from the PRIME study.** *Presenting Author: Jean-Yves Douillard, Centre René Gauducheau, Nantes, France*

**Background:** ESMO guidelines recommend upfront treatment with an active combination regimen for mCRC pts with multiple metastases and those with more limited disease (Schmoll et al, 2012). Panitumumab (pmab) + FOLFOX4 is an active regimen that improved overall survival (OS) vs FOLFOX4 alone in the 1st-line treatment of *RAS* WT mCRC (PRIME study). In this exploratory analysis of PRIME, we report the efficacy of pmab + FOLFOX4 vs FOLFOX4 in pts with non-LLD. **Methods:** PRIME was a randomized (1:1) phase 3 study comparing the efficacy and safety of pmab 6.0 mg/kg Q2W + FOLFOX4 vs FOLFOX4 in pts with no prior chemotherapy for mCRC. In this exploratory analysis conducted when ≥80% of pts had an OS event, median progression-free (PFS) and OS were estimated for pts with *RAS* WT (*KRAS/NRAS* exons 2-4 assessed, including codon 59) non-LLD. 3-year OS rates were also evaluated. Data were summarised descriptively and tested for significance using Cox's proportional hazards models. **Results:** Of the 505 pts with *RAS* WT mCRC, 416 had non-LLD. Treatment arms were well balanced with respect to baseline sex, age and metastatic sites. Overall, 82% of pts had liver involvement, 51% had ≥3 metastatic sites (median 3 [range 1-6]) and median LDH was 373 (range 4-5780) U/L. Median PFS and OS were longer in *RAS* WT non-LLD pts receiving pmab + FOLFOX4 vs FOLFOX4 (Table). 3-year OS rates were 31% vs 23% for non-LLD pts receiving pmab + FOLFOX4 vs FOLFOX4, respectively. Numeric benefits were also observed in LLD patients receiving pmab + FOLFOX4. **Conclusions:** This post-hoc analysis suggests that the PFS and OS benefits observed with 1st-line pmab + FOLFOX4 vs FOLFOX4 in the overall PRIME population are also seen in the subgroup of pts who have non-LLD. Clinical trial information: NCT00364013.

| | Non-LLD (n=416) | | LLD (n=89) | |
|---|---|---|---|---|
| | Pmab + FOLFOX4 (n=205) | FOLFOX4 (n=211) | Pmab + FOLFOX4 (n=48) | FOLFOX4 (n=41) |
| PFS events, n | 181 | 192 | 38 | 37 |
| Median PFS, months | 11.1 | 8.0 | 11.3 | 9.9 |
| HR (95% CI); p value[a] | 0.73 (0.60-0.90); 0.0027 | | 0.75 (0.48-1.19); 0.2223 | |
| OS events, n | 166 | 186 | 32 | 31 |
| Median OS, months | 23.8 | 18.4 | 40.7 | 33.4 |
| HR (95% CI); p value[a] | 0.78 (0.63-0.96); 0.0185 | | 0.71 (0.43-1.16); 0.1737 | |

Abbreviations: CI, confidence intervals; HR, hazard ratio. [a] Descriptive p value.

**3551 General Poster Session (Board #14), Sat, 8:00 AM-11:45 AM**

**Phase 1 study of biweekly (Q2W) anti-EGFR monoclonal antibody (mAb) mixture Sym004 in patients (pts) with metastatic colorectal cancer (mCRC) resistant to previous anti-EGFR treatment.** *Presenting Author: Guillem Argilés, Department of Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain*

**Background:** Preclinical models suggest that WT KRAS mCRC may retain EGFR dependency despite resistance developed to anti-EGFR mAb treatment (eg, cetuximab or panitumumab). Sym004 is the first-in-class drug mixture of two mAbs targeting non-overlapping epitopes of EGFR causing augmented receptor degradation. Cohorts of weekly 9 and 12 mg/kg from the multicenter phase 1 trial exploring multiple doses and schedules of Sym004 have recently reported antitumor activity and a tolerable safety profile. **Methods:** We here report safety (primary endpoint) and efficacy (exploratory endpoint) from the two Sym004 Q2W cohorts of this trial. Eligible pts had WT KRAS mCRC with prior clinical benefit to anti-EGFR mAbs and subsequent progression during or within 6 months after treatment cessation. Sym004 was administered until disease progression or unacceptable toxicity. **Results:** A total of 29 pts (median age was 64 years; 62% had liver metastasis [non-]target lesions; 86% had >2 prior lines of therapy) were treated at 12 (N=12) and 18 mg/kg (N=17) Sym004 Q2W. Drug-related AEs were manageable with dose reduction and supportive medication. Grade ≥3 toxicities in 12 and 18 mg/kg cohorts were skin rash (3/12 [25%]; 6/17 [35%]; no grade 4) and hypomagnesemia (3/12 [25%]; 6/17 [35%]). Grade 3 diarrhea was seen in one pt of each cohort (8%; 6%). Infusion-related reactions were observed in 2/29 (7%) pts (grade 1 and 2, each). Efficacy assessments are shown in the Table. **Conclusions:** Single-drug Sym004 was well tolerated and antitumor responses seen at 18 mg/kg Q2W in the first assessment at week 4-8 suggest clinical activity of Sym004 in anti-EGFR mAb resistant WT KRAS mCRC pts. The early benefit:risk profile remained favorable; no new toxicities were found. Clinical trial information: NCT01117428.

| Variable | 12mg/kg/Q2W (N=12) | 18mg/kg/Q2W (N=17) |
|---|---|---|
| Proportion of pts who progressed during vs. 1-6 months after previous anti-EGFR, N (%) | 6 (50) vs. 6 (50) | 11 (65) vs. 6 (35) |
| Mean baseline sum of longest diameter of target lesions, cm | 11.6 | 12.1 |
| Antitumor response at first CT/MRI imaging (week 4-8), N (%) | | |
| PR | 0 | 1 (7) |
| SD | 3 (33) | 11 (73) |
| PD | 6 (67) | 3 (20) |
| Any tumor shrinkage | 2 (22) | 6 (40) |
| Progression-free survival, months | 1.4 | 3.3 |

**3552 General Poster Session (Board #15), Sat, 8:00 AM-11:45 AM**

**Impact of chemotherapy partner on efficacy of targeted therapy in metastatic colorectal cancer (mCRC): A meta-analysis.** *Presenting Author: David Chan, Royal North Shore Hospital, St Leonards, Australia*

**Background:** In metastatic colorectal cancer (mCRC), the question of whether efficacy of targeted therapy is affected by chemo partner remains unresolved. Studies of chemotherapy (chemo) added to epidermal growth factor receptor (EGFR) inhibitors (EGFRI: cetuximab, panitumumab) and anti-vascular endothelial growth factoragents (VEGF) (bevacizumab, aflibercept) have reported mixed outcomes. We undertook systematic review to explore efficacy of these combinations according to chemotherapy partner. **Methods:** Randomized controlled trials were sought evaluating the combination of chemo with targeted therapy, categorized according to therapy class (EGFR or VEGF) and chemo partner (oxaliplatin (ox) or irinotecan (iri)). The impact of fluoropyrimidine (FP) regimen (bolus, infusional, or oral) was also explored. Only *KRAS* exon 2 wild type (WT) subpopulations were included in EGFR analysis. The primary endpoint was overall survival (OS) with secondary endpoints of progression-free survival (PFS), overall response rate (ORR) and toxicity. Meta-analysis was performed according to CONSORT guidelines and standard methods with hazard ratios (HR) and odds ratios (OR) computed. **Results:** We identified 21 trials evaluating 9,629 patients. For EGFRI, OS (eight trials, 3,499 pts) was improved in combination with iri, HR 0.87 (95% CI 0.78-0.97) but not ox with HR 1.01 (95% CI 0.91-1.13). PFS (n=3473) was also improved with iri with HR 0.74 (95% CI 0.65-0.83) but not ox (HR 0.92, 95% CI 0.83-1.02). Overall response rate (n=3436) OR for iri was 3.09 (95% CI 2.47-3.86) and OR for ox was 1.36 (95% CI 1.12-1.64). The iri-ox interaction p-value was 0.07 for OS, 0.006 for PFS and <0.00001 for ORR. Overall grade 3/4 (all toxicity) OR for iri was 2.53 (95% CI 2.06-3.11) and ox OR 1.89 (95% CI 1.40-2.54). Two trials (n=151) directly compared iri-EGFRI with ox-EGFRI. No significant differences in efficacy were observed. For anti-VEGF therapy (11 studies, 5,290 pts), there was no significant difference in OS, PFS, ORR or toxicity according to chemo regimen used. The choice of FP did not affect efficacy. **Conclusions:** The meta-analysis shows superior efficacy when EGFRI are combined with irinotecan-based chemo regimens compared to oxaliplatin-based regimens. Chemo interaction was not observed with anti-VEGF therapy.

**3553 General Poster Session (Board #16), Sat, 8:00 AM-11:45 AM**

**Pulmonary metastasectomy in colorectal cancer patients with previously resected liver metastasis: Pooled analysis.** *Presenting Author: Samer Salah, Department of Medical Oncology, King Hussein Cancer Center, Amman, Jordan*

**Background:** Data addressing the outcomes and patterns of recurrence following pulmonary metastasectomty (PM) in patients with colorectal cancer (CRC) and previously resected liver metastasis are very limited. **Methods:** We searched the PubMed for studies assessing PM in CRC and gathered individual data for patients who had PM and a previous curative liver resection. The influence of potential factors on overall survival (OS) was analyzed through univariate and multivariate analysis. Furthermore, the influence of patterns of recurrence following PM on post-recurrence survival was investigated. **Results:** Between 1983 and 2009, 146 patients from five studies underwent PM and had previous liver resection. The median interval from resection of liver metastasis until detection of lung metastasis and the median follow up from PM were 23 and 48 months respectively. Sixty seven (46%) underwent intra-operative thoracic lymph node (LN) sampling; nine of them (13%) had pathologically confirmed LN involvement, and 48 (33%) received perioperative chemotherapy. Five-year OS and recurrence free survival following PM were 54% and 29% respectively. Factors predicting inferior OS in univariate analysis included thoracic LN involvement and size of largest lung nodule ≥ two cm. In multivariate analysis, thoracic LN involvement was the only independent factor (HR 4.86, 95% CI: 1.56-15.14, $P = 0.006$). Ninety-three patients had recurrence following PM. Data on dates and pattern of recurrence was available for 74 patients, the five-year post- recurrence survival for patients with lung only recurrence treated with repeated PM (n=21), lung only recurrence treated with chemotherapy (n=20), liver only recurrence (n=10), and all other patterns of recurrence (n=23) were 60%, 0%, 18%, and 5% respectively, $p < 0.0001$. **Conclusions:** PM offers a chance for long term survival in selected patients with CRC and previously resected liver metastasis. Thoracic LN involvement predicted poor prognosis; therefore, significant efforts should be undertaken for adequate staging of the mediastinum prior to PM. Also, adequate intra-operative LN sampling allows proper prognostic stratification and enrollment in novel adjuvant therapy trials.

**3554 General Poster Session (Board #17), Sat, 8:00 AM-11:45 AM**

**Neoadjuvant mFOLFOX6 for stage II/III rectal cancer patients with a T3/T4 tumor.** *Presenting Author: Junichi Koike, Gastroenterological Surgery, Omori Medical Center, Toho University School of Medicine, Tokyo, Japan*

**Background:** The efficacy and safety of neoadjuvant modified FOLFOX6 (mFOLFOX6) therapy in stage II/III rectal cancer patients with a T3/T4 tumor is yet to be determined. **Methods:** Stage II/III (Ra/Rb) rectal cancer patients aged 20–80 years of age with a T3/T4 tumor were enrolled in this phase II multicenter study. Accrual of patient data began in August 2011 with a planned patient population set at 50. All patients had an Eastern Cooperative Oncology Group performance status of 0–1. The primary endpoint was preoperative response rate, and the secondary endpoints were histological effect, R0 resection rate, pCR rate, down-staging rate, neoadjuvant therapy completion rate, occurrence of adverse events, the incidence of postoperative complications, and three-year disease-free survival. Computed tomography was performed after four courses of neoadjuvant mFOLFOX6 therapy. Patients with progression disease (PD) underwent resection of the primary lesion, while those without PD received another two courses of treatment. Treatment was discontinued when resection was not possible in patients with PD. **Results:** Registered patients in July 2013 totaled 53 (male n=41, female n=12) with a mean age of 60 (38–77). The number of patients with T3 and T4 tumors was 42 and 10, and patients at stages II and III were 10 and 42, respectively. One patient withdrew due to consent retraction. Median relative dose intensity of mFOLFOX6 therapy was 93.2% for L-OHP, 5-FU, and l-LV. Treatment completion was achieved in 96.2% and 84.6% for four and six courses, respectively, and withdrawal was due to patient's discretion, not adverse events. Surgery was performed in 78.8% of patients. Serious (grade ≥3) adverse events included neutropenia (n=5), leukopenia (n=1), thrombocytopenia (n=1), febrile neutropenia (n=1), nausea (n=1), vomiting (n=1), and peripheral neuropathy (n=2). The rates of R0 resection, pCR, and sphincter preservation, were 91.0%, 10.3%, and 82.9%, respectively. Postoperative complications included suture failure (n=3), wound infection (n=2), pneumonia (n=1), and intestinal obstruction (n=1). **Conclusions:** Neoadjuvant therapy using mFOLFOX6 is a safe and efficacious treatment option for rectal cancer, especially locally advanced disease. Clinical trial information: UMIN000006583.

**3555 General Poster Session (Board #18), Sat, 8:00 AM-11:45 AM**

**CA 11-19 as a tumor marker for the diagnosis of colorectal cancer.** *Presenting Author: Bergein F Overholt, Gastrointestinal Associates, Knoxville, TN*

**Background:** Colorectal cancer remains the second most frequent cause of cancer deaths in both sexes in the United States. Both fecal and blood tests using tumor related antigens are increasingly being used to monitor treatments and in some cases aid in diagnosing colorectal cancers. However, higher sensitivity and specificity are needed before an acceptable tumor antigen blood test for colon cancer is clinically useful. **Methods:** Using double monoclonal ELISA analysis, a new colon cancer antigen, CA 11-19, (100 kDa glycoprotein) was measured in 670 colonoscopy confirmed patients including normal, benign GI diseases, polyps and colon cancer in a blinded IRB approved study. **Results:** Using a cutoff of below 6.4 units/ml as normal, CA 11-19 was positive (>6.4) in 132 of 139 of colorectal cancer cases. 100% of 63 cases of Stage I and II were positive. Sensitivity of CA 11-19 for diagnosis of colorectal cancer was 95%. Negative results were found in 94% of normals (175/187) and 80% of benign GI diseases (161/202). The specificity for the assay was 80.2% for all benign groups combined (426 negative assays for 531 benign patients). **Conclusions:** Ca 11-19 is a serologic tumor marker for colorectal cancer with a demonstrated sensitivity of 95% and a specificity of 80%. Diagnostically, a positive assay result increases the odds of finding colorectal cancer by a factor of five. The test appears to be highly sensitive for detection of early stage colorectal cancer. Additional prospective studies are needed to validate the use of CA 11-19 as an aid in the diagnosis of colorectal cancer.

**3556 General Poster Session (Board #19), Sat, 8:00 AM-11:45 AM**

**Patterns of progression, treatment of progressive disease, and postprogression survival in the new EPOC study.** *Presenting Author: Sian Alexandra Pugh, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom*

**Background:** The New EPOC study randomised patients with operable or borderline operable colorectal liver metastasis to perioperative chemotherapy with or without cetuximab. Recruitment to the trial was halted in November 2012 because the progression free survival was significantly worse in the arm receiving cetuximab (20·5 vs. 14·1 months, HR 1·48 95%CI 1·04-2·12 p=0·03). Given this unexpected trial result acquisition of progression data was undertaken. **Methods:** There were 257 *KRAS* wild-type patients who were randomised to chemotherapy alone (arm A) or chemotherapy with cetuximab (arm B). Data regarding sites and treatment of progressive disease were obtained using case report forms for the 110 (arm A n=48, arm B n=62) *KRAS* wild-type patients with progressive disease at the cut-off date for analysis of November 2012. Post-progression survival (PPS) was calculated using the Kaplan-Meier method. **Results:** The liver was the most frequent site of progression (arm A 46% (22/48); arm B 53% (33/62)) with liver only disease accounting for the majority of those progression events (arm A 91% 20/22; arm B 79% 26/33). Overall there was no difference between the arms in respect of the distribution of progressive disease pre- or postoperatively. Further treatment for progressive disease is known for 64 patients (arm A 26/48; arm B 38/62) of whom 56 received further chemotherapy, most frequently irinotecan based. Fourteen patients received cetuximab as a further line agent (arm A n=9, arm B n=5). There was a trend towards an inferior PPS in arm B (median PPS 18·7 months arm A; 15·9 months arm B, HR 1·69 p=0·131). Of the 25 patients in whom post-progression surgery with curative intent was undertaken, 24 were still alive at a median follow-up of 11·6 months. **Conclusions:** Both the distribution of progressive disease and further treatment are as expected for such a cohort and are evenly balanced between the arms. Despite this there is a trend towards an inferior survival post progression in those receiving cetuximab for whom revisional surgery is not appropriate. Clinical trial information: 22944367.

**3557^ General Poster Session (Board #20), Sat, 8:00 AM-11:45 AM**

**Survival outcomes in the PRIME study for patients (pts) with *RAS/BRAF* wild-type (WT) metastatic colorectal cancer (mCRC), by baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS).** *Presenting Author: Marc Peeters, Antwerp University Hospital and University of Antwerp, Edegem, Belgium*

**Background:** In PRIME, panitumumab (pmab) + FOLFOX4 improved overall survival (OS) for *RAS* WT mCRC pts vs FOLFOX4 alone (Douillard et al 2013). Prespecified subgroup analysis identified only ECOG PS ≥2 as a negative predictive factor for pmab efficacy; *BRAF* mutant (MT) status was a strong negative prognostic factor. Here, we further evaluate the benefit:risk profile of pmab in pts with ECOG PS 0/1 *RAS/BRAF*WT mCRC. **Methods:** PRIME was a randomized (1:1) phase 3 1st-line mCRC study comparing pmab 6.0 mg/kg Q2W + FOLFOX4 vs FOLFOX4. This exploratory analysis, conducted when ≥80% of pts had an OS event, included pts with *RAS/BRAF* WT (*KRAS/NRAS* exons 2-4 [incl. codon 59] and *BRAF* exon 15 assessed) mCRC. Median progression-free (PFS) and OS were estimated by baseline ECOG PS (stratification factor). Data were summarised descriptively and tested for significance using Cox's proportional hazards models. **Results:** Of 439 pts with *RAS/BRAF* WT mCRC, 438 had baseline ECOG PS recorded. Pts were well balanced with respect to sex, age and metastatic sites. Median PFS and OS were longer in ECOG PS 0/1 *RAS/BRAF* WT mCRC pts receiving pmab + FOLFOX4 vs FOLFOX4 (Table). Corresponding values were numerically shorter in ECOG PS 2 pts receiving pmab. Among *RAS* WT/*BRAF*MT pts, 49 were ECOG 0/1 at baseline (pmab + FOLFOX4 vs FOLFOX4 median PFS 6.7 vs 5.4 months, p=NS and OS 11.1 vs 9.1 months; p=NS); only 4 pts were ECOG 2. **Conclusions:** This post hoc analysis suggests that the PFS and OS benefits observed in pts with *RAS/BRAF* WT mCRC receiving pmab + FOLFOX4 are confined to those with a baseline ECOG PS of 0/1. Clinical trial information: NCT00364013.

| | ***RAS/BRAF* WT (n=438)** | |
|---|---|---|
| | **Pmab + FOLFOX4 (n=222)** | **FOLFOX4 (n=216)** |
| **ECOG 0/1 (n=411)** | | |
| **Median PFS (95% CI), months** | 12.3 (10.0-14.5) | 9.3 (7.7-10.6) |
| **HR (95% CI); p value[a]** | 0.69 (0.56-0.86); <0.001 | |
| **Median OS (95% CI), months** | 29.7 (25.2-32.7) | 23.1 (19.1-26.0) |
| **HR (95% CI); p value[a]** | 0.71 (0.57-0.88); 0.002 | |
| **ECOG 2 (n=27)** | | |
| **Median PFS, months** | 6.4 (2.7-14.6) | 7.6 (3.7-11.1) |
| **HR (95% CI); p value[a]** | 0.94 (0.38-2.31); 0.891 | |
| **Median OS, months** | 7.6 (4.6-28.7) | 8.9 (5.3-13.0) |
| **HR (95% CI); p value[a]** | 0.95 (0.41-2.21); 0.904 | |

Abbreviations: CI, confidence intervals; HR, hazard ratio. [a] Descriptive p value.

**3558^ General Poster Session (Board #21), Sat, 8:00 AM-11:45 AM**

**Second-line therapies in patients with *KRAS* wild-type metastatic colorectal cancer (mCRC) after first-line therapy with FOLFIRI in combination with cetuximab or bevacizumab in the AIO KRK0306 (FIRE 3) trial.** *Presenting Author: Dominik Paul Modest, Department of Medical Oncology, Klinikum Grosshadern, University of Munich, Munich, Germany*

**Background:** AIO KRK0306 (FIRE 3) trial compared first-line therapy with FOLFIRI plus either cetuximab (arm A) or bevacizumab (arm B) in 592 patients with *KRAS* exon 2 wild-type metastatic colorectal cancer (mCRC). We investigated choice and duration of second-line therapies, as well as overall survival (OS) and OS from beginning of second-line therapy according to second-line treatment. **Methods:** The protocol recommended second-line therapy with FOLFOX plus bevacizumab vs. irinotecan plus cetuximab in arm A vs. B, but physician were free to choose any regimen. second-line treatment was defined as any new anticancer drug for mCRC following first-line therapy. Duration of second-line therapy was calculated as time from first to last application of second-line treatment. **Results:** There were 260/297 patients in arm A and 250/295 patients in arm B who were alive after first-line therapy. Of those, 78.5% of patients arm A and 76.4% in arm B received second-line therapy so far. First-line progression free survival (PFS) according to second-line antibody use was associated with 9.2 (anti-vascular endothelial growth factor [VEGF]), comparing to 9.7 (anti-epidermal growth factor receptor [EGFR]) and 11.3 months (no mAB); p=0.001. Correspondingly, OS was 25.2 (anti-VEGF) vs. 23.7 (anti-EGFR) vs. 30.8 months (no mAB), p=0.02. First-line PFS according to seconnd-line oxaliplatin (Ox) use was associated with 9.9 (Ox), comparing to 9.9 months (no Ox); p=0.56. OS according to Ox-use was 27.1 (ox) vs. 29.1 months (no Ox); p=0.10. 2nd-line therapy was administered for a median of 17.2 weeks in arm A and 14.0 weeks in arm b (p=0.08). Second-line regimens with antibody-crossover were administered for a median of 23.9 weeks in arm A and 16.1 weeks arm B (p=0.06). Updated results might be presented at the annual meeting. **Conclusions:** This retrospective analysis indicates that second-line application of antibodies was favoured in patients with shorter first-line PFS, suggesting that preplanned second-line therapy may not reflect therapeutic reality. Correspondingly, second-line treatment without antibodies compared to antibody-based regimens was associated with longer OS. A trend towards longer second-line therapy was observed in favour of patients receiving cetuximab as first-line therapy. Clinical trial information: NCT00433927.

**3559 General Poster Session (Board #22), Sat, 8:00 AM-11:45 AM**

**Cell-free DNA levels in colorectal cancer patients treated with irinotecan, healthy controls, and non-cancer patients with comorbidity.** *Presenting Author: Karen-Lise Garm Spindler, Department of Oncology, Aarhus University Hospital, Aarhus, Denmark*

**Background:** The present study investigated the clinical value of total cell free DNA (cfDNA) measurement in metastatic colorectal cancer patients treated with second-line irinotecan monotherapy. **Methods:** Patient treated with second-line irinotecan for metastatic colorectal cancer (n=100), a cohort of healthy controls with and without co-morbidity (n=70 and 100, respectively) were included. CfDNA was quantified by an in-house developed qPCR (*Spindler* et al 2012) from plasma samples drawn prior to the first cycle of chemotherapy and at time of progression. **Results:** CfDNA levels were significantly higher in cancer patients compared to controls, with a clear capability for discriminating between the groups (AUC 0.82, p<0.0001). Patients with high levels had a shorter outcome compared to those with lover levels. The cohort independent upper normal limit (UNL) divided patients into high and low risk groups. The PFS was 2.1 months (95% CI 2.0-3.4), and 6.5 (95% CI 4.2-7.2) months, (HR 2.53 (95% CI 1.57-4.06), p=<0.0001) and OS 7.4 months (95% CI 4.3-8.7) and 13.8 months (95% CI 11.9-18.9), (HR 2.52 (95% CI 1.54-4.13), p<0.0001), respectively**.** Cox regression multivariate analysis showed a PFS Hazard Ratio of 1.4 (95% CI 1.1-1.7) for each increase in cfDNA quartile, p=0.03, and 1.6 (1.3-2.0) for OS, p<0.0001, respectively. CfDNA levels measured at time of progression showed similar consistent prognostic value. **Conclusions:** CfDNA measurement contains important clinical information and could become a useful tool for prediction of outcome from chemotherapy in mCRC.

**3560 General Poster Session (Board #23), Sat, 8:00 AM-11:45 AM**

**Phase II trial of panitumumab plus FOLFOX4 or FOLFIRI in subjects with KRAS wild-type colorectal cancer and liver-limited disease: The PLANET study.** *Presenting Author: Albert Abad, University Hospital Germans Trias i Pujol-ICO, Barcelona, Spain*

**Background:** Downsizing with chemotherapy (CT) unresectable liver-limited disease (LLD) can permit resection and prolonged survival in patients (pts) with colorectal cancer (CRC). We assessed the value of adding panitumumab (P) to standard CT in this setting. **Methods:** This was a phase II, open-label, randomized, multicenter study which included pts≥18 years with wild-type (WT) *KRAS* exon 2 metastatic CRC and LLD fulfilling one of the following criteria: ≥4 metastases; at least 1 metastasis>10 cm in diameter; or technically not resectable. Pts were randomized 1:1 to receive P-FOLFOX4 or P-FOLFIRI every two weeks. The primary endpoint was the objective response rate. **Results:** There were77 pts analyzed (38 received P-FOLFOX4 and 39 P-FOLFIRI). Not confirmed response was noted in 70.1% pts (73.7% with P-FOLFOX4 and 66.7% with P-FOLFIRI). After a median of 8 P infusions in both groups, 51.9% underwent surgical resection of liver metastases (44.7% and 59.0%, respectively). The resection rate (R0+R1) was 77.5% (76.5% and 78.3%). Median progression-free survival was 12.5 months with P-FOLFOX4 and 12.6 months with P-FOLFIRI (p=0.943). Preliminary median overall survival was 32.5 and 42.4 months. Median pre-surgery relative dose-intensity (RDI) for panitumumab was 79.8% with P-FOLFOX4 and 87.5% with P-FOLFIRI, and RDI for CT was 83.0% and 88.7%. Peri-operative safety was similar between groups (22.2% and 18.5% of pts with any adverse event). Neutropenia grade 3/4 (P-FOLFOX4 39.5% vs P-FOLFIRI 10.3%; p=0.0029) and neuropathy (P-FOLFOX4 13.2% vs P-FOLFIRI 0%;p=0.025), were the only statistically significant differences in grade 3/4 adverse events. It was possible to determine the *RAS* status (exon 2,3,4 of *KRAS*/*NRAS*) in 83.1% of the pts. In the subset of pts with *RAS* WT the response rate increases to 75.5% pts (77.8% with P-FOLFOX4 and 73.1% with P-FOLFIRI). **Conclusions:** In this selected population with WT *KRAS* CRC and LLD, panitumumab plus CT offers the possibility of rapid tumour shrinkage and potentially curative hepatic resection. Similar efficacy and safety results were obtained with either P-FOLFOX4 or P-FOLFIRI schema. Clinical trial information: NCT00885885.

**3561 General Poster Session (Board #24), Sat, 8:00 AM-11:45 AM**

**Impact of delay in adjuvant oxaliplatin-based chemotherapy for stage III colon cancer.** *Presenting Author: Renata D'Alpino Peixoto, BC Cancer Agency, Vancouver, BC, Canada*

**Background:** Less than 8 weeks (w) has been recommended as the optimal time to initiate adjuvant chemotherapy (AC) based upon two meta-analyses suggesting worse OS with delayed AC. However, neither included studies with oxaliplatin-based chemotherapy and the impact of its delay remains uncertain. **Methods:** Records of pts who initiated AC with either 5-FU or capecitabine plus oxaliplatin for stage III colon cancer between 2006 and 2011 at the BC Cancer Agency were reviewed. Cox proportional hazards models were used to analyze the impact of timing of AC on RFS. Pts were categorized into initiation of AC within 8 w (G1) and after 8 w (G2) **Results:** 635 pts (52% male) with a median age of 62 yrs (range 26–80) were included. Median lymph nodes examined and involved were 15 and 3, respectively. Median time from surgery to initiation of AC was 8.3 w (SD 18.58). At a median follow-up of 57.9 months, 176 pts (27.7%) have recurred and 118 (18.6%) have died. 5y-RFS was 70.9% (95% CI 65.2-76.5) for G1 and 72.1% (95%CI 67.2-77) for G2. On multivariate analysis, T stage, N stage, obstruction and perforation were identified as poor prognostic factors for RFS. Timing for AC did not have prognostic significance (HR 1.03, p = 0.83). **Conclusions:** In our population-based study, time to oxaliplatin-based AC following stage III colon resection did not impact on RFS. Contrary to most of the existing data which is primarily based on 5FU-based AC, delay of oxaliplatin-based therapy beyond 8 w is not associated with inferior outcomes.

**Prognostic factors for RFS – univariate and multivariate analysis.**

| Variables | Univariate HR | p value | Multivariate HR | p value |
|---|---|---|---|---|
| Age | 1.0 | 0.49 | 1.0 | 0.55 |
| <65 | 1.11 | | 1.09 | |
| ≥65 | | | | |
| Male | 1.0 | 0.19 | 1.0 | 0.22 |
| Female | 1.21 | | 1.20 | |
| Grade | 1.0 | 0.04 | 1.0 | 0.72 |
| 1/2 | 1.44 | | 1.06 | |
| 3 | | | | |
| LVI | 1.0 | < 0.001 | 1.0 | 0.05 |
| no | 1.89 | | 3.12 | |
| yes | | | | |
| PNI | 1.0 | 0.005 | 1.0 | 0.84 |
| no | 1.69 | | 1.04 | |
| yes | | | | |
| T | 1.0 | < 0.001 | 1.0 | 0.003 |
| 1/2 | 2.69 | | 2.16 | |
| T3 | 5.42 | | 3.27 | |
| T4 | | | | |
| N1 | 1.0 | < 0.001 | 1.0 | <0.001 |
| N2 | 2.11 | | 1.80 | |
| Examined LN | 1.0 | 0.85 | 1.0 | 0.05 |
| ≤12 | 0.97 | | 0.72 | |
| >12 | | | | |
| Obstruction | 1.0 | < 0.001 | 1.0 | 0.007 |
| no | 2.18 | | 1.73 | |
| yes | | | | |
| Perforation | 1.0 | < 0.001 | 1.0 | 0.002 |
| no | 3.40 | | 2.45 | |
| yes | | | | |
| Location | 1.0 | 0.02 | 1.0 | 0.07 |
| right | 1.40 | | 1.32 | |
| left | | | | |
| Time surgery-chemo | 1.0 | 0.60 | 1.0 | 0.83 |
| ≤ 8 w | 1.08 | | 1.03 | |
| > 8 w | | | | |

**3562 General Poster Session (Board #25), Sat, 8:00 AM-11:45 AM**

**Comparison of ColoPrint risk classification with clinical risk in the prospective PARSC trial.** *Presenting Author: Ramon Salazar, Early Clinical Research Unit, Institut Català d'Oncologia, L´Hospitalet-Barcelona, Spain*

**Background:** The 18-gene expression profile, ColoPrint, has been developed and validated for identifying risk of recurrence in patients with early stage colon cancer (CC). In a pooled stage 2 validation study ColoPrint identified 63% of patients as Low Risk with a 3-yr recurrence free survival (RFS) of 93% while High Risk patients had a 3-yr RFS of 82% with a HR of 2.7 (p=0.001). PARSC is a prospective study for the assessment of recurrence risk in stage II CC patients using ColoPrint. ColoPrint classification is compared to NCCN risk classification. **Methods:** The study enrolled 501 patients with histologically proven stage 2 CC from 31 institutes in Europe, USA, and Asia between October 2008 and September 2013. Synchronous tumors were excluded. ColoPrint results were not disclosed to the physician and patient. Treatment was at the discretion of the physician, adhering to NCCN approved regimens or a recognized alternative. A McNemars test is performed to compare ColoPrint with NCCN risk classification. A p- value ≤ 0.05 indicates the two tests differ significantly. **Results:** ColoPrint classified 352 (70%) patients as Low Risk and 149 (30%) as High Risk. 97 patients (19%) received adjuvant chemotherapy. In the ColoPrint Low Risk group, 66 (19%) patients received adjuvant chemotherapy and 31 (21%) of ColoPrint High Risk patients received chemotherapy. According to NCCN high risk factors (T4, high grade (exclusive of MSI-H), lymphovascular/perineural invasion, perforation/obstruction, <12 nodes examined, positive margins) 274 (55%) patients were NCCN Low Risk and 227 were NCCN High Risk. 82 (30%) of the NCCN Low Risk patients are ColoPrint High Risk. 160 (70%) of the NCCN High Risk patients are ColoPrint Low Risk. MSI-status was assessed in 96 (18%) patients of which 33 were MSI high and 63 were MSS. All MSI high were classified as ColoPrint Low Risk. **Conclusions:** The PARSC study is the first prospective study to compare genomic and clinical risk assessment and we observed marked differences between NCCN risk classification and ColoPrint. The clinical validity of these methods will be based on the outcomes at 3 and 5 years. Clinical trial information: NCT00903565.

| P<0.0001 | ColoPrint low risk | ColoPrint high risk | Total |
|---|---|---|---|
| NCCN low risk | 192 | 82 | 274 |
| NCCN high risk | 160 | 67 | 227 |
| Total | 352 | 149 | 501 |

**3563 General Poster Session (Board #26), Sat, 8:00 AM-11:45 AM**

**Association outcome with genes involved in immune response and checkpoints in patients with resected colorectal liver metastases.** *Presenting Author: Stefan Stremitzer, USC Norris Comprehensive Cancer Center, Los Angeles, CA*

**Background:** In patients with colorectal liver metastases (CLM), liver resection offers the chance of cure and long-term survival. The liver is a highly immunogenic organ harboring approximately 80% of the body's tissue macrophages. Emerging data demonstrate a critical role of an immune response for cancer treatment. In this study we investigated genetic variations within genes involved in immune response and checkpoints and their association with recurrence and outcome in patients with CLM. **Methods:** Genomic DNA was extracted from formalin-fixed paraffin embedded resected bevacizumab-pretreated CLM from 149 patients [median age 62 years (range 30-80), 58.4% male, median follow-up 3.9 years (range 0.02-7.7)]. Single nucleotide polymorphisms (SNP) in nine genes associated with immune surveillance and checkpoints (CCL2, CCR2, LAG3, CD73, PDCD1, PDL1, IDO1, CTLA4, CD24) were analyzed by direct Sanger DNA sequencing and evaluated for association with response, recurrence-free survival (RFS) and overall survival (OS). **Results:** In univariate analysis, rs3739319 (IDO1) and rs8734 (CD24) showed a significant difference in three-year OS rate [(G/G or G/A 75%, A/A 49%; HR (95% CI) 2.52 (1.33, 4.80), P=0.007) and (G/G 63%, G/A or A/A 76%; HR (95% CI) 0.53 (0.28, 0.97), P=0.042), respectively]. In multivariate analysis adjusted for age, number of metastases, size of metastases and time since diagnosis of colorectal cancer, rs3739319 remained significant (HR (95% CI) 2.04 (1.03, 4.03), P=0.040). Recursive partitioning analyses revealed that rs8734 and rs3739319 were the dominant SNPs predicting histological response and OS, respectively. **Conclusions:** Our data suggest that gene variations within genes involved in immune response and checkpoints are associated with outcome in patients with resected CLM. These data might lead to improved treatment strategies modulating anti-tumor immune response by targeting novel immune checkpoints.

**3564 General Poster Session (Board #27), Sat, 8:00 AM-11:45 AM**

**Influence of genetic variations of the angiopoietin and pericyte pathways in resected colorectal liver metastases.** *Presenting Author: Stefan Stremitzer, USC Norris Comprehensive Cancer Center, Los Angeles, CA*

**Background:** Liver resection in patients with colorectal liver metastases (CLM) offers the chance of cure and long-term survival. Angiogenesis is essential for tumor growth and progression. Genes involved in angiopoietin and pericyte pathways may be escape mechanisms for anti-vascular endothelial growth factor (VEGF) therapy. Therefore, we investigated whether genes of the angiopoietin and pericyte pathways have an influence on recurrence and outcome in patients with CLM treated with bevacizumab based chemotherapy. **Methods:** Genomic DNA was extracted from resected bevacizumab-pretreated CLM (FFPE) from 149 patients [median age 62 years (range 30-80), 58.4% male, median follow-up 3.9 years (range 0.02-7.7)]. Single nucleotide polymorphisms (SNP) in nine genes (ANGPT1, ANGPT2, TIE2, PDGF-B, PDGFR-B, IGF-1, TGF-B1, RALBP1, RGS5) were analyzed by direct Sanger DNA sequencing and evaluated for association with response, recurrence-free survival (RFS) and overall survival (OS). **Results:** In univariate analysis, rs329007 (RALBP1) showed a significant difference in RFS (A/A 14.0 months, A/G or G/G 9.2 months; HR 1.60, P=0.024) and rs1800818 (PDGF-B) in three-year OS rate (A/A 78%, A/G 69%, G/G 53%; HR 1.37 and 2.12, P=0.048). In multivariate analysis adjusted for age, number of metastases, size of metastases and time since diagnosis of colorectal cancer, rs329007 remained significant (HR 1.99, P=0.002). With respect to radiological response, rs1800818 and rs329007 showed a significant difference [(G/G 71%, A/G or A/A 86%, P=0.042) and (A/A 78%, A/G or G/G 94%, P=0.018), respectively]. With respect to histological response, rs329007 showed significant different rates between the groups (A/A 36% major histological response (MjHR), 34% partial histological response (PHR), 30% no histological response (NHR); A/G or G/G 46% MjHR, 13% PHR, 41% NHR, P=0.029). Recursive partitioning analyses revealed that rs329007 and rs1800818 were the dominant SNPs predicting histological response and OS, respectively. **Conclusions:** Our data suggest that genetic variations in genes involved in the angiopoietin and pericyte pathways may be predictive and/or prognostic biomarkers in patients with resected CLM treated with bevacizumab based chemotherapy.

**3565 General Poster Session (Board #28), Sat, 8:00 AM-11:45 AM**

**Influence of genetic variants of genes potentially associated with brain metastases on overall survival in 70 colorectal cancer patients.** *Presenting Author: Matthias Preusser, Department of Medicine I and Comprehensive Cancer Center CNS Tumours Unit, Medical University of Vienna, Vienna, Austria*

**Background:** Brain metastases (BM) in colorectal cancer (CRC) are rare, developing in only 0.3-9% of the patients, and considered a late-stage manifestation of the disease. The aim of this study was to investigate whether genetic variants of genes from integrin, invasion- and adhesion-mediating, angiogenic and tumor suppressing pathways, involved in overcoming the blood-brain barrier are associated with outcome. **Methods:** Genomic DNA was extracted from formalin-fixed paraffin embedded resected BM from 70 patients with histologically proven CRC. Single nucleotide polymorphisms (SNP) in seven genes (*CXCR4*, *MMP9*, *ST6GALNAC5*, *ITGAV*, *ITGB1*, *ITGB3*, *KLF4*) were analyzed by direct Sanger DNA sequencing and evaluated for association with overall survival (OS) from resection of BM. Only SNPs with an allele frequency of ≥10% were analyzed. **Results:** In univariate analysis, rs17577 (MMP9) and rs4642 (ITGB3) showed a significant difference in OS [(G/G 7.4 months, G/A 5.1 months; HR (95% CI) 1.83 (0.95-3.53), P=0.044) and (A/A or A/G 8.0 months, G/G 4.3 months; HR (95% CI) 2.31 (1.08-4.93), P=0.014), respectively]. In multivariate analysis adjusted for baseline characteristics (primary tumor site, age at diagnosis of CRC, BM location, Karnofsky performance status), rs2236599 (KLF4), rs10171481 (ITGAV), rs1883778 (ST6GALNAC5), and rs2680880 (CXCR4) were significant in OS [(G/G 7.4 months, G/A or A/A 4.8 months; HR (95% CI) 2.12 (1.01-4.45), P=0.048), (A/A or A/G 5.3 months, G/G 15.5 months; HR (95% CI) 0.39 (0.18-0.85), P=0.018), (G/G 4.6 months, G/A or A/A 9.4 months; HR (95% CI) 0.53 (0.30-0.93), P=0.028) and (A/A 6.4 months, A/T 9.3 months, T/T 4.6 months; HR (95% CI) 0.45 (0.22-0.89) and 1.54 (0.75-3.15), P=0.005), respectively]. Recursive partitioning analyses revealed that rs4642 is the dominant SNP predicting OS. **Conclusions:** This study suggests for the first time a prognostic effect of the genetic variations within genes involved in the blood-brain barrier breach. Further analyses are needed to confirm these findings.

**3566 General Poster Session (Board #29), Sat, 8:00 AM-11:45 AM**

**Analysis of progression-free survival in the new EPOC study in an "all wild-type" population.** *Presenting Author: John A. Bridgewater, Department of Medical Oncology, University College London Cancer Institute, London, United Kingdom*

**Background:** The phase 3 new EPOC study, randomised *KRAS* wild-type (WT) patients with resectable or suboptimally resectable colorectal cancer liver metastases (CRLM) 1:1 to receive chemotherapy with or without cetuximab before and after liver resection. The primary end point was progression free survival (PFS). The trial demonstrated a detriment in PFS following the addition of cetuximab to chemotherapy from 20.5 to 14.1 months. *KRAS* was determined using pyrosequencing in codons 12, 13, and 61 (HR 1·48 95% CI 1·04-2·12 p=0.03). Subsequently, benefit from epidermal growth factor inhibition was shown to be improved following restriction to an all *RAS* WT population in patients with advanced disease (Douillard NEJM 2013). We describe a further analysis of PFS in an all WT new EPOC population. **Methods:** Samples of tumor from the primary colorectal and liver resections were obtained. Patients were further analysed using MiSeq for *KRAS* (codon 12, 13, 61, 117 and 146), *BRAF* (V600E), *NRAS* (12, 13, 61, 117 and 146), *PIK3CA* (547 and 1047). Those without any mutation were classed as "all WT". Additional qPCR was performed for MET, AREG, EREG, EGFR, HER2-4, PTEN and NT5E. Survival analyses were completed using the Kaplan-Meier method and the log-rank test. **Results:** To date 106 samples of primary tumor and 103 samples of CRLM have been analysed corresponding to 155 of the 236 *KRAS* WT patients. Further mutations were found in samples from 22 patients in the *KRAS* WT group (16 *KRAS*, 12 *NRAS*, 3 *PIK3CA,* and 6 *BRAF* mutations). Paired samples of primary tumour and CRLM were analysed for 47 patients. Three mutations were matched between the primary and corresponding CRLM, with the remaining 13 mutations (six in the primary tumor, seven in CRLM) not found in the paired sample. Analysis of PFS in the all WT population of patients previously included in the primary analysis (chemo alone arm n=48, chemo plus cetuximab arm n=54) demonstrated a similar trend in detriment in median PFS of 20.5 months to 16.4 months respectively (HR 1.34 95% CI (0.76-2.36) p = 0.32). **Conclusions:** The addition of cetuximab to chemotherapy and surgery for operable CRLM in *KRAS* wild-type patients results in an inferior PFS. More stringent selection of an all WT cohort does not significantly alter the detriment observed in the *KRAS* WT population. Clinical trial information: 22944367.

**3567 General Poster Session (Board #30), Sat, 8:00 AM-11:45 AM**

**Randomized controlled trials (RCTs) examining continuous (CS) versus intermittent strategies (IS) of delivering systemic treatment (Tx) for untreated metastatic colorectal cancer (mCRC): An updated meta-analysis from the Cancer Care Ontario program in evidence-based care.** *Presenting Author: Scott R. Berry, Sunnybrook Odette Cancer Centre, University of Toronto, Toronto, ON, Canada*

**Background:** There is varied impact on efficacy demonstrated in individual RCTs of CS vs IS of delivering systemic Tx for mCRC. Our meta-analysis of the available RCTs was updated to include results of the CAIRO3 trial. **Methods:** RCTs that compared a CS versus IS of delivering systemic Tx were identified by a systematic search and review. The results of identified trials were clinically homogeneous (Table) so the data were pooled using Review Manager software (RevMan 5.2). Overall survival (OS) hazard ratios (HRs) were extracted from the most recently reported trial results. A random effects model was used for all pooling. **Results:** 11 RCTs were identified (n= 4,809). For the 8 trials with available OS HRs, the Tx patients received after induction was: none (5 trials, n=3,036), fluoropyrimidine (1 trial, n=620), biologic (2 trials, n=852). Results of the meta-analysis are summarized in the Table (HR>1 favors CS). Sensitivity analyses demonstrated results were generally robust across induction and maintenance regimens. One sensitivity analysis of the 3 trials (CAIRO3, OPTIMOX2, COIN, n=2,389) with combination Tx induction and no maintenance Tx until progression revealed a statistically, but non-clinically significant benefit for continuous treatment (HR=1.10, 95% CI 1.00-1.20, p=0.05). QOL (data from 3 trials) was either the same in both arms (2 trials with no maintenance Tx, n=911) or improved in the IS arm (1 trial with no maintenance Tx, n=1,630). **Conclusions:** IS of delivering systemic Tx for mCRC do not result in a clinically significant reduction in OS compared to a CS of delivery whether or not maintenance therapy is included. QOL is the same or better with an IS.

| | OS HR (95% CI) | Test for overall effect - Z | Heterogeneity chi$^2$ (df) | $I^2$ (%) |
|---|---|---|---|---|
| **All trials (n=4,508*)** | 1.03 (0.96 – 1.10) | 0.89 (p=0.38) | 6.01 (7) (p=0.54) | 0 |
| **Trials with no maintenance Tx (n=3036*)** | 1.03 (0.94 – 1.14) | 0.68 (p=0.50) | 5.03 (4) (p=0.28) | 20 |
| **Trials with maintenance Tx (n=1,472*)** | 1.00 (0.88 – 1.14) | 0.01 (p=0.99) | 0.69 (2) (p=0.71) | 0 |

* n = number of patients in trials with available HRs.

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**3568 General Poster Session (Board #31), Sat, 8:00 AM-11:45 AM**

**Updated analysis of *KRAS/NRAS* and *BRAF* mutations in study 20050181 of panitumumab (pmab) plus FOLFIRI for second-line treatment (tx) of metastatic colorectal cancer (mCRC).** *Presenting Author: Marc Peeters, Antwerp University Hospital and University of Antwerp, Edegem, Belgium*

**Background:** Previously, extended *RAS* analysis from this study showed a trend toward improvements in HR on OS and PFS with pmab + FOLFIRI vs FOLFIRI in WT *RAS* group vs WT *KRAS* exon 2 group. Here we report updated *RAS* data and new analysis by *BRAF* status. **Methods:** The primary objective was to assess the tx effect of pmab + FOLFIRI vs FOLFIRI on OS and PFS based on *RAS/BRAF* mutation status in the primary analysis population. Bidirectional Sanger sequencing was used to detect mutations in *KRAS* exons 3, 4 and *NRAS* exons 2, 3, 4, and *BRAF* exon 15 in patients (pts) with known WT *KRAS* exon 2 mCRC. **Results:** Overall *RAS/BRAF* ascertainment rate was 85% (n=1014/1186). 18% of WT *KRAS* exon 2 pts harbored additional *RAS* mutations (n=107/597). The incidence of *BRAF* mutations was 8.3% (45/541). Efficacy is shown (table). Tx HR for pts with WT *RAS* was 0.81 (95% CI: 0.63, 1.03; *P*=0.08) for OS and 0.70 (95% CI: 0.54, 0.91; *P*=0.007) for PFS. **Conclusions:** Improvements continued to be observed in the tx effect of pmab + FOLFIRI vs FOLFIRI on OS and PFS in WT *RAS* group vs WT *KRAS* exon 2 group in this update. Pts with MT *RAS* mCRC are unlikely to benefit by the addition of pmab to FOLFIRI, similar to pts with MT *KRAS* exon 2 mCRC. *BRAF* mutations appear to be associated with reduced OS among pts without *RAS* mutations regardless of tx arm. These findings support *RAS* testing to determine potentially appropriate pts with mCRC for pmab tx. Clinical trial information: NCT00339183.

| | Pmab + FOLFIRI (N = 303) | FOLFIRI (N = 294) | HR (95% CI) | Descriptive p |
|---|---|---|---|---|
| WT *RAS*,[a] n | 208 | 213 | | |
| Median OS - mos | 16.2 | 13.9 | 0.81 | 0.08 |
| 95% CI | 14.5, 19.7 | 11.9, 16.0 | 0.63,1.03 | |
| Median PFS - mos | 6.4 | 4.6 | 0.70 | 0.007 |
| 95% CI | 5.5, 7.4 | 3.7, 5.6 | 0.54,0.91 | |
| MT *RAS*,[b] n | 299 | 294 | | |
| Median OS - mos | 11.8 | 11.1 | 0.91 | 0.34 |
| 95% CI | 10.4, 13.1 | 10.2, 12.4 | 0.76, 1.10 | |
| Median PFS - mos | 4.8 | 4.0 | 0.86 | 0.14 |
| 95% CI | 3.7, 5.5 | 3.6, 5.5 | 0.71, 1.05 | |
| WT *RAS*/WT *BRAF*[c] | 186 | 190 | | |
| Median OS - mos | 18.7 | 15.4 | 0.83 | 0.15 |
| 95% CI | 15.7, 20.3 | 13.0, 17.9 | 0.64,1.07 | |
| Median PFS - mos | 6.9 | 5.5 | 0.68 | 0.006 |
| 95% CI | 5.8, 8.0 | 3.9, 5.9 | 0.51,0.90 | |
| WT *RAS*/MT *BRAF*[d] | 22 | 23 | | |
| Median OS - mos | 4.7 | 5.7 | 0.64 | 0.20 |
| 95% CI | 2.8, 9.0 | 3.5, 7.3 | 0.32,1.28 | |
| Median PFS - mos | 2.5 | 1.8 | 0.69 | 0.34 |
| 95% CI | 1.7, 3.5 | 1.8, 3.1 | 0.32,1.49 | |

[a] WT in *KRAS* and *NRAS*exons 2, 3, and 4. [b] MT in any *KRAS* or *NRAS* exon 2, 3, or 4. [c] WT for all *RAS* and *BRAF* exons. [d] WT for all *RAS* and MT *BRAF* exons.

**3569 General Poster Session (Board #32), Sat, 8:00 AM-11:45 AM**

**Multivariate prospective pharmacogenetic analysis in patients with resectable metastatic colorectal cancer (mCRC) receiving FOLFOX chemotherapy.** *Presenting Author: Marie-Christine Etienne-Grimaldi, Centre Antoine Lacassagne, Nice, France*

**Background**: To prospectively test the predictive value of gene polymorphisms related to fluorouracil (FU) and oxaliplatin (Oxa) pharmacodynamics in mCRC patients receiving FOLFOX regimens. **Methods:** 205 mCRC patients out of 284 included in the MIROX trial (GERCOR group) were enrolled (67 women, 138 men; mean age 60). All received a FOLFOX regimen (FOLFOX4 for 104 patients, FOLFOX7 for 101 patients). Maximum toxicity (NCI-CTCAE) for each toxic pattern along with best response (RECIST criteria) were recorded. Polymorphisms of genes relevant for FU, thymidylate synthase (*TYMS*, 5'UTR repeats and 3'UTR deletion), dihydropyrimidine dehydrogenase (*DPYD*, IVS14+1 G>A), 5-10methylenetetrahydrofolate reductase (*MTHFR*, 677C>T and 1298A>C), and for Oxa, glutathione S-transferase pi (*GSTP1*, 105Ile>Val), xeroderma pigmentosum (*ERCC2*, 751Lys>Gln), were determined (blood). **Results:** 62% of patients presented at least a grade 3-4 (G3-4) toxicity (29.8% neutropenia, 22% digestive toxicity (nausea/vomiting/diarrhea/mucositis)). Global toxicity, hematotoxicity and vomiting were significantly more frequent in women. Patients homozygous for the deficient *MTHFR* 1298C allele (favouring elevated methylenetetrahydrofolate concentrations) had a significantly higher risk of developing G3-4 neutropenia as compared to others (OR 3.1, 95%CI 1.1-8.6, adjusted on gender), and tended to present a greater risk of digestive toxicity (OR 2.4, 95%CI 0.9-7.0). Patients with *ERCC2* 751Lys/Gln or Gln/Gln genotype had a greater global toxicity as compared to others (OR 2.30, 95%CI 1.25-4.24, adjusted on gender), and a greater digestive toxicity (OR 2.35, 95%CI 1.1-5.1, adjusted on gender). Among the 3 patients with *DPYD* mutation (heterozygous) only 2 developed G3-4 toxicity. Response (51.8% CR+PR) was significantly lower in *MTHFR* 677TT patients relative to others (OR 0.16, 95%CI 0.05-0.52). *ERCC2* 751Lys/Gln+Gln/Gln genotype tended to be associated with longer DFS relative to Lys/Lys (RR 0.74, 95%CI 0.51-1.07). **Conclusions:** Present data confirm previous findings showing that toxicity and response to FOLFOX therapy may be driven by *MTHFR* germinal polymorphisms. Clinical trial information: NCT00268398.

**3570 General Poster Session (Board #33), Sat, 8:00 AM-11:45 AM**

**Bichemotherapy versus single-agent therapy with 5FU in elderly patients with metastatic colorectal cancer: A meta-analysis.** *Presenting Author: Gaetan Des Guetz, Oncology Department, Hôpital Avicenne, HUPSSD, UCOG 93 (APHP), Bobigny, France*

**Background**:The clinical benefit of first-line bi-chemotherapy (FOLFOX or FOLFIRI) compared to single therapy (5FU) in metastatic elderly patients (> 70 or > 75 years old) with colo-rectal cancer (CRC) is controversial. Therefore, we undertook a meta-analysis (MA) of all published phase III studies. **Methods:** We performed a PubMed search using key-words: metastatic colo-rectal cancer, phase III studies, oxaliplatin, irinotecan, survival. We also screened ASCO and the European Society for Medical Oncology (ESMO) proceedings. Few studies have been published corresponding to our inclusion criteria. The efficacy outcomes were overall survival (OS) and progression free survival (PFS). Toxicity was also examined when available. Hazard ratios (HRs) with their 95 % confidence interval (CI) were collected from the studies and pooled. By convention, HRs < 1 corresponded to a better outcome. P values < 0.05 were considered statistically significant. A fixed-effect model was used. We used Comprehensive Meta-Analysis software (Biostat, Englewood, NJ, USA). **Results:** This MA included five original studies (Mitry, and Koopman both assessing irinotecan; De Gramont, Seymour and Ducreux assessing oxaliplatin) and an already published MA of four trials comparing FOLFIRI with 5FU (Saltz, Douillard, Köhne and Seymour). Our MA included 1,225 patients (70 % men). For age, we chose a cut-off of 70 years for oxaliplatin and a cut-off of 75 years for irinotecan. The PS score was 0-1 in about 90% of patients except for the studies by Mitry and Seymour FOCUS2 which included 30% of PS2 patients. Overall, bi-therapy, compared to 5FU alone, did not improve OS (HR=1.00; CI: 0.89-1.13) but significantly improved PFS (HR=0.82; CI: 0.72-0.93). When assessed separately, FOLFIRI and FOLFOX significantly improved PFS (HR=0.83; 0.68-1.00, and HR=0.81; 0.68-0.97 respectively). The main grade 3/4 toxicities for FOLFIRI were diarrhea , nausea, vomiting, neutropenia, which occurred significantly more often than with 5FU alone. **Conclusions**: Addition of oxaliplatin or irinotecan to 5FU in metastatic CRC significantly improved PFS in elderly patients more than 70-year old, but was associated with an increased risk of toxicity for irinotecan.

**3571 General Poster Session (Board #34), Sat, 8:00 AM-11:45 AM**

**Biomarker validation study: Genes involved in ubiquitin proteasome system (UPS) dependent EGFR-degradation for prediction of efficacy in metastatic colorectal cancer patients treated with cetuximab.** *Presenting Author: Sebastian Stintzing, USC Norris Comprehensive Cancer Center, Los Angeles, CA*

**Background:** Epidermal growth factor receptor (EGFR) turnover is a highly regulated process controlling the amount of receptor proteins available for antibody binding. The ubiquitin proteasome system (UPS) is responsible for EGFR degradation. The single nucleotide polymorphism (SNP) rs895374 is located in UbcH7, an E2 ligase conducting neddylation of HECT E3 ligases involved in EGFR degradation. Neddylation activates E3 ligases and switches the balance between degradation and recycling towards degradation. We have previously reported that rs895374 correlates with progression free survival (PFS) in patients (n=108) treated with cetuximab in two phase II studies of further-line treatment. The aim of this study was to validate the predictive value of rs895374 in an independent cohort of cetuximab treated patients with a cetuximab-free chemotherapy arm serving as negative control. **Methods:** Genomic DNA was isolated from tissue samples of 455 patients (median age 64 years, male 64.2%) treated in first-line with either FOLFIRI cetuximab (n=218) or FOLFIRI bevacizumab (n=237) enrolled in the FIRE-3 trial (NCT00433927). The cetuximab arm served as validation for our previous results whereas the bevacizumab arm served as negative control arm to confirm the predictive value of this SNP. **Results:** The minor allele A was associated with shorter PFS in the FOLFIRI + cetuximab validation set, (10.5 months vs. 8.2 months; logrank p=0.005; HR 0.66 (0.47-0.89)). In the FOLFIRI plus bevacizumab arm, no difference in PFS were seen (10.3 months versus 10.5 months, logrank p=0.85; HR 1.03 (0.77-138)). rs895374 was neither associated with tumor response nor with median overall survival. **Conclusions:** The predictive value of rs895374 for cetuximab treatment could be validated and no prognostic value could be established. This is the first report proving that germline polymorphisms in the degradation process predict efficacy of cetuximab in patients with metastatic colorectal cancer. As the process of EGFR recycling is an important mechanism of cetuximab resistance, novel anti-EGFR antibodies like Sym004 may overcome resistance mechanisms by preventing EGFR recycling.

**3572 General Poster Session (Board #35), Sat, 8:00 AM-11:45 AM**

**Molecular profiling of patients (pts) with advanced colorectal cancer (CRC): Princess Margaret Cancer Center experience.** *Presenting Author: Joanne Wing-Yan Chiu, Princess Margaret Cancer Centre, Toronto, ON, Canada*

**Background:** In routine clinical practice the prevalence of somatic mutations other than *KRAS* G12/13, *PIK3CA,* and *BRAF* in colorectal cancer (CRC) has not been well described. This study reports molecular profiling of pts with advanced CRC in clinical setting. **Methods:** Patients (pts) with advanced CRC are enrolled in an ongoing institution-wide screening program. Molecular profiling is performed on formalin-fixed and paraffin-embedded (FFPE) archival tissues using a customized Sequenom panel (23 genes, 279 mutations) or the Illumina MiSeq TruSeq Cancer Panel (48 genes, 212 amplicons, ≥500x coverage) in our Clinical Laboratory Improvement Amendments-certified laboratory. *PTEN* is determined by immunohistochemistry (IHC), with H score <1 defined as negative. Statistical analysis was performed with chi-square tests. **Results:** From March 2012 to October 2013, 190 pts were enrolled. At least one mutation was found in 55% (82/153) and 89% (33/37) of pts using Sequenom or MiSeq platforms respectively ($p<0.01$). Of all 190 pts, *KRAS* G12/13 mutation was identified in 35%, and non-G12/13 *KRAS*, *BRAF*, or *NRAS* mutations were present in 5% , 6%, and 4% respectively. Other mutations found included *PIK3CA* (13%, 24/190), *CTNNB1*, *ERBB2*, *FGFR3*, and *EGFR* (1% each). MiSeq detected additional mutations including *KRAS* A146 or L19F (4/37), *SMAD4* (4/37), *FRXW7* (3/37), *APC* (15/37), *TP53* (26/37), *ERBB4* (1/37), *PTEN* (1/37), and *IDH1* (1/37). Co-mutation with *KRAS* was found in 63% of pts with *PIK3CA* mutation and 80% of pts with *APC* mutation. Of 85 pts with known *PTEN* IHC status, 19% were negative. A higher average number of mutations was observed in right- versus left-sided CRC ($p<0.01$). Mutations with known clinical significance (*RAS* and *BRAF*) were collectively more prevalent in right colon ($p<0.01$). **Conclusions:** Targeted next-generation DNA sequencing identifies more genomic alterations than SNP genotyping. Current strategy of anti-epidermal growth factor receptor therapy in *KRAS* G12/13 wild type pts might not benefit >15% of pts due to presence of other *RAS/BRAF* mutations. Clinically relevant genomic alterations are more likely to be detected in right colon.

**3573 General Poster Session (Board #36), Sat, 8:00 AM-11:45 AM**

**FCγRIIa and FCγRIIIa polymorphisms (SNPs) and cetuximab (C) benefit in the EXPERT-C trial.** *Presenting Author: Francesco Sclafani, The Royal Marsden NHS Foundation Trust, London and Surrey, United Kingdom*

**Background:** FCγRIIa-H131R and FCγRIIIa-V158F SNPs have been reported to enhance the immune-mediated effects of monoclonal antibodies including cetuximab (C) in metastatic colorectal cancer (CRC). Although the importance of antibody-dependent cell mediated cytotoxicity could be potentially higher in the adjuvant setting, there are no data on the relationship between these SNPs and C in patients (pts) with early stage disease. We performed a pharmacogenomic analysis of EXPERT-C, a randomised phase II trial of neoadjuvant CAPOX followed by chemoradiotherapy, surgery, and adjuvant CAPOX ± C in high-risk, locally advanced rectal cancer. **Methods:** SNP analysis was performed on DNA extracted from peripheral blood samples. Kaplan-Meier method and Cox regression analysis were used to calculate survival estimates and compare treatment arms. **Results:** A blood sample was available for genotyping in 105/164 (64%) pts (CAPOX=54, CAPOX-C=51) who were representative of the study population. Baseline characteristics were evenly allocated between the two treatment arms. Twenty five (23.8%) were homozygous for FCγRIIa-131H, 52 (49.5%) heterozygous (131H/R), and 28 (26.7%) homozygous for 131R. 13 (12.4%) were homozygous for FCγRIIIa-158V, 48 (45.7%) heterozygous (158V/F), and 44 (41.9%) homozygous for 158F. No deviation from the Hardy-Weinberg equilibrium or association with tumour *RAS* status was observed. FCγRIIa-131R (HR 0.38, p=0.058) and FCγRIIIa-158F alleles (HR 0.21, p=0.007) predicted progression-free survival (PFS) in pts treated with C. In the CAPOX-C arm, carriers of both 131R and 158F alleles had a statistically significant improvement in PFS (5-yrs 78.4%, HR 0.22, p=0.002) and overall survival (OS) (5-yr 86.4%, HR 0.24, p=0.018) when compared to pts homozygous for 131H and/or 158V (5-yr PFS 35.7%, 5-yrs OS 57.1%). An interaction between C benefit and presence of 131R and 158F alleles was found for PFS (p=0.017) and remained significant after adjusting for prognostic variables (p=0.003). **Conclusions:** This is the first study investigating FCγRIIa and FCγRIIIa SNPs in early stage CRC pts treated with C. Our findings suggest an increased clinical benefit from C in this patient population in the presence of 131R and 158F alleles.

**3574 General Poster Session (Board #37), Sat, 8:00 AM-11:45 AM**

**Pharmacokinetic (PK)-guided optimization of 5-fluorouracil (5FU) exposure in colorectal cancer (CRC) patients: U.S.-based clinical practices experience.** *Presenting Author: Fadi S. Braiteh, Comprehensive Cancer Centers of Nevada, Las Vegas, NV*

**Background:** Multiple studies have demonstrated how PK-guided dosing to optimize infusional 5FU exposure improves both response rates and toxicities. With 5FU PK testing now available using a rapid, reliable immunoassay, we present US-based oncologists' experience with individualizing 5FU dosing based on PK in patients with adjuvant or metastatic CRC. **Methods:** Between June 5, 2013 and January 17, 2014, Saladax Biomedical Laboratories (a CLIA-certified lab) determined 5FU plasma levels (My5-FU assay) in 631 samples collected ~24+6Hr after the start of 5FU continuous infusion from 240 CRC patients (n=250 therapy lines). Systemic 5FU exposure (calculated as area under the curve [AUC]) and dose adjustment recommendations to achieve target range (AUC = 20 – 30 mg*hr/L) were reported to physicians. Evaluable cycle pairs were defined as two consecutive cycles with AUC results. Actual vs. target AUC, recommended vs. actual dose adjustment, and ability to adjust exposure to target range were evaluated. **Results:** Majority of AUC results (62%) were outside the target range in the first sample from each therapy line where exposure was determined, irrespective of 5FU dosing or regimen. In 288 cycle pairs, 201 (69%) were outside the target range: doses were decreased in 48% of the 40 above target range, and doses were increased in 51% of the 161 below target range. No dose change was made in 89% of the 87 within the target range. In 101 cycle pairs out of target range where a dose adjustment consistent with recommendation was made, 42% moved into the target range. **Conclusions:** 5FU exposure optimization is feasible in the US clinical setting, consistent with other reports. Body surface area based 5-FU dosing results in frequent under dosing (48%). Majority (62%) of dose adjustment recommendations were followed in subsequent cycles. PK-guided dose adjustment is a practical approach to personalize optimal 5FU exposure.

| | 5FU Dose (mg/m$^2$) in first samples received for testing | | | |
|---|---|---|---|---|
| AUC range (mg*Hr/L) | All doses (600–3,840) | < 2,400 | 2,400 | > 2,400 |
| AUC below range (<=19) | 48% | 61% | 44% | 34% |
| AUC in target range (20 – 30) | 38% | 27% | 42% | 47% |
| AUC above range (>=31) | 14% | 12% | 14% | 19% |
| # of samples | 250 | 74 (30%) | 144 (57%) | 32 (13%) |

**3575 General Poster Session (Board #38), Sat, 8:00 AM-11:45 AM**

**Panex: A pooled analysis of EXPERT and EXPERT-C, two trials of neoadjuvant chemotherapy (NACT) and chemoradiotherapy (CRT) in high-risk locally advanced rectal cancer (LARC).** *Presenting Author: Francesco Sclafani, The Royal Marsden NHS Foundation Trust, London and Surrey, United Kingdom*

**Background:** After the use of preoperative radiotherapy and TME, survival of LARC has reached a plateau. More effective therapies, predictive/prognostic factors for treatment selection and valid endpoints for clinical trials are needed. We report the results of PANEX, a pooled analysis of EXPERT and EXPERT-C, the two largest trials of neoadjuvant CAPOX followed by CRT, TME and adjuvant CAPOX ± cetuximab in MRI-defined, high-risk, LARC. **Methods:** Individual patient data were collected from the central database of each trial. Survival endpoints were analysed using Kaplan-Meier methods and multivariate Cox-regression. **Results:** 269 patients (EXPERT=105, EXPERT-C=164) were included. Baseline features: T3c/T3d (60%), T4 (22%), CRM+ (63%), distal tumour (61%), N+ (72%), EMVI (71%). Radiologic response was 62% after NACT and 80% after CRT. Surgery was performed in 91% (R0 in 87%) and T/N downstaging was achieved in 56%/55% of cases. Pathologic complete response rate was 19%. After a median follow-up of 69 mo, 5-year local progression-free survival (PFS), distant PFS, PFS and overall survival (OS) were 94%, 79%, 70% and 73%, respectively. Baseline and treatment-related factors with statistically significant independent prognostic value in multivariate analyses are shown in the Table. **Conclusions:** Short- and long-term outcomes of NACT followed by CRT in high-risk LARC compare favourably with those reported with standard CRT in risk-unselected patients. Age, T4 and EMVI may be used as baseline factors for patient stratification and treatment selection. Tumour downstaging may be a surrogate endpoint to use in future phase II trials of NACT.

| Variable | Local PFS | Distant PFS | PFS | OS |
|---|---|---|---|---|
| Baseline[1] | - | EMVI HR 2.07 p=0.03 | Age HR 1.52 p=0.04 | Age HR 1.68 p=0.02<br>T4 HR 1.75 p=0.02 |
| Treatment-related[2,3] | - | T downstaging HR 0.51 p=0.03<br>N downstaging HR 0.49 p=0.02 | T downstaging HR 0.47 p=0.002 | T downstaging HR 0.36 p<0.001 |

[1]Include: trial, treatment with cetuximab, age, sex, WHO PS, T3c/d, T4, EMVI, CRM+, distal tumour. [2]Include: T/N downstaging, R0 resection, pCR. Also, adjusted for significant baseline variables. [3]R0 vs R1/R2 resection significant for all outcome measures.

**3576 General Poster Session (Board #39), Sat, 8:00 AM-11:45 AM**

**Chemotherapy use in stage III colon cancer: A National Cancer Data Base (NCDB) analysis.** *Presenting Author: Sumit Dahal, Institute of Medicine, Tribhuvan University, Kathmandu, Nepal*

**Background:** Adjuvant chemotherapy in stage III colon cancer improves overall survival, however, prior studies have shown that it is underused. We analyzed different factors that may influence its use. **Methods:** This is a retrospective study of stage III colon cancer patients (n=207,718) diagnosed between 2000 and 2011 in the NCDB. NCDB contains ~70% of new cancer diagnosis from >1,500 American College of Surgeons-accredited cancer programs in the United States and Puerto Rico. Chi-square test was used to determine any difference in characteristics of patients who did or did not receive chemotherapy. **Results:** 35% of all stage III colon cancer patients did not receive adjuvant chemotherapy. The use of chemotherapy had increased in recent years. Its use was lower in whites, females, patients ≥60 years, patients with one or more comorbidities, non-academic centers and those with medicare insurance, lower education and income levels (all p<.0001; Table). Non-white and uninsured were more likely to be <60 years. **Conclusions:** This is the largest study to determine the use of chemotherapy in stage III colon cancer. More than one-third did not receive adjuvant chemotherapy, although its use has increased in more recent years. Age was one of the most important determinants of chemotherapy use, which may explain higher rates in non-white and uninsured. In addition to patient characteristics, race, gender and socioeconomic factors influence chemotherapy use. These findings have important implications for health care reform.

**Chemotherapy use in stage III colon cancer patients.**

| | % of cases receiving chemotherapy |
|---|---|
| **Treatment facilities** | |
| Academic hospitals | 64 |
| Other hospitals | 62 |
| **Year of treatment** | |
| 2000-2002 | 59 |
| 2003-2006 | 62 |
| 2007-2011 | 64 |
| **Age** | |
| < 60 years | 82 |
| ≥ 60 years | 55 |
| **Gender** | |
| Male | 65 |
| Female | 60 |
| **Race/ethnicity** | |
| White | 61 |
| Black | 65 |
| Hispanics | 66 |
| **Insurance status** | |
| Private | 77 |
| Not insured | 73 |
| Medicaid | 70 |
| Medicare | 52 |
| **Education (% with high school degree)** | |
| ≤ 69% | 61 |
| 70-88% | 62 |
| > 88% | 63 |
| **Household Income** | |
| < $28,000 | 59 |
| $28,000 - $48,999 | 62 |
| ≥ $49,000 | 63 |
| **Charlson Comorbidity Score** | |
| None | 67 |
| ≥1 | 55 |
| **Distance traveled to treatment facility** | |
| < 100 miles | 62 |
| ≥ 100 miles | 59 |

P-value significant for all comparison at <0.0001.

**3577 General Poster Session (Board #40), Sat, 8:00 AM-11:45 AM**

**Do patients achieving pathologic complete response (pCR) following neoadjuvant treatment for locally advanced rectal cancer (LARC) need adjuvant chemotherapy?** *Presenting Author: Anis Hamid, Alfred Health, Melbourne, Australia*

**Background:** Optimal treatment for locally advanced rectal cancer (LARC) includes neoadjuvant short-course radiotherapy (SCRT) or long-course chemoradiotherapy. One advantage of long-course treatment is potential for tumour downstaging to pathologic complete response (pCR) in 10-15%, a sub-group with an excellent long-term prognosis. Uncertainty exists regarding the need for post-operative chemotherapy in such patients. We aimed to review the treatment and outcomes of all consecutive patients achieving pCR following neoadjuvant treatment for LARC. **Methods:** All patients undergoing neoadjuvant treatment for LARC at two academic centers between 1999-2012 were identified and their resection histopathology reports reviewed to identify patients with pCR. These cases were reviewed for initial stage, pre- and post-operative treatment, local and distant recurrences as well as OS. **Results:** There were 53 (15.5%) of 342 consecutive patients undergoing curative-intent surgery achieved pCR (ypT0N0). 2/41 (4.9%) undergoing SCRT, and 51/301 (16.9%) undergoing long-course radiotherapy (LCRT) had pCR. Of 53 pCR patients, 46 were staged T3/T4 pre-operatively, all remaining were T2, node-positive except 2 patients who were T2, node-negative. Between patients who did and did not achieve pCR, there was no significant difference in age, Eastern Cooperative Oncology Group (ECOG) (0 vs 1+), the proportion undergoing SCRT versus LCRT (2/53 vs. 39/289 respectively, p=0.06) or the time from completing LCRT to surgery (p=0.32). 63% of pCR patients received adjuvant 5-FU. These patients were younger (mean age 54 vs 71 years; p<0.001), however there was no difference in ECOG. No pCR patients developed local recurrence and only 2 distant recurrences occurred. 5-year OS was 91%, and no difference in RFS or OS was seen between those who did and did not receive adjuvant 5-FU. **Conclusions:** Our findings support previous studies showing excellent outcomes (>90% 5-year DFS and OS) for patients with pCR after neoadjuvant treatment for LARC. We further demonstrate no significant difference in OS or RFS between pCR patients who did and did not receive adjuvant 5-FU. This data adds to growing evidence suggesting that there may be no advantage in administering adjuvant 5-FU to this patient population.

**3578 General Poster Session (Board #41), Sat, 8:00 AM-11:45 AM**

**Early predictors of improved long-term outcomes in first-line antiangiogenics plus chemotherapy (anti-ANG/CT) in metastatic colorectal cancer (mCRC): Analysis of individual patient (pt) data from the ARCAD database.** *Presenting Author: Everardo D. Saad, Dendrix Research, Sao Paulo, Brazil*

**Background:** Early tumor shrinkage (ETS, ≥20% decrease from baseline) is associated with improved progression-free survival (PFS) and overall survival (OS) in mCRC pts treated with epidermal growth factor receptor inhibitors. We compared the relative merits of ETS and early objective tumor response (EOTR; CR/PR by RECIST) vs. standard Best Overall Response (BOR) and Confirmed Response (ConfR) in mCRC pts treated with 1st-line anti-ANG/CT. **Methods:** Data were available from 4,776 pts enrolled on 8 randomized trials of bevacizumab (N=6), cediranib (N=1), or both (N=1). ETS, EOTR, BOR and ConfR were assessed at 6, 8/9 and 12 weeks (wks). Associations were assessed by stratified Cox models with a landmark approach. The relative prediction accuracy of distinguishing pts at high vs. low risk of progression/death was compared by C-index (c, higher values indicate better accuracy). **Results:** All response endpoints were significantly associated with PFS and OS (P≤0.001 for all hazard ratios [HRs]) (see Table). Adjusting for age, performance status, # of metastases and prior therapy, significance remained. ETS showed larger effect size than EOTR. For PFS, the prediction accuracy was similar across time points or endpoints. For OS, compared with earlier time points, ETS and EOTR at 12 wks produced larger risk reduction, with similar prediction accuracy as BOR. **Conclusions:** Early response-based endpoints are significantly associated with improved PFS and OS in mCRC pts treated with anti-ANG/CT. The prediction performance of early response based on tumor measurement is as good as for standard RECIST response. Assessment of these endpoints as surrogates for PFS/OS at the trial level is ongoing.

| | ETS | | EOTR | | BOR | | ConR | |
|---|---|---|---|---|---|---|---|---|
| **Wks** | **HR (95% CI)** | **c** | **HR (95% CI)** | **c** | **HR (95% CI)** | **c** | **HR (95% CI)** | **c** |
| **PFS** | | | | | | | | |
| **6** | .77 (.69-.86) | .55 | .80 (.71-.91) | .53 | .72 | .55 | .86 | .52 |
| **8/9** | .74 (.67-.82) | .55 | .81 (.72-.91) | .53 | (.67-.79) | | (.78-.94) | |
| **12** | .74 (.66-.84) | .54 | .80 (.71-.90) | .54 | | | | |
| **OS** | | | | | | | | |
| **6** | .63 (.54-.73) | .58 | .64 (.54-.76) | .56 | .45 | .61 | .60 | .56 |
| **8/9** | .58 (.50-.66) | .59 | .63 (.53-.74) | .56 | (.40-.49) | | (.53-.69) | |
| **12** | .51 (.44-.59) | .59 | .53 (.46-.62) | .60 | | | | |

Abbreviations: CI, confidence interval.

**3579 General Poster Session (Board #42), Sat, 8:00 AM-11:45 AM**

**Comparative effectiveness of contemporary adjuvant chemotherapy among older rectal cancer patients.** *Presenting Author: Jennifer Leigh Lund, Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC*

**Background**: Guidelines for stage II and III rectal cancer in the US recommend neoadjuvant chemoradiation therapy (CRT), curative resection, and adjuvant chemotherapy. This paradigm is based on early trials without neoadjuvant CRT and extrapolations from colon cancer. Recent trials have called into question whether adjuvant chemotherapy improves overall survival (OS) among patients treated with neoadjuvant CRT. We sought to examine whether chemotherapy improves OS in patients treated with neoadjuvant CRT or radiation therapy (RT) and surgery in real world settings. **Methods:** We identified a population-based cohort of 1,431 older (65+ years) non-metastatic rectal cancer patients diagnosed from 2004-2009 using the Surveillance, Epidemiology and End Results program (SEER)-Medicare data, who underwent neoadjuvant CRT or RT and curative resection. We described patterns of adjuvant chemotherapy using binomial regression models and evaluated the comparative effectiveness of: 1) any adjuvant chemotherapy vs. no adjuvant chemotherapy and 2) adjuvant oxaliplatin+5-fluorouracil (5-FU)/capecitabine vs. 5-FU/capecitabine on OS using Cox proportional hazards regression models and propensity score (PS) matching to adjust for measured covariates. **Results:** In total, 744 patients (52%) received adjuvant chemotherapy; most received oxaliplatin (53%). Older age, lower pathologic stage, and being widowed were associated with a lower likelihood of receiving adjuvant chemotherapy. Unadjusted and PS adjusted survival was superior in patients treated with chemotherapy (adjusted hazard ratio (aHR)=0.71, 95% confidence interval (CI): 0.57, 0.89). Among patients receiving adjuvant therapy, older age, earlier year of diagnosis, lower stage, and higher census tract poverty level were associated with a lower likelihood of receiving oxaliplatin. The addition of oxaliplatin to 5-FU/capecitabine did not improve OS after PS matching (aHR=1.15, 95% CI: 0.78, 1.70). **Conclusions:** Our results suggest that older non-metastatic rectal cancer patients benefit from adjuvant chemotherapy; however, the addition of oxaliplatin to 5-FU/capecitabine may not provide any incremental benefit.

**3580 General Poster Session (Board #43), Sat, 8:00 AM-11:45 AM**

**LGR5 rs17109924 to predict chemoresistance to 5FU-based chemotherapy in adjuvant colon cancer.** *Presenting Author: Armin Gerger, Division of Clinical Oncology, Department of Internal Medicine, Medical University of Graz, Graz, Austria*

**Background:** We recently investigated 25 germline polymorphisms in a comprehensive panel of genes that have been previously associated with colon cancer stem cell genes to predict tumor recurrence in patients with stage III and high-risk stage II colon cancer treated with 5-FU based chemotherapy. We found the minor alleles of CD44 rs8193 C>T, ALCAM rs1157 G>A and LGR5 rs17109924 T>C being significantly associated with increased time to recurrence (TTR). In this study we validated these molecular biomarkers in a large and independent study cohort to clarify their predictive and/or prognostic role. **Methods:** A total of 599 consecutively collected patients with stage II and III colon cancer were included in this validation study. Genomic DNA was analyzed for CD44 rs8193, ALCAM rs1157, and LGR5 rs17109924 by TaqMan 5'-exonuclease assays. **Results:** The mean age at time of diagnosis was 64 years (std 11), with a median follow-up time of 4.2 years (range 0.1-16.6). Tumor recurrence was observed in 185 (30.9%) patients with a stage III and stage II dependent probability of three-year recurrence of 37.1% (std 2.5) and 16.5% (std 2.3), respectively. Adjuvant chemotherapy was received by 393 (65.6%) of the patients. The tested gene variants CD44 rs8193 and ALCAM rs1157 did not show a statistically significant association with TTR in the analyses. However, patients carrying at least one C allele in LGR5 rs17109924 had a significantly increased TTR compared to patients carrying the homozygous T/T (HR 0.60, 95%CI 0.37-0.98; P=0.043). Stratified by adjuvant chemotherapy, LGR5 rs17109924 was highly significant for patients receiving adjuvant chemotherapy (P=0.007) whereas no association was found for patients without adjuvant chemotherapy (P=0.633). Also after adjusting for sex, age, stage, number of resected lymph nodes, lymphovascular, vascular, and perineural invasion in the multivariate Cox analysis LGR5 rs17109924 remained significant (HR 0.38, 95%CI 0.19-0.79; P=0.009) for patients with adjuvant chemotherapy. **Conclusions:** We confirmed in a large and independent study cohort that LGR5 rs17109924 is a predictive molecular biomarker for 5-FU based adjuvant chemotherapy in patients with colon cancer.

**3581 General Poster Session (Board #44), Sat, 8:00 AM-11:45 AM**

**The prognostic and therapeutic value of EpHA2 in early colorectal cancer (CRC).** *Presenting Author: Sonali Dasgupta, CCRCB, Queen's University, Belfast, Belfast, United Kingdom*

**Background:** EpHA2 is a 130 kD transmembrane glycoprotein belonging to ephrin receptor subfamily and involved in angiogenesis/tumour neovascularisation. High EpHA2 mRNA level has recently been implicated in cetuximab resistance. Previously, we found high EpHA2 levels in a panel of invasive colorectal cancer (CRC) cells, which was associated with high levels of stem-cell marker CD44. Our aim was to investigate the prognostic value of EpHA2 and subsequently correlate expression levels to known clinico-pathological variables in early stage CRC. **Methods:** Tissue samples from 509 CRC patients were analysed. EpHA2 expression was measured using IHC. Kaplan-Meier graphs were used. Univariate and multivariate analyses employed Cox Proportional Hazards Ratio (HR) method. A backward selection method (Akaike's information criterion) was used to determine a refined multivariate model. **Results:** EpHA2 was highly expressed in CRC adenocarcinoma compared to matched normal colon tissue. In support of our preclinical invasive models, strong correlation was found between EpHA2 expression and CD44 and Lgr5 staining ($p<0.001$). In addition, high EpHA2 expression significantly correlated with vascular invasion ($p=0.03$).HR for OS for stage II/III patients with high EpHA2 expression was 1.69 (95%CI: 1.164-2.439; $p=0.003$). When stage II/III was broken down into individual stages, there was significant correlation between high EpHA2 expression and poor 5-years OS in stage II patients (HR: 2.18; 95%CI: 1.28-3.71; $p=0.005$).HR in the stage III group showed a trend to statistical significance (HR: 1.48; 95%CI=0.87-2.51; $p=0.05$). In both univariate and multivariate analyses of stage II patients, high EpHA2 expression was the only significant factor and was retained in the final multivariate model. Higher levels of EpHA2 were noted in our *RAS* and *BRAF* mutant CRC cells, and silencing EpHA2 resulted in significant decreases in migration/invasion in parental and invasive CRC sublines. Correlation between *KRAS/NRAS/BRAF*mutational status and EpHA2 expression in clinical samples is ongoing. **Conclusions:** Taken together, our study is the first to indicate that EpHA2 expression is a predictor of poor clinical outcome and a potential novel target in early stage CRC.

**3582 General Poster Session (Board #45), Sat, 8:00 AM-11:45 AM**

**Identifying an early indicator of drug efficacy in patients (pts) with metastatic colorectal cancer (mCRC): A prospective evaluation of circulating tumor cells (CTC), 18F-fluorodeoxyglucose positron-emission tomography (PET), and the RECIST criteria.** *Presenting Author: Brigette Ma, State Key Laboratory of Oncology in South China, Sir Y K Pao Centre for Cancer, Department of Clinical Oncology, Hong Kong Cancer Institute and Prince of Wales Hospital, The Chinese University of Hong Kong, Sha Tin, Hong Kong*

**Background:** The early determination of drug response is a keystone in oncology, and CTC is a promising biomarker in mCRC. This study investigated the prognostic significance of a novel dual-endpoint of 'PET and CTC response' at 4 weeks (wk), and of the conventional RECIST response at 10 wks post-1$^{st}$line chemotherapy (chemo). **Methods:** All pts had a whole-body (WB) PET-CT (contrast) and CTC analysis (7.5ml blood) at baseline, a plain PET-CT and CTC analysis at 4 wks, and a WB-CT at 10 wks after starting chemo. CTCs were isolated using the cancer cell enrichment and detection kit (Milenyi Biotech). A positive CTC is defined as having: a positive red staining, round-to-oval morphology, size = or > 2 times that of lymphocyte. Evaluable lesions must have a SUVmax = or > 2 on PET and be measurable based on RECIST (version 1.0 and 1.1). PET response is defined as = or > 30% drop in the sum of SUVmax of target lesions, and CTC response is defined as 'any level of drop', or a 'CTC < 3 cells' at 4 wks. **Results:** 70 pts have been recruited. The mean age was 63.9 yrs, 70% had oxaliplatin-based chemo. At a median follow-up of 13.6 months, 38 pts have died. At baseline, 1 pt did not have PET and CTC. At 10wks, 7 pts did not have the PET done. In a multivariate analysis, CTC level < 3 cells at 4 wks (p=0.048, odds ratio, OR = 0.106, 95% CI=0.011-0.985) was an independent predictor of OS. RECIST response (both versions, $p < 0.05$, OR = 0.021 to 0.179) predicted PFS. **Conclusions:** In this early analysis, CTC level at 4 wks and RECIST-response at 10 wks are associated with survival in pts with mCRC. The prognostic significance of dual 'PET and CTC response' at 4 wks will be reported. The optimal cut-off for a drop in SUVmax and CTC will be explored. Clinical trial information: NCT01163305.

**3583 General Poster Session (Board #46), Sat, 8:00 AM-11:45 AM**

**Hepatic oligometastases treated with stereotactic body radiation therapy: Updated 10-year analysis of the Indiana University experience.** *Presenting Author: Ben Goodman, Indiana University, Indianapolis, IN*

**Background:** Stereotactic body radiation therapy (SBRT) is a non-invasive, effective technique in the treatment of a limited number of liver metastases from solid tumors. We present the 10 year update of our single institution SBRT experience outcomes and toxicity. This is thought to be the largest single institution experience present in the literature. **Methods:** We treated 81 patients 89 different times, for a total of 106 lesions. Inclusion criteria were patients with 1-3 liver metastases without evidence of extra-hepatic progression, and at least 700 cc of liver (minus the GTV) receiving less than 1500 cGy. The majority of patients had colorectal primary cancers. Other diagnoses included: Non-colorectal GI, breast, ovarian, NSCLC, and others. Among the lesions treated the majority received prior chemotherapy. **Results:** The median overall survival was 31 months. Kaplan Meier survival estimates at 12, 24, 36, and 48 months were 85%, 61%, 34%, and 18%. The local control rate was 94% with Kaplan Meier estimates at 12, 24, 36, and 48 months being 95%, 90%, 90% and 90%. The observed toxicities noted among the 106 treatments included mostly CTC grade 1-2 toxicity with only two grade 4 and one grade 5 toxicity. There was no difference in the toxicity based on the primary site. The majority of patients had grade 1 to 2 non-hepatic GI toxicity, grade 1-2 fatigue or grade 1-2 chest wall pain. The most severe toxicity noted was 1 patient with grade 5 hepatic toxicity and 2 patients with grade 4 hepatic toxicity. In addition, two patients developed grade 1 pleural effusions thought to be secondary to treatment. Parameters affecting toxicity were evaluated based on grade 4-5 hepatic toxicity. Generalized estimating equation models were fit to test for an association between each categorical factor and grade 4-5 hepatic toxicity. Linear mixed models were used to test for an association between each continuous factor and grade 4-5 hepatic toxicity. The only patient with grade 5 toxicity was treated three different times to a total of four lesions. **Conclusions:** Stereotactic body radiation therapy is a safe and effective treatment for patients with 1-3 liver metastases with a limited toxicity profile.

**3584 General Poster Session (Board #47), Sat, 8:00 AM-11:45 AM**

**A randomized controlled trial evaluating efficacy of adjuvant oral uracil-tegafur (UFT) with leucovorin (LV) after resection of colorectal cancer liver metastases: The UFT/LV study.** *Presenting Author: Akira Kobayashi, First Department of Surgery, Shinshu University School of Medicine, Matsumoto, Japan*

**Background:** Surgical resection has been accepted as the standard therapy for colorectal cancer liver metastases (CRLM), however, high recurrence incidence even after curative resection remains an unsolved problem. There is no established adjuvant chemotherapy for CRLM, although efficacy of several adjuvant treatments for stage III colorectal cancer has been confirmed. Oral UFT/LV is one of the standard therapies in stage III colorectal cancer. We conducted this randomized, open-label, phase III trial to evaluate efficacy of adjuvant UFT/LV therapy for CRLM (stage IV). **Methods:** A patient undergoing curative resection of CRLM was randomly assigned to either UFT/LV or surgery alone (control) group. In the UFT/LV group, 5 cycles of adjuvant UFT/LV (UFT 300mg/m$^2$ and LV 75 mg/day for 28 days followed by 7 days rest in one cycle) were administered. The primary endpoint was relapse-free survival (RFS), while secondary endpoints were overall survival (OS) and safety. **Results:** Between February 2004 and December 2010, total 180 patients were enrolled to this trial, among whom 3 patients were ineligible for analysis. The baseline characteristics were well-balanced in the UFT/LV (n=88) and control (n=89) groups. Median follow-up was 4.76 years. The 3y-RFS rate in the UFT/LV group was 38.6%, which was significantly higher than the control group (32.3%). The hazard ratio for relapse in the UFT/LV relative to the control was 0.56 (95% confidence interval: 0.38-0.83, P=0.003). The 3y-OS rates were similar between the UFT/LV and control groups (82.8% vs. 81.6%, P=0.41). In the UFT/LV group without treatment-related death, the scheduled cycles was completed in 45 patients among 82 (54.9%), and the mean dose intensity ratio was 70.8%. As adverse events at any grade, hyperbilirubinemia (28.0%), liver dysfunction (23.2%), diarrhea (26.9%) and anorexia (28.0%) occurred. **Conclusions:** Adjuvant UFT/LV therapy is effective to prevent recurrence after surgical resection of CRLM. Clinical trial information: C000000013.

**3585 General Poster Session (Board #48), Sat, 8:00 AM-11:45 AM**

**Colon cancer: Characteristics and survival rates in young versus old patients.** *Presenting Author: Shams Aziz Mistry, McLaren Regional Medical Center, Flint, MI*

**Background:** Colon cancer is detected at a later stage in younger patients (YP) (< 50 years) probably due to lack of screening in this age group. There has been an increased incidence of colon cancer (1.6%) in YP, but they are underrepresented in research studies. The aim of our study is to compare characteristics of colon cancer and survival outcome in YPs (18-49 years) vs older patients (>50) using the Surveillance, Epidemiology, and End Results (SEER) database. **Methods:** Using the SEER database (1991-2010), we reviewed patients > 18 years of age with colon cancer. Multivariate Cox regression analysis was used to evaluate risk adjusted outcomes and to predict the hazard of dying. Kaplan Meier method was used to estimate the survival function. **Results:** We included 375,443 patients in our study. YPs with colon carcinoma were more likely to be African American (15.7% vs 10.6%; p<0.001), Hispanic (13.5% vs 6.7%; p<0.001) and Asian (9.2% vs 6.3%; p<0.001) as compared to the older age group. YPs were more likely to present with distant metastasis (27.7% vs 19.1%; p<0.001) and had more poorly differentiated tumors (20.3 % vs 18.0%; p< 0.001). YPs also received more cancer directed surgery (92.6 % vs 91%; p<0.001) compared to their older counterparts. Five year survival was better for younger patients in all stages{table 1}. After controlling for gender, race, marital status, grade, stage, cancer specific surgery and post-operative radiation, we found that age is an independent predictor of death, and younger patients with colon cancer had a lower risk of dying (HR 0.767; p<0.001). **Conclusions:** Previous studies of YPs with colon cancer were found to have either equivalent or better survival in stages II and IV compared to older patients. Our study shows that young patients less than 50 years of age have more advanced stages of colon cancer at diagnosis but have better stage specific survival in all stages.

**Five-year survival rate for colon cancer patient.**

| Stage of colon cancer | Young (< 50 yrs) N=29,276 | Older (≥ 50 years) N=346,167 | P-value |
|---|---|---|---|
| **Localized** | 95.6% | 91.1% | <0.001 |
| **Regional** | 76.7% | 72.8% | <0.001 |
| **Distant** | 20.3% | 16.8% | <0.001 |
| **Unstaged** | 69.3% | 50.4% | <0.001 |

**3586 General Poster Session (Board #49), Sat, 8:00 AM-11:45 AM**

**Updated results of the SOFT study: A randomized phase III trial of S-1/oxaliplatin (SOX) plus bevacizumab versus 5-FU/*l*-LV/oxaliplatin (mFOLFOX6) plus bevacizumab in patients with metastatic colorectal cancer (mCRC).** *Presenting Author: Masato Nakamura, Aizawa Hospital, Matsumoto, Japan*

**Background:** As previously reported (Yamada Y, et al. Lancet Oncol. 2013 Dec;14(13):1278-86), the SOFT study demonstrated that SOX plus bevacizumab (SOX+Bev) was non-inferior to mFOLFOX6 plus bevacizumab (mFOLFOX6+Bev) in terms of the primary endpoint of progression-free survival (PFS). We now report the final overall survival (OS) after a median follow-up of more than 3 years. **Methods:** The SOFT study was an open-label, non-inferiority, randomized phase III trial. Chemotherapy-naïve patients with mCRC, an ECOG PS of 0-1, and adequate organ functions were randomized to receive either mFOLFOX6+Bev (5 mg/kg of bevacizumab, followed by 200 mg/m$^2$ of *l*-leucovorin given simultaneously with 85 mg/m$^2$ of oxaliplatin, followed by a 400 mg/m$^2$ bolus of 5-FU on day 1 and then 2,400 mg/m$^2$ of 5-FU as an intravenous infusion over the course of 46 h, every 2 weeks) or SOX+Bev (7.5 mg/kg of bevacizumab, 130 mg/m$^2$ of oxaliplatin on day 1, and 40−60 mg of S-1 twice daily for 2 weeks, followed by a 1-week rest). The primary endpoint was PFS. Patients' data were finally updated in September 2013. **Results:** At this final analysis, the median survival time(MST) was 29.7 months (95% CI: 26.5−33.1) with mFOLFOX6+Bev and 29.6 months (95% CI: 25.8−34.7) with SOX+Bev (median follow-up, 37.7 months). The HR for OS was 1.018 (95% CI: 0.823−1.258). Median PFS was 11.7 months (95% CI: 10.9−13.3) with mFOLFOX6+Bev and 12.2 months (95% CI: 10.7−13.0) with SOX+Bev. The HR for PFS was 1.051 (95% CI: 0.876−1.262), and the p value for non-inferiority was 0.0115 (median follow-up, 31.2 months). In the subgroup analysis of PFS and OS, we recorded no clinically significant interactions between the assigned regimen and any factors. The safety profile was almost similar to primary analysis results. **Conclusions:** In this study, the MST was at least 29.5 months in both groups, indicating similar OS. Our results reconfirmed that SOX+Bev is non-inferior to mFOLFOX6+Bev in terms of PFS as first-line treatment for mCRC. SOX+Bev can thus be used instead of mFOLFOX6+Bev. Clinical trial information: JapicCTI-090699.

**3587 General Poster Session (Board #50), Sat, 8:00 AM-11:45 AM**

**Randomized controlled trial on the skin toxicity of panitumumab in third-line treatment of KRAS wild-type metastatic colorectal cancer: HGSG1001 (Japanese Skin Toxicity Evaluation Protocol with Panitumumab: J-STEPP)—Additional analysis of antitumor efficacy.** *Presenting Author: Yoshimitsu Kobayashi, Department of Gastroenterology and Hepatology, Hokkaido University Hospital, Sapporo, Japan*

**Background:** Panitumumab (Pmab) has demonstrated efficacy in patients with KRAS wild-type metastatic colorectal cancer (mCRC). Although the STEPP study (Lacouture M. E. et al. J Clin Oncol. 2010; 28: 1351-7.) showed that pre-emptive skin treatment reduced skin toxicities compared with reactive treatment among patients receiving Pmab, data for Asians has not been reported. We planned a randomized, open-label trial to verify the differences between pre-emptive and reactive treatment for skin toxicities in Japanese patients. **Methods:** Patients receiving third-line Pmab-containing regimens for mCRC were randomly assigned 1:1 to pre-emptive (skin moisturizers, sunscreen, topical steroid, and minocycline) or reactive (only skin moisturizers) skin treatment. The primary endpoint was the cumulative incidence of ≥grade 2 skin toxicities during the 6-week treatment period. Retrospectively, a dermatologist reviewed skin toxicities, in a blinded manner, using photographs. **Results:** Of 95 enrolled patients, 47 were assigned to pre-emptive, and 48 to reactive treatment. The incidence of ≥grade 2 skin toxicities during the 6-week treatment period (investigators' assessment) was 21.3% and 62.5% (risk ratio [RR], 0.34; 95% CI, 0.19 to 0.62; P < 0.001) for the pre-emptive and reactive treatment groups, respectively. A similar trend was observed in central review (18.6% and 50.0%, respectively [RR, 0.37; 95% CI, 0.19 to 0.74; P = 0.002]). There were no statistical differences in progression free survival (3.6 vs 4.0 months; hazard ratio [HR], 1.20; 95% CI, 0.78 to 1.84; P = 0.413), time to treatment failure (3.0 vs 3.5 months, [HR, 1.23; 95% CI, 0.80 to 1.89; P = 0.343]), and overall response rate (13.3% vs 18.2%; P = 0.530) between pre-emptive and reactive treatment groups. **Conclusions:** Pre-emptive skin treatment could reduce the severity of skin toxicities during Pmab treatment, and did not affect the anti-tumor efficacy of Pmab. Our data clearly validate that pre-emptive treatment can also be recommended in Japanese patients. Clinical trial information: 000004883.

**3588 General Poster Session (Board #51), Sat, 8:00 AM-11:45 AM**

**Effect of 12-week home-based exercise program on fasting insulin in stage II-III colorectal cancer survivors: A randomized controlled trial.** *Presenting Author: Mi Kyung Lee, Yonsei University, Seoul, South Korea*

**Background:** High insulin levels may be associated with an increased risk of colorectal cancer (CRC) development and recurrence. However, the effect of exercise on fasting insulin level in colorectal cancer survivors has not been fully studied. We conducted a randomized control trial to determine the effect of a 12-week home based exercise program on fasting insulin, body composition, and fitness in stage II-III CRC survivors. **Methods:** 123 stage II-III CRC survivors between 4 and 102 weeks after standard cancer therapy (surgery, chemotherapy, and/or radiation therapy) were randomly assigned to either the 12-week home-based exercise (n=62) or usual care (n=61) group. The goal of the home-based exercise was to increase the level of physical activity of the participants to 18-27 MET hours per week. The primary outcome measurement was fasting insulin and secondary outcome measurements were body composition and fitness level. **Results:** A total of 99 (80.5%) participants completed the trial. After 12 week of home-based exercise program, fasting insulin level was significantly reduced in exercise group while it did not change in control group (Ex, 6.09±3.96 vs. 4.93±3.41 μU/ml; Con, 6.74±3.40 vs. 6.73±3.01 μU/ml, between group $p$=0.045). Furthermore, percent body fat was significantly reduced (Ex, 27.53±8.59 vs. 26.83±8.41%; Con, 27.18±7.02 vs. 27.85±7.11 %, between group $p$=0.033), and 6-min walk test (Ex, 580.72±82.09 vs. 611.54±74.51 m; Con, 598.06±65.03 vs. 606.03±58.26 m, between group $p$=0.041), Chair Stand test (Ex, 19.71±6.53 vs. 23.08±5.06; Con, 23.87±6.20 vs. 23.83±4.31, between group $p$=0.004), and push up (Ex, 15.21±9.68 vs. 20.89±11.83; Con, 15.44±13.03 vs. 12.59±10.98, between group $p$ <0.000) were significantly improved in exercise group. **Conclusions:** The 12-week home based exercise intervention decreased fasting insulin and percent body fat, and improved fitness in stage II-III CRC survivors. The current study was supported by the National Research Foundation of Korea (2013K2A1A2054437) and the National R&D Program for Cancer Control, Ministry of Health & Welfare, Republic of Korea (1120230).

**3589 General Poster Session (Board #52), Sat, 8:00 AM-11:45 AM**

**Four-year survival in patients (pts) undergoing liver surgery after neoadjuvant triplet hepatic artery infusion (HAI) and intravenous cetuximab (IV-CET) for previously treated and unresectable liver metastases from kras *wt* colorectal cancer (LM-CRC) (European trial OPTILIV, NCT00852228).** *Presenting Author: Francis Levi, Medical Oncology Department, INSERM U776, Paul Brousse Hospital, Villejuif, France*

**Background:** IV chemotherapy (chemo) downsizes LM-CRC in most pts. Yet less than 15% of those with previously unresectable LM and prior chemo undergo successful complete macroscopic LM resection (R0-R1). 4-y survival is 42% in all pts with LM resection (Livermetsurvey). Purpose is to determine disease-free survival (DFS) and OS in pts with R0-R1 partial hepatectomy after neoadjuvant HAI of irinotecan, oxaliplatin, and 5-fluorouracil and IV-CET for LM-CRC in the first multicenter trial testing this strategy. **Methods:** The 9 centers accrued 64 pts with 1-3 prior chemo, bilateral LM (84% pts), a median number of 10 LM, with largest diameter of 53 mm, spread in a median of 6 segments. First intent LM surgery was deferred for high LM number (72% of the pts), large size (69%), ill location (61%), extra-hepatic disease (2%), or other cause (12%). Liver surgery was performed whenever R0-R1 became feasible at q6-9 weeks multidisciplinary review. **Results:** LM surgery occurred 2.6 to 19.4 months (mo) after inclusion (median, 5.3). Single-, two- or three-stage R0-R1 hepatectomies were performed in 15, 3 and 1 pt respectively**.** LM resection was associated with younger age (median, 52 vs 60 y, p=0.01), less liver involvement (≤25% vs >25% tumor replacement, 68% vs 38% of the pts, p=0.025; median N of segments involved, 5 vs 7, p=0.015), and 1 rather than 2-3 prior chemo (46% vs 20% of the pts, p=0.01). Resection rate did not differ according to sex, PS, primary tumor stage or grade, LM bilaterality and number, prior resections, extrahepatic disease, or objective response rate (42% vs 40%). Median DFS was 15.7 mo [95% CI, 10- 21], with LM recurring in 11 pts (58%). Median OS was 18.7 mo [13-24] with no 4-y survivor among the 45 pts without LM resection. In contrast, median OS was 35 mo [31-40] in the 19 resected patients, with 45% [10.3 - 79.7] survival at 4-y (p<0.001). **Conclusions:** The combination of IV-CET with HAI-IFO deserves upfront evaluation as a most effective neoadjuvant treatment option within a medico-surgical strategy aiming at the eradication of LM-CRC. Clinical trial information: NCT00852228.

**3590 General Poster Session (Board #53), Sat, 8:00 AM-11:45 AM**

**Benefit of EGFR-inhibition therapy for metastatic colorectal cancer patients with KRAS-mutated tumors and high plasma TIMP-1 level: Results from the NORDIC VII study.** *Presenting Author: Nils Brunner, Department of Veterinary Disease Biology, Faculty of Health and Medical Sciences, University of Copenhagen, Frederiksberg, Denmark*

**Background:** *RAS* status is the only biomarker to select patients with metastatic colorectal cancer (mCRC) for therapy with an epidermal growth factor receptor (EGFR) inhibitor. However, not all K*RAS*wild-type tumors respond to EGFR-inhibition, and some patients with mutated tumors may still benefit from therapy. To improve selection of patients for treatment with EGFR inhibitors, new biomarkers are needed. Plasma Tissue Inhibitor of Metalloproteinases-1 (TIMP-1) induces intracellular signalling activating the Akt-survival pathway, and we hypothesize that high TIMP-1 levels interact with the signalling of EGFR and thereby with the anti-tumor effects of EGFR inhibitors. The present study tests the above hypothesis in patients included in the NORDIC VII Study. **Methods:** mCRC patients were randomized to Nordic FLOX +/- cetuximab (Tveit et al., JCO, 2012). Pre-treatment plasma samples (n=426) were analysed for TIMP-1 using the MAC15 antibody kinetic ELISA. **Results:** Univariate Cox analyses including all patients showed that high pre-treatment plasma TIMP-1 was significantly associated with shorter PFS (P = .003), and OS (P < .0001). Multivariate analysis (not including treatment) demonstrated that high plasma TIMP-1 was an independent biomarker of OS (P = .016). A significant interaction between plasma TIMP-1, *KRAS* status and treatment (+/- cetuximab) was demonstrated for OS (P = .002). Patients with *KRAS* mutated tumors and high TIMP-1 level (> 3$^{rd}$quartile) had a significantly longer OS if treated with cetuximab (HR, .48; 95% CI, .25 to .93) compared to patients not treated with cetuximab. **Conclusions:** Patients with KRAS mutated tumors and a high plasma TIMP-1 level seem to benefit from EGFR-inhibition therapy. Based on these results we propose a novel hypothesis on the interaction between EGFR-1 signalling and TIMP-1.

**3591 General Poster Session (Board #54), Sat, 8:00 AM-11:45 AM**

**Coexisting KRAS and PIK3CA exon 20 mutations as a potential poor-prognosis factor in metastatic colorectal cancer (mCRC).** *Presenting Author: Maria Elena Elez Fernandez, Vall d'Hebron University Hospital, Barcelona, Spain*

**Background:** Molecular screening and biomarker enrichment strategies in mCRC clinical trials have demonstrated to have an impact in treatment benefit and prognosis. The data obtained from these strategies progressively incorporated in routine clinical practice, may lead to the obtention of relevant information to optimize treatment decisions. **Methods:** From 01/2011 to 12/2013, 415 patients (pts) with advanced chemorefractory mCRC underwent genetic tumor profiling as part of Vall d'Hebron University Hospital Phase I Trial Molecular Prescreening Program. Mutation (MT) profiling was performed by single-base extension chemistry followed by mass detection (MassARRAY, Sequenom) including 268 frequent hotspots in 25 oncogenes, among them, KRAS, BRAF, NRAS, and PIK3CA. **Results:** We found a KRAS MT incidence of 48% (199/415 pts), slightly above other reported studies. The PIK3CA, BRAF and NRAS MT rates were 14% (58/415), 6.5% (27/415) and 3% (12/415) respectively. Coexisting KRAS and PIK3CA MT were found in 44 out of 199 pts (22.1%). PIK3CA MT were more frequently detected in the helical domain (HD, exon 9) than in the kinase domain (KD, exon 20). Among KRAS wild type (WT) pts, HD *vs.* KD MT were detected at approximately a 2:1 ratio (8 HD, 4 KD), consistent with previous reports. Interestingly, in the KRAS MT background, the ratio of MT in HD *vs.* KD in PIK3CA was dramatically increased in our population with a 14:1 ratio (41 HD, 3 KD). Upon dissecting the KRAS MT group, we found G13D MT to show a very low coexistence with PIK3CA MT (3/36 pts, 8%) in contrast to other series in less heavily pretreated populations. **Conclusions:** This study represents a thorough profiling of frequent oncogene MT in mCRC. Our analysis shows that certain profiles such as coexisting KRAS and PIK3CA-KD MT or KRAS G13D and PIK3CA MT seem to be underrepresented in our heavily pretreated population. Therefore, these findings suggest that both groups would be of particular poor prognosis. Nevertheless, this observation must be confirmed in larger and prospective series representing overall mCRC population.

**3592^ General Poster Session (Board #55), Sat, 8:00 AM-11:45 AM**

**AIO KRK0306, FIRE3 trial: CEA and CA19-9 influence outcome of patients with KRAS exon wild-type metastatic colorectal cancer (mCRC) receiving first-line therapy with FOLFIRI plus cetuximab or bevacizumab.** *Presenting Author: Marlies Michl, Department of Hematology and Oncology, Klinikum Großhadern and Comprehensive Cancer Center, LMU Munich, Munich, Germany*

**Background:** To examine the impact of tumor marker response of carcinoembryonic antigen (CEA) and carbohydrate-antigen 19-9 (CA19-9) on overall survival (OS) and progression free survival (PFS) in patients with KRAS wild-type mCRC receiving first line chemotherapy in the FIRE3-trial comparing FOLFIRI + cetuximab (cet) vs. FOLFIRI + bevacizumab (bev). **Methods:** Baseline tumor marker levels, the time to nadir (in days; d) and the percentage of tumor marker decrease observed at the nadir compared with baseline were analyzed. The percentage was 0 for no change and negative if the tumor marker increased. Comparisons relied on Mann-Whitney U tests for independent groups and Wilcoxon signed-rank tests for dependent ones. ROC analysis resulted in a cut-off value using the maximum of sensitivity and specificity for best response. **Results:** For analysis of CEA, 472/592 pts (cet arm: 230 pts; bev arm: 242 pts) were eligible and for CA19-9, 439/592 pts (cet arm: 209 pts; bev arm: 230 pts). Baseline CEA (log) and CA19-9 (log) levels both significantly correlated with OS ($p=0.008$ and $p<0.0001$, respectively), but not with PFS ($p=0.26$ and $p=0.15$, respectively). For CEA and CA19-9 median time to nadir was comparable for both study arms, however in all patients CA19-9 nadir occurred earlier than CEA nadir ($p<0.0001$). Extent of CEA nadir significantly differed between treatment arms (cet arm: median: 83.0%; IQR: 40.9%-94.7%; bev arm: median: 72.3%; IQR: 26.3%-91.0%; $p=0.003$). A similiar trend was observed for CA19-9 nadir (cet arm: median: 64.3%; IQR: 13.4%-90.7%; bev arm: 47.0%; IQR: 1.7%-86.4%; $p=0.085$). In univariate analysis, a CEA decrease of more than 75% correlated with longer OS (33.2 vs. 22.9 mo; $p<0.0001$; HR 0.63; 95%CI: 0.50–0.80) and PFS (11.7 vs. 9.0 mo; $p=0.007$; HR 0.67; 95%CI: 0.62–0.93). **Conclusions:** In this analysis, we demonstrate that a greater decrease of CEA during therapy correlates with longer survival and the depth of CEA decrease is significantly greater in the cetuximab-arm compared to the bevacizumab-arm. Clinical trial information: NCT00433927.

**3593 General Poster Session (Board #56), Sat, 8:00 AM-11:45 AM**

**Constitutive single nucleotide polymorphisms (SNP) assessment for predicting tolerability and efficacy of triplet hepatic artery infusion (HAI) and intravenous cetuximab (IV-CET) in patients (pts) with liver metastases from colorectal cancer (LM-CRC) (European trial OPTILIV, NCT00852228).** *Presenting Author: Francis Levi, Medical Oncology Department, INSERM U776, Paul Brousse Hospital, Villejuif, France*

**Background:** The combination of IV-CET and HAI of irinotecan , oxaliplatin and 5-fluorouracil displayed high activity as 2-4$^{th}$chemotherapy line for initially unresectable wt KRAS LM-CRC, yielding a macroscopic complete resection rate (R0+R1) of 29.7% and an overall survival of 25.7 months (Ducreux, ASCO 2013). The purpose is to identify the pts whose constitutive SNPs predict for best outcomes on this neoadjuvant protocol. **Methods:** 192 constitutive SNPs from 36 pharmacogenetically-relevant genes were analysed in pt blood cells using the ADME PGx panel with the MassArray platform (Sequenom, USA). Relations between polymorphic genes with minor SNPs and grade distribution for main toxicities per pt over 6 courses, best tumor response, and R0+R1, were explored using Mann Whitney or Fisher Exact test. **Results:** Gene polymorphisms were assessed in 52/64 registered pts with unresectable LM-CRC (16F; 36M), aged 33-76 years with good PS (0-1: 98%) receiving IV-CET + IFO-HAI as 2$^{nd}$ line for 21 pts (40%) and 3$^{rd}$-4$^{th}$line for 31 pts (60%). Main grade 3-4 toxicities were neutropenia (40%), abdominal pain (29%), fatigue (21%), and diarrhea (17%). Objective response was achieved in 20 pts (39%). Secondary R0-R1 LM resection was performed in 14/52 pts (27%). None of the minor SNPs in the 36 genes studied was a potential predictor of LM resection, nor displayed any significant relation with pt characteristics except for Cyp2C19 and sex ($p<0.05$). Best objective response was associated with minor SNPs in SLC22A2 ($p=0.049$) and UGT2B15 ($p=0.011$). Neutropenia, fatigue and diarrhea were associated with minor SNPs in Cyp2C19 ($p<0.05$). Neutropenia was further related to minor SNPs in Cyp1A2 ($p = 0.017$) and SLC22A1 ($p=0.027$), while diarrhea was predicted by minor SNPs in Cyp2D6A ($p<0.05$). **Conclusions:** This selected pharmacogenetics analysis revealed six genes involved in drug metabolism and transport whose minor SNPs predicted safety and efficacy outcomes and could warrant treatment adjustment for pts on neoadjuvant triplet HAI and IV-CET for LM-CRC. Clinical trial information: NCT00852228.

**3594 General Poster Session (Board #57), Sat, 8:00 AM-11:45 AM**

**The role of JAK1/2-STAT3 as acute resistance mechanism to MEK inhibition in BRAF-mutant colorectal cancer cell lines.** *Presenting Author: Basak Celtikci, Queen's University, CCRCB, Belfast, United Kingdom*

**Background:** Oncogenic mutations in *BRAF* occur in 8% of patients with advanced colorectal cancer (CRC) and have been shown to correlate with poor prognosis. In contrast to *BRAF* mutant (MT) melanoma, where the BRAF inhibitor Vemurafenib (PLX4032) has shown significant increases in response rates and overall survival, only minor responses to Vemurafenib treatment have been reported in *BRAF*MT CRC. Clear understanding of the vulnerabilities of *BRAF*MT CRC is important, and identification of druggable targets uniquely required by *BRAF*MT CRC tumours has the potential to fill a gap in the therapeutic armamentarium of advanced CRC. The aim of this study was to identify novel resistance mechanisms to MEK inhibition in *BRAF*MT CRC. **Methods:** Paired *BRAF*MT/WT RKO and VACO432 CRC cells and non-isogenic *BRAF*MT LIM2405, WiDR, HT-29 and COLO205 CRC cells were used. Changes in protein expression/activity were assessed by Western Blotting. Interactions between MEK1/2 and JAK1/2 or c-MET inhibition were assessed using the MTT cell viability assays and Flow Cytometry. Apoptosis was measured using Western Blotting for PARP, cleaved caspase 3, 8 and 9, and caspase 3/7 and 8 activity assays. **Results:** Treatment with MEK1/2 inhibitors AZD6244, trametinib, UO126 and PD98059 resulted in acute increases in STAT3 activity in the *BRAF*MT RKO and VACO432 cells but not in their *BRAF*WT clones and this was associated with increases in JAK2 activity. Inhibition of JAK/STAT3 activation using gene specific siRNA or small molecule inhibitors TG101348 or AZD1480, abrogated this survival response and resulted in synergy and significant increases in cell death when combined with MEK1/2 inhibitors AZD6244 or trametinib in *BRAF*MT CRC cells. The RTK c-MET is activated upstream of STAT3 following MEK1/2 inhibition. Inhibition of c-MET and MEK1/2, using pharmacological inhibitors (crizotinib and AZD6244), results in synergy and increased cell death in *BRAF*MT CRC cells. **Conclusions:** We have identified JAK/STAT3 activation as an important escape mechanism for *BRAF*MT CRC following MEK1/2 inhibition in vitro. Combinations of JAK/MEKi or MET/MEKi can be a potential novel treatment strategy for poor prognostic *BRAF*MT advanced CRC patients.

**3595 General Poster Session (Board #58), Sat, 8:00 AM-11:45 AM**

**Clinical course of patients with oxaliplatin-associated neuropathy: N08CB (Alliance).** *Presenting Author: Deirdre R. Pachman, Mayo Clinic, Rochester, MN*

**Background:** Oxaliplatin is commonly associated with acute neuropathy, as well as a more troublesome chronic neurotoxicity. Details regarding the clinical course of these toxicities are not well defined. **Methods:** Acute and chronic oxaliplatin-induced peripheral neuropathy were evaluated in patients with colon cancer receiving adjuvant FOLFOX (fluorouracil, leucovorin, oxaliplatin) in a previously reported calcium/magnesium neuropathy prevention trial (Loprinzi JCO 2013). Acute neuropathy was assessed using daily questionnaires for 6 days starting with each cycle of FOLFOX. Chronic neurotoxicity was assessed using the EORTC QLQ-CIPN20 tool before each dose of oxaliplatin and at 1, 3, 6, 12, and 18 months after chemotherapy. **Results:** 89% of patients (308/346) had at least one acute neuropathy symptom (Sx) with the first cycle of FOLFOX: sensitivity to touching cold items (71%), sensitivity to swallowing cold items (71%), throat discomfort (63%), or muscle cramps (42%). Acute neuropathy Sx occurred within a day after oxaliplatin, peaked at day 3, then improved. These Sxs, however, did not resolve completely between treatments and were about twice as severe in cycles 2-12, than in cycle 1. Cycle 1 acute neuropathy Sx severity predicted acute Sx severity in subsequent cycles. Regarding the chronic neurotoxicity, tingling was the most severe Sx (1.91 out of 1-4), followed by numbness (1.72), and then pain (1.28). During chemotherapy, hand Sxs (1.70) were more prominent than feet Sxs (1.57). Following chemotherapy completion, sensory Sxs initially continued to worsen, on average, with improvement beginning approximately 3 months post-chemotherapy. By 18 months, residual numbness/tingling was more severe in feet than in hands. Patients with more severe acute neuropathy during the first cycle of therapy had more chronic sensory neurotoxicity ($P<0.0001$). **Conclusions:** Acute oxaliplatin-associated neuropathy Sxs do not completely resolve between treatment cycles and are only half as severe on the first cycle compared with subsequent cycles. There is a correlation between the severity of acute and chronic neuropathy. Hand Sxs are more severe during therapy, while feet symptoms become more prominent during follow up. Clinical trial information: NCT01099449.

**3596 General Poster Session (Board #59), Sat, 8:00 AM-11:45 AM**

**Modified FOLFOXIRI plus cetuximab (cet) as induction treatment in unresectable metastatic colorectal cancer (mCRC) patients (pts): Preliminary results of the phase II randomized Macbeth trial by GONO group.** *Presenting Author: Chiara Cremolini, U.O. Oncologia Medica 2, Azienda Ospedaliero-Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy*

**Background:** Phase II trials investigated the combination of a triple chemotherapy regimen with anti-EGFR monoclonal antibodies reporting promising activity but some concerns about the safety profile. The optimal maintenance regimen to be adopted following chemotherapy + an anti-EGFR is also not well established. The aims of MACBETH trial are to evaluate the activity and safety of 1st-line mFOLFOXIRI plus cet and to explore the role of maintenance with cet or bev in unresectable and molecularly selected mCRC pts. The study initially enrolled *KRAS* exon 2 wt pts, but after amendment only *RAS* and *BRAF*wt pts were eligible. **Methods:** Pts are randomized to receive an induction treatment of up to 8 cycles of mFOLFOXIRI + cet (cet 500 mg/sqm, irinotecan 130 mg/sqm, oxaliplatin 85 mg/sqm, 5 l-LV 200 mg/sqm, 5FU infusion 2400 mg/sqm over 48h q2w), followed by cet until disease progression (PD) or the same regimen followed by bev until PD. Primary endpoint is 10 months-Progression Free Rate (10m-PFR). Target accrual is 136 pts. **Results:** Between November 2011 and January 2014, 212 pts were screened and 94 pts were randomized in 18 Italian centers. At the data cut-off of Dec 2013, 72 pts completed the induction phase. Pts' characteristics were: median age 59 yrs, ECOG PS 0 92%, synchronous metastases 79%, multiple sites of disease 60%, *NRAS* mutated 4.2%, *BRAF* mutated 2.8%. The median number of administered cycles was 8. Main grade 3-4 toxicities were neutropenia (34.7%), febrile neutropenia (2.7%), diarrhoea (21.3%), skin rash (14.7%), stomatitis (6.7%), neurotoxicity (2.7%). One (1.4%) and 50 (69.4%) pts achieved CR and PR, respectively (RR in the intention to treat population: 70.8%). Ten (13.9%) pts reported SD (DCR: 84.7%) and 4 (5.6%) progressed. Seven (9.7%) pts did not undergo response assessment. Out of 65 pts evaluable for RECIST response, RR and DCR were 78.5% and 93.8%, respectively. **Conclusions:** A short "induction" treatment with mFOLFOXIRI + cet, according to the present schedule, shows a feasible safety profile with encouraging activity. The trial is still ongoing and updated results will be presented. Clinical trial information: 2011-000840-70.

**3597 General Poster Session (Board #60), Sat, 8:00 AM-11:45 AM**

**Molecular profiling of EGFR pathway according to location of colorectal cancer (CRC): Analysis of 1,001 patients in single institute.** *Presenting Author: Eiji Shinozaki, Department of Gastroenterology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan*

**Background:** Location of colon cancer (right-sided versus left-sided) was reported as a predictor of benefit from cetuximab in the subanalysis of NCIC CTG CO.17 trial. On the other hand, retrospective analyses have identified *KRAS* including codon61, codon146, *BRAF*, *NRAS*, or *PIK3CA* mutations as potentially negative predictive factors for anti EGFR treatments. This analysis aimed to reveal the prevalence of these mutations in the EGFR pathway according to location of CRC in a large cohort. **Methods:** Consecutive patients of 1,001 CRC from January 2012 to October 2013 were analyzed in this study. Multiplex genotyping of EGFR pathway was performed on archival samples using Luminex Assay (MABGEN and GENOSEARCH Mu-PACK, MBL) for *KRAS* including codons 61 and 146, *BRAF*, *NRAS*, and *PIK3CA*. We examined the correlation among mutation profile, clinical data and location of CRC. Statistical analysis was conducted by chi-square test. **Results:** The incidence of mutations; *KRAS* codon12 and 13, codon61 and 146, *BRAF*, *NRAS* and *PIK3CA* were 38%, 4.6%, 5.1%, 3.5% and 9.1%, respectively. So called all *RAS* mutations accounted for 47% in this cohort. The difference of prevalence according to the location of CRC was confirmed in *KRAS* codon 12 and 13, *BRAF*. The respective proportion of mutations were 55.9%, 14% for right sided(R), 30.6%, 5.5% for left sided(L), 37.2%, 1% for rectal(RC) CRC (*KRAS*: R vs L, RC $P<0.01$, *BRAF*: R vs L vs RC $P<0.01$). **Conclusions:** According to the location of CRC the incidence of *KRAS* codon 12 and 13, *BRAF* mutation were different. Increased *BRAF* mutation in R ,which was strong negative prognostic factor could affect unfavorable outcome of anti EGFR treatment.

**3598 General Poster Session (Board #61), Sat, 8:00 AM-11:45 AM**

**Compliance and safety of neoadjuvant intensity modulated radiotherapy (IMRT) with concurrent capecitabine for locally advanced rectal cancer: Updated results from a phase II trial (ChiCTR-TNC-10001094).** *Presenting Author: Yongheng Li, Peking University Cancer Hospital, Beijing, China*

**Background:** We have prospectively studied the neoadjuvant IMRT with concurrent capecitabine followed by TME for locally advanced rectal cancer to assess efficacy, compliance and toxicity in a phase II trial. Here, we report updated results. **Methods:** A total of 260 patients with clinical stage II-III mid-low rectal cancer received IMRT and surgery from December 2008 to May 2013. Patients received IMRT with gross targeting volume (GTV)/ clinical targeting volume (CTV) of 50.6/41.8 Gy in 22 fractions plus concurrent capecitabine (825 mg/m$^2$twice daily) in 30 days. The interval from IMRT to surgery is 6 to12 weeks. The short-term results were analyzed. **Results:** The compliance rate is 99.6%, one patient discontinued treatment following 17 fractions of radiation for diarrhea. There was no Grade 4 toxicity recorded. The incidence of Grade 3 toxicities is 5.8%, including: diarrhea (4.2%), neutropenia (1.5%) and radiation dermatitis (0.4%). The toxicity was listed in the Table. Pathological complete response occurred in 18.5% (48/260) of patients. Anastomotic leakage rate was 2.6% (4/152) in patients with sphincter preservation. Perineal wound infection (20.8%, 20/96) or skin dehiscence (8.3%, 8/96) were main complications in patients who received abdominoperineal excision. Surgical re-interventions were needed in three patients and no mortality was recorded. **Conclusions:** Neoadjuvant IMRT plus concurrent capecitabine for rectal cancer achieved high rate of pCR, excellent compliance and minor acute toxicity. This high intensity regimen might be considered as a component for intensified treatment with induction or consolidation chemotherapy to maximize the effect to achieve clinical complete response in future trials. Clinical trial information: 10001094.

**Toxicities during the neoadjuvant treatment.**

| Toxicity | Total (%) | G1 | G2 | G3 | G4 |
|---|---|---|---|---|---|
| Neutropenia | 116 (44.6%) | 90 (34.6%) | 22 (8.5%) | 4 (1.5%) | |
| Thrombocytopenia | 12 (4.6%) | 8 (3.1%) | 4 (1.5%) | | |
| Diarrhea | 231(88.8%) | 170 (65.4%) | 50 (19.2%) | 11 (4.2%) | |
| Radiation dermatitis | 235 (90.4%) | 210 (80.8%) | 24 (9.2%) | 1 (0.4%) | |
| Fatigue | 71 (27.3%) | 67 (25.8%) | 4 (1.5%) | | |
| Vomiting | 40 (15.4%) | 37 (14.2%) | 3 (1.2%) | | |

**3599 General Poster Session (Board #62), Sat, 8:00 AM-11:45 AM**

**Validation of the NSABP neoadjuvant rectal score (NAR) in a prospective phase II study evaluating an experimental regimen and a standard chemoradiation cohort with molecular genotyping.** *Presenting Author: Theodore S. Hong, Massachusetts General Hospital, Boston, MA*

**Background:** NSABP recently proposed replacing pCR with a new neoadjuvant rectal score (NAR) based on clinical downstaging from pre to post-treatment, pathologic (yp) stage. The NAR formula yields values from 0-100; higher scores indicate poor prognosis. In NSABP R04 (n=1479), the mean NAR = 15.61 with SD of 14.37, and OS hazard ratio/unit (HR) = 1.04 ($p<0.0001$). NAR showed a stronger association with OS than pCR, and was proposed as a new endpoint for phase II trials. We sought to evaluate the prognostic significance of NAR in two previously published datasets. **Methods:** Patient (pt) data from 2 IRB approved, previously published studies were used. Study 1 was a phase I/II study evaluating bevacizumab (bev) and erlotinib (erl) with neoadjuvant chemoradiation (CRT) (Ann Oncol 2014;25:121-6). Study 2 was a retrospective review of pts receiving 5-FU/RT (J Gastrointest Canc epub 2013, PMID24006244), with mutational analysis. All pts had pretreatment M0 and T3/4 or node + disease by MRI. Study 1 had 32 pts, with a pCR rate of 33%. Study 2 had 79 pts, with a pCR rate of 21.5%. NAR = [ 5pN- 3(cT-pT) + 12]$^2$/ 9.61 where pN = yp nodal stage (0,1,2), cT = clinical T-stage (1,2,3,4), and pT= yp T stage (0,1,2,3,4). The NAR score's association with DFS was tested as a pseudocontinuous variable in a Cox model, and is reported as a HR/unit. **Results:** In study 1, the mean NAR = 12.67 (SD =12.20): DFS HR 1.12 (1.04, 1.21, p=0.004). In study 2, mean NAR = 16.85 (SD = 16.17), DFS HR = 1.07 (1.03, 1.12, p=0.001). Mutational frequency in study 2 was KRAS 43%, APC 17%, BRAF 4%, NRAS 4%, PIK3CA 4%, TP53 11%. For study 2 pts with any mutation, mean NAR = 18.90 (SD =15.66): DFS HR 1.07 (1.01, 1.14, p=0.025). For study 2 pts with NO mutation, mean NAR = 13.85 (SD =16.69): DFS HR 1.07 (1.01, 1.13, p=0.004). **Conclusions:** Higher NAR was associated with worse DFS in a standard CRT cohort and an experimental phase II cohort, confirming the findings in NSABP R04. The mean NAR of 12.67 in the bev/erl study compares favorably to both NSABP R04 (15.61) and the retrospective CRT cohort (16.85). In study 2, pts with no mutation had a lower NAR than those with a mutation (13.85 vs 18.90), suggesting more favorable prognosis.

**3600 General Poster Session (Board #63), Sat, 8:00 AM-11:45 AM**

**Gender and tumor location as predictors for efficacy: Influence on endpoints in first-line treatment with FOLFIRI in combination with cetuximab or bevacizumab in the AIO KRK 0306 (FIRE3) trial.** *Presenting Author: Volker Heinemann, Department of Medical Oncology, Klinikum Grosshadern, University of Munich, Munich, Germany*

**Background:** FIRE-3 compared first-line therapy with FOLFIRI plus either cetuximab or bevacizumab in 592 KRAS exon 2 wild-type mCRC patients. We analyzed the efficacy dependent on gender and primary tumor location within the RAS wild-type population (n=342). **Methods:** Primary tumor location was defined as follows: right sided CRC (RCRC): coecum to hepatic flexure; left sided CRC (LCRC): splenic flexure to rectum. Colon transversum tumors (n=9) were excluded. Differences in response (ORR) and survival (PFS/OS) within both treatment arms were calculated using two-sided Fisher´s exact and logrank test, respectively. **Results:** In location wise comparison LCRC shows better efficacy results (ORR, PFS and OS) when compared with RCRC especially in the cetuximab arm (Table). Female gender has a trend towards lower tumor response rates, shorter PFS and OS when compared to male patients. **Conclusions:** MCRC is a heterogeneous disease. Treatment efficacy depends on primary tumor location and patients' gender. Effects were more prominent in patients receiving FOLFIRI plus cetuximab where male patients with LCRC tumors are favored.

| | FOLFIRI + Cetuximab n=167 | | | FOLFIRI + Bevacizumab n=166 | | |
|---|---|---|---|---|---|---|
| | RCRC n=30 | LCRC n=137 | p | RCRC n=39 | LCRC n=127 | p |
| ORR (%) | 46.7 | 70.1 | 0.019# OR: 2.7 | 48.7 | 62.2 | 0.14# OR: 1.7 |
| PFS (mo) | 6.9 | 10.8 | <0.0001* HR: 0.35 | 8.8 | 10.5 | 0.065* HR: 0.69 |
| OS (mo) | 16.1 | 38.7 | <0.0001* HR: 0.26 | 22.7 | 28.0 | 0.034* HR: 0.63 |
| | female n=44 | male n=123 | p | male n=54 | male n=112 | p |
| ORR (%) | 54.5 | 69.9 | 0.095# OR: 1.9 | 55.6 | 60.7 | 0.61# OR: 1.24 |
| PFS (mo) | 9.2 | 10.6 | 0.005* HR: 0.60 | 9.1 | 10.3 | 0.051* HR: 0.70 |
| OS (mo) | 27.9 | 36.4 | 0.12* HR: 0.71 | 25.9 | 24.8 | 0.8* HR: 1.05 |

Abbreviations: Bev, bevacizumab; Cet, cetuximab; OR, Odds ratio; HR, hazard ratio; mo, months. *= logrank p; #= two-sided Fisher's exact p.

**3601 General Poster Session (Board #64), Sat, 8:00 AM-11:45 AM**

**Survival following stage II/III colon cancer (CC): Accent-based comparison versus matched general population (MGP).** *Presenting Author: Lindsay A. Renfro, Mayo Clinic, Rochester, MN*

**Background:** The post-treatment survival experience of CC patients (pts) is well described in the literature, which states that cure is a probable outcome for some pts; formal survival comparisons vs. MGP are limited. **Methods:** Data from 32,745 pts enrolled to 25 randomized adjuvant trials conducted from 1977-2012 in 41 countries were pooled and 8 years of follow-up considered. The observed long-term survival experience of ACCENT pts was compared to the expected survival from a sex, age, country, and year MGP, overall and by stage (II, III), sex, treatment (surgery, 5FU, 5FU+oxaliplatin), age (< 70, 70+), year (pre/post 1990), and recurrence (Y/N). Comparisons were made at randomization (rand) and repeated conditional on survival to 1, 3, 5 years. CC/MGP equivalence was tested and observed Kaplan-Meier rates compared with expected MGP rates 3 years out from each landmark. **Results:** Within each ACCENT cohort, long-term survival of CC pts remained statistically worse than the MGP, though it improved over time given survival to certain landmarks. Among those surviving 5 years, stage II, oxaliplatin-treated, elderly, and recurrence-free pts achieved subsequent 3 year survival rates within 5% of the MGP; pts without recurrence had subsequent 3 yr. survival within 0.5% of MGP. **Conclusions:** Among CC pts on clinical trials who survive up to 5 years, subsequent long-term survival remains poorer than a MGP, but notably stage II, age 70+, received oxal, and recurrence-free pts achieve similar rates. These findings emphasize the need for access to quality care and the continued need for improved treatment/follow-up strategies.

**% Diff (MGP - CC) survival 3 yrs post baseline time point.**

| Baseline time point | All | Stage II | Stage III | Trt Surg | Trt 5FU | Trt Oxal | Age <70 | Age 70+ | Sex M | Sex F | 1990 Pre | 1990 Post | Recur Y | Recur N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rand | 14 | 4.8 | 18 | 19 | 14 | 8.6 | 15 | 12 | 13 | 15 | 17 | 14 | - | - |
| 5 yr | 5.2 | 2.8 | 6.6 | 7.1 | 5.2 | 4.5 | 5.7 | 3.1 | 5.2 | 5.3 | 5.8 | 5.1 | 46 | 0.5 |

**3602 General Poster Session (Board #65), Sat, 8:00 AM-11:45 AM**

**Genetic variants of TCF7L2 and AXIN2 predict gender and tumor location-dependent clinical outcome in FIRE-3 trial: A validation study.** *Presenting Author: Yan Ning, USC Norris Comprehensive Cancer Center, Los Angeles, CA*

**Background:** Wnt signaling pathway genes TCF7L2 and AXIN2 complex control the proliferation and differentiation of intestinal epithelial cells. Our previous study showed that TCF7L2 and AXIN2 polymorphisms(SNPs) were associated with clinical outcome of mCRC patients(pts) treated with first line FOLFIRI/BEV from TRIBE (arm A) and PROVETTA trials (n=455) (ASCO 2013#3566). Our data demonstrated that the association of TCF7L2rs7903146 and AXIN2 rs2240308 snps with PFS and OS is depended on gender and location. The goal of the current study was to prospectively validate our previous findings in mCRC pts enrolled in FIRE-3 clinical trial, which treated with either first line FOLFIRI/BEV or FOLFIRI/cetuximab. **Methods:** Genomic DNA was isolated from tissue samples of 592 pts (patient characteristics gender, median age median follow up) treated with first-line FOLFIRI/ bevacizumab (n=295) or FOLFIRI cetuximab (n=297) from the FIRE-3 trial (NCT00433927). All pts were KRAS exon 2 wild-type. The bevacizumab arm served as validation arm whereas the cetuximab arm served as control arm. **Results:** Our data validated that TCF7L2rs7903146 and AXIN2 rs2240308 snps could predict clinical outcome when adjusted by pts gender and tumor location. 1) In right-sided tumors, Female pts with any T allele of TCF7L2rs7903146 were associated with significantly longer PFS(median=13 mos) (HR: 0.38; 95% CI: 0.15, 0.97) in comparison to those carrying C/C genetype(median=5.7 mos, P = 0.04), which is consistent with our previous data. 2) In left-sided tumors, Female pts with AXIN2 rs2240308 any A allele had shorter OS(median=24.8 mos)(HR: 2.87; 95% CI: 1.07,7.76; P = 0.026) compared to those with G/G variants(median=44.3 mos), which validated our previous data. No significant difference in control arm. **Conclusions:** In this study, we prospectively validated the predictive value of TCF7L2 rs7903146 and AXIN2 rs2240308 snps in mCRC pts treated with first-line FOLFIRI/BEV. More importantly, This is first time confirmed that this predictive value is dependent on gender and tumor location in over 900 mCRC pts, suggesting Wnt signaling may play different role in female vs male and in right vs left side tumors.

**3603 General Poster Session (Board #66), Sat, 8:00 AM-11:45 AM**

**Final results from NSABP protocol R-04: Neoadjuvant chemoradiation (RT) comparing continuous infusion (CIV) 5-FU with capecitabine (Cape) with or without oxaliplatin (Ox) in patients with stage II and III rectal cancer.** *Presenting Author: Carmen Joseph Allegra, National Surgical Adjuvant Breast and Bowel Project, University of Florida, Gainesville, FL*

**Background:** The two primary aims of NSABP R-04 were 1) Can the oral fluoropyrimidine, Cape be substituted for the standard of care in the curative setting of Stage II & III rectal cancer namely, CIV 5-FU, during neoadjuvant RT; and 2) Can the addition of Ox enhance the activity of fluoropyrimidine sensitized RT? **Methods:** Pts with clinical stage II or III rectal cancer undergoing preoperative RT (4,500cGy in 25 fractions over 5 wks + boost of 540cGy-1080cGy in 3-6 daily fractions) were randomly assigned to one of four chemotherapy regimens in a 2x2 design: CVI 5-FU (225mg/m$^2$ 5 days/wk), with or without intravenous Ox (50mg/m$^2$ /wk x 5) or oral Cape (825 mg/m$^2$ BID 5 days/wk), with or without Ox (50mg/m$^2$/wk x 5). The primary endpoint was local-regional (L-R) tumor control that included L-R tumor recurrence, less than a complete surgical resection, and no surgery for any reason. **Results:** From July 2004 to August 2010, 1,608 patients were randomly assigned and 99.2% were eligible for analysis. There were no significant differences in 3 year L-R tumor event rates (11.2 vs 11.8%), 5 year DFS (66.4 vs 67.7%), or 5 year OS (79.9 vs 80.8%) between regimens using 5-FU vs Cape; and, 11.2 vs 12.1%, 69.2 vs 64.2%, and 81.3 vs 79.0% for Ox vs no Ox for the three endpoints of L-R events, DFS, and OS. The addition of Ox was associated with significantly more overall and grade 3-4 diarrhea (p<0.0001). Three-year rates of L-R recurrence among all pts who underwent R0 resection ranged from 2.9 – 4.6%. An unplanned subset analysis did not show significant differences for the use of Ox regardless of T-stage or ypCR status. **Conclusions:** CVI 5-FU or oral Cape combined with RT produced similar outcomes for L-R control, DFS and OS, and establishes Cape as a standard of care in the pre-op rectal setting. Ox did not improve L-R failure rate, DFS, or OS for any patient risk group but did add significant toxicity. Molecular studies using this fully annotated tissue bank are on-going. Support: U10-CA-12027, U10-CA-37377, U10-CA-69651, U-10-CA-69974; Sanofi; Roche. Clinical trial information: NCT00058474.

**3604 General Poster Session (Board #67), Sat, 8:00 AM-11:45 AM**

**Circulating DNA as a strong multimarker prognostic tool in metastatic colorectal cancer patients.** *Presenting Author: Safia El Messaoudi, IRCM INSERM, Montpellier, France*

**Background:** The aim of our study was to evaluate the prognostic role of various circulating cell-free DNA (cfDNA) parameters in metastatic colorectal cancer (mCRC) patients. **Methods:** We used a novel method, termed Intplex, which determines simultaneously from plasma, total cfDNA concentration, cfDNA fragmentation level, *KRAS/BRAF* mutational status, and cfDNA mutation load (% of mutant cfDNA). These parameters were tested in a mCRC patient cohort (n=98), which enabled validation of plasma DNA as a liquid biopsy to detect *KRAS/BRAF* mutations using the STARD criteria . **Results:** Median overall survival (OS) of the patients of the full cohort was 22 months (IC 95% [16.9-28.1]). Data confirmed *BRAF* mutational status as an excellent factor of poor prognosis (median OS, 22.9 vs. 3.4 months; relative risk (RR)=8.9, (IC95% [3.1-25.4], P<0.001) compared to *KRAS* mutational status (RR=1.1, IC 95% [0.7-1.9], P=0.66). OS was statistically different in patient groups with lower total cfDNA concentrations (median=28.1 months) compared with those with higher total cfDNA concentrations (median=17.8 months) than the median (RR=1.94, IC 95% [1.2-3.2], P=0.009). By using the multivariate Cox model, total cfDNA conc. proved statistically to be a strong, independent prognostic factor (P=0.035). Median OS was 31.1 and 11.1 months (P=0.121; RR=1.8, IC 95% [0.9-3.8]) in patients with lower and higher mutation loads than the median (10.3%). This difference was confirmed statistically when considering the mutant cfDNA conc. median (i.e. 3.1 ng/ml, RR=2.4, P=0.015). The fragmentation level did not appear to discriminate patients with regards to survival. CEA level at the conventional threshold conc. (5 ng/ml) was as a moderate prognostic factor (OS, 27.1 vs. 21.8 months; RR=1.24, 95% IC [0.7-2.2], P=0.48). **Conclusions:** Our study demonstrates for the time in a large cohort of mCRC patients that in addition to providing an advantageous alternative to tumor-tissue analysis for point mutation detection, other cfDNA parameters, such as total conc. and mutation load, are strong prognostic factors. Thus, prospective studies are needed to confirm multi-marker cfDNA analysis as a simple tool to help define the best care management options.

**3605 General Poster Session (Board #68), Sat, 8:00 AM-11:45 AM**

**CpG island methylator phenotype (CIMP) and outcome differences for African Americans (AA) and Caucasians (C) treated with FOLFOX4 or the combination with bevacizumab (B) in patients (pts) with metastatic colorectal cancer (MCRC): Results from the Eastern Cooperative Oncology Group study E3200.** *Presenting Author: Edith P. Mitchell, Kimmel Cancer Center of Thomas Jefferson University, Philadelphia, PA*

**Background:** The relationship between race and poorer clinical outcomes with systemic chemotherapy in patients with metastatic colorectal cancer is uncertain. CIMP High has been associated with a lack of survival benefit from 5-fluorouracil (5FU)-based chemotherapy while conflicting results for chemotherapy combinations have been reported. We analyzed outcomes for AA and C patients enrolled in E3200 and evaluated for CIMP in pts with adequate tissue samples. **Methods:** A total of 820 pts enrolled in E3200 were randomized to one of three treatments: FOLFOX4, bevacizumab, or the combination. Overall survival (OS), progression free survival (PFS) and response rates (RR) and CIMP were analyzed according to race. Demographic information was collected by data management personnel at study sites and reported at registration. CIMP was analyzed in 281 pts with adequate tissue specimens; 261 were C and 20 AA. **Results:** There were no differences for AA and C in regards to number of metastatic sites, performance status, gender, prior therapy and age distribution. Prediction of tumor response did not differ according to treatment arm based on CIMP. AA had worse OS (p=0.03), PFS (p=0.08) and RR (p=0.02) than C pts. CIMP showed significant interaction with differences between AA and C pts. There was improved OS and PFS for C pts with CIMP values less than the median than those above while AA showed better survival with values greater than the median. **Conclusions:** These results suggest outcome differences based on race in the treatment of MCRC in pts may be associated with molecular features. Additional studies are required to elucidate the cause for the observed variation. [caption[Cox proportional hazards analyses comparing CIMP high versus CIMP low[/caption] Clinical trial information: NCT00897819.

| | All | C | AA |
|---|---|---|---|
| **OS HR** | 1.26 | 1.32 | 0.22 |
| **p-value** | 0.051 | 0.029 | 0.012 |
| **PFS HR** | 1.43 | 1.51 | 0.54 |
| **p-value** | 0.0048 | 0.0023 | 0.28 |

Interaction tests between CIMP and race: OS,p = 0.0004; PFS, p=0.0097.

**3606 General Poster Session (Board #69), Sat, 8:00 AM-11:45 AM**

**Impact of PI3K aberrations on efficacy of perifosine (P), x-PECT: A phase III randomized study of P plus capecitabine (PC) versus placebo plus capecitabine (C) in refractory metastatic colorectal cancer (mCRC) patients.** *Presenting Author: Cathy Eng, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** P is an oral, synthetic alkylphospholipid that affects several signaling pathways, including PI3K/Akt. The X-PECT trial randomized 468 patients (pts) to PC (50 mg po QD) or C (1000 mg/m$^2$BID, D1-14 q21D). We hypothesized pts having PI3K aberrations (PIK3CA and PTEN loss) would derive greater benefit from P for response rate, progression-free survival (PFS) and/or overall survival (OS). X-PECT did not meet its primary endpoint of OS (p = 0.32). Here we present the final tissue correlatives. **Methods:** Archival formalin-fixed paraffin-embedded (*FFPE)*tissues were requested on all pts. Sequenom MassARRAY (MALDI-TOF MS) was utilized for detection of *PIK3CA, PI3KR1, Akt, Ras,* and *Raf* mutations (MT). *PTEN* expression was assessed by IHC. Reverse phase protein array (RPPA) was evaluated in fresh frozen specimens, paired pre- and post-one cycle from pts at MD Anderson. Kaplan-Meier method was used to estimate median OS and PFS; Cox proportional hazard regression analysis and log rank test were applied to evaluate OS and PFS with patient demographics and markers. Wilcoxon rank sum test and Fisher's exact test were performed for continuous or categorical variables. **Results:** 272 pts had FFPE tissue samples. 57% of pts were male. 45% of all pts had a *KRAS* MT; *NRAS* (1%); *BRAF* (3%); *PIK3CA* (9%); *Akt* (<1%), and loss of PTEN by IHC (16%). Loss of PTEN or *PIK3CA* MT were noted in 25% of pts. *Ras* WT was noted in 50% of all pts. Univariate analysis noted no difference for PFS for loss of PTEN/*PIK3CA* MT [p=0.32; HR= 0.81, (95% CI: 0.54-1.23)] or for *Ras*MT (p=0.11; HR=1.34, (95% CI: .93-1.92)]. RPPA data of 9 pts was available; only 6 pts (5 placebo pts) with paired pre- and on-treatment samples were evaluable. C alone was associated with reduction in p-Akt T308 (p=0.05), downstream target p-PRAS40 T246 (p=0.03), as well as proliferation marker PCNA (p<0.01). **Conclusions:** The presence of a *PIK3CA* MT or loss of PTEN occurred in 25% of refractory mCRC pts but did not improve the efficacy of perifosine. Capecitabine alone appeared to inhibit *Akt* signaling and proliferation. Additional studies are needed for validation. Clinical trial information: NCT01097018.

**3607 General Poster Session (Board #70), Sat, 8:00 AM-11:45 AM**

**Rechallenge with anti-EGFR–based therapy in metastatic colorectal cancer: Impact of intervening time interval and prior anti-EGFR response.** *Presenting Author: Xiaochun Liu, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** This retrospective study aims to investigate the activity of retreatment with anti-EGFR-based therapy in order to explore the concept of clonal evolution by evaluating the impact of prior activity and intervening time interval. **Methods:** One hundred and four *KRAS*-wild-type metastatic colorectal patients (pts) were re-treated on phase I or I/II clinical trials containing anti-EGFR therapy after progressing on prior cetuximab or panitumumab. Physician-recorded response (CR, PR, SD >=6 months) were used for prior treatment evaluation, and the best response per RECIST criteria were used for the re-treatment evaluation. The multivariate analysis was constructed with response on prior treatment, interval time between the two treatments, age, race, gender, Royal Marsden Hospital prognostic score, and performance status. **Results:** Pt characteristics were: 72% Caucasian, 66% < 60 years of age, 51% female gender, median PS 1, 84% normal albumin, and 76% elevated LDH levels. Re-treatment anti-EGFR agents were cetuximab (n=89) or cetuximab plus erlotinib (n=15). The median interval time between prior and re-treatment was 4.55 months (range: 0.46-58.7). Pts who responded to the prior cetuximab or panitumumab were more likely to respond to the re-treatment compared to the non-responders in both univariate ($p$ = 0.005) and multivariate analyses (OR: 3.45, 95% CI: 1.35, 8.85, $p$ = 0.01). The response rate in re-treatment also correlated with interval time between the two anti-EGFR based therapies ($p$ = 0.044). Moreover, median PFS on re-treatment was marginally increased in prior responders (4.37 months, 95% CI: 2.92, 5.82) compared to prior non-responders (2.37 months, 95% CI, 1.52, 3.22) in univariate ($p$ = 0.056) and multivariate analysis (HR: 0.67, 95% CI: 0.42-1.08, $p$ = 0.101). **Conclusions:** Our data supports the concept of clonal evolution though the impact appears less robust than previously reported (Santini et al. 2012). Further work to validate which pts benefit from re-challenge treatment post progression is needed.

**3608 General Poster Session (Board #71), Sat, 8:00 AM-11:45 AM**

**S-1 plus oxaliplatin versus capecitabine plus oxaliplatin for first-line treatment of patients with metastatic colorectal cancer: Updated results from a phase 3 trial.** *Presenting Author: Young Suk Park, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

**Background:** We report updated progression free survival (PFS) and overall survival (OS) data from the trial which compared capecitabine plus oxaliplatin (COX) vs S-1 plus oxaliplatin (SOX) for first line treatment with metastatic colorectal cancer. **Methods:** This trial was a randomised, two arm, non-inferiority phase 3 comparison of COX (capecitabine 1000 mg/m2 twice daily on days 1-14 and oxaliplatin 130 mg/m2 on day 1) vs SOX (S-1 40mg/m2 twice daily on days 1-14 and oxaliplatin 130 mg/m2 on day 1). The primary end point was to show non-inferiority of SOX relative to COX in terms of PFS. A follow-up exploratory analysis of PFS and OS was performed. **Results:** The intent to treat (ITT) population comprised 340 patients (SOX arm: 168 and COX arm: 172). Updated median PFS was 7.1 months (95% CI 6.4-8.0) in the SOX group and 6.3 months (4.9-6.7) in the COX group (hazard ratio[HR], 0.83 [0.66-1.04]; p=0.10). The median OS was 19.0 months (15.3-23.0) in the SOX group and 18.4 months (14.1-20.7) in the COX group (HR, 0.86 [0.68-1.08]; p=0.19). Subgroup analyses according to principal demographic factors such as sex. age, ECOG performance status, primary tumour location, measurability, previous adjuvant therapy and number of metastatic organs and liver metastasis showed no interaction between treatment and any characteristic. **Conclusions:** Updated survival analysis shows that SOX is similar to COX, confirming the primary analysis for PFS. The SOX regimen could be an alternative first line doublet chemotherapy strategy for patients with metastatic colorectal cancer. Clinical trial information: NCT00677443.

**3609 General Poster Session (Board #72), Sat, 8:00 AM-11:45 AM**

**Single nucleotide polymorphisms (SNPs) in vascular endothelial growth factor (*VEGF*) family genes as predictive or prognostic biomarkers in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of the phase III MAX study.** *Presenting Author: Fiona J.M. Chionh, Ludwig Institute for Cancer Research, Melbourne, Australia*

**Background:** Adding bevacizumab (B) to chemotherapy (CT) improves survival outcomes in pts with mCRC. Pt subgroups benefiting most from B need to be identified. SNPs in genes for VEGF-A and its receptors VEGF-R1/–R2 can affect their expression/production. We hypothesised these may be prognostic and/or predictive biomarkers for response and survival outcomes in pts treated with CT and B for mCRC. **Methods:** We analysed tissue from 325 of 471 pts (69%) randomised to capecitabine (C), or C + B, or C + B + mitomycin for mCRC. We performed Taqman SNP genotyping assays on available (in order of preference) normal (51%), adenoma (2%), or malignant (47%) FFPE tissue. 16 candidate SNPs in *VEGF-A* ($n$ = 6), *-R1* ($n$ = 4), and *-R2* ($n$ = 6), all in Hardy-Weinberg equilibrium with minor allele frequency ≥ 10%, were analysed for associations between genotype and response rate (RR), progression-free survival (PFS) and overall survival (OS). We assessed if SNP genotypes were predictive of B efficacy using tests for B treatment - SNP genotype interactions. **Results:** Of the SNPs analysed, *VEGF-A* rs25648 major allele C was significantly associated with improved PFS and OS, including when adjusted for B treatment (Table), but not associated with RR ($p$= 0.30). Other than B treatment, no clinico-pathologic variables were associated with survival outcomes. There were no significant interactions between B treatment and any SNP genotypes. **Conclusions:** *VEGF-A* rs25648 was an independent prognostic biomarker for PFS and OS in pts with mCRC, with allele C conferring improved prognosis, but was not predictive of B efficacy. This finding is biologically plausible as rs25648 is in the *VEGF-A* 5'UTR/promoter region, and in previous studies the CC genotype has been associated with lower VEGF-A levels/expression.

| rs25648 genotype | Reference | HR (95% CI), median (months PFS | HR (95% CI), median (months OS | HR (95% CI) adjusted for B treatment PFS | HR (95% CI) adjusted for B treatment OS |
|---|---|---|---|---|---|
| CC $n$ = 236 | CT/TT $n$ = 82 | 0.66 (0.51 – 0.85), 8.6 *vs* 6.4 | 0.70 (0.52 – 0.92), 21.4 *vs* 17.3 | 0.61 (0.49 – 0.83) | 0.70 (0.55 – 0.92) |
| TT $n$ = 69 | CC/CT $n$ = 249 | 1.66 (1.25 – 2.19), 6.0 *vs* 8.5 | 1.53 (1.13 – 2.06), 17.0 *vs* 21.4 | 1.72 (1.25 – 2.19) | 1.53 (1.13 – 2.06) |

**3610 General Poster Session (Board #73), Sat, 8:00 AM-11:45 AM**

**Perturbations in PI3K pathway and cyclin dependent kinase (CDK) pathway to predict complete responders in CRC patients treated with ADAPT therapy.** *Presenting Author: Edward H. Lin, Seattle Cancer Care Alliance, Seattle, WA*

**Background:** Aspirin or selective COX-2 inhibitor may improve overall survival (OS) in colorectal cancer (CRC) patients with PIK3CA mutations. However, routine use of anti-inflammatory agents in metastatic CRC patients remains controversial. We showed that 3-year maintenance celecoxib, also a stemness inhibitor coupled with capecitabine in a two-step ADAPT (activating dormant tumor cells and potentiate targeting) therapy led to 40% complete responders (CR) whose median survival reached 92.7 months in patients with unresectable stage IV CRC (Lin et al. AACR LBA254). We sought to determine genetic aberrations and related pathways as predictor of CR to ADAPT therapy. **Methods:** We retrospectively reviewed 50 consecutive stage IV CRC patients who had achieved CR with ADAPT therapy alone or in conjunction with metastectomy between 2006-2012 at University of Washington. All patients were tested for a panel of 199 cancer-related genes (UW Oncoplex) with Illumina deep sequencing platform **Results:** We select first 25 patients as training set to derive classifier for CR versus none CR that were at first blind to biostaticians. We found that genes involved in the PI3K pathway were significantly mutated in the CR group whereas CDK pathways were altered in the none CR group ($p < 0.0001$, sensitivity 91.7%, specificity 76.9%). CR events were independent of other worst prognostic factors including K-ras, B-raf, and p53. In vitro treatment of CRC cell lines with ADAPT drugs confirms strongest PI3K pathway inhibition effects ($p = 0$) and cell cycle pathway ($p < 0.05$). Validation set analysis will be reported at the meeting. **Conclusions:** Altered PI3Kand CDK pathways predict CR from ADAPT therapy in advanced unresectable CRC patients. Ongoing retrospective and prospective phase II ADAPT studies intend to validate these above findings. Funded by Gateway for Cancer Research and Lyon Foundation.

**3611 General Poster Session (Board #74), Sat, 8:00 AM-11:45 AM**

**Functional genomic screens and identification of signaling pathways in oxaliplatin-resistance in colorectal cancer.** *Presenting Author: Niharika B. Mettu, Duke University Medical Center, Durham, NC*

**Background:** In colorectal cancer, many patients develop resistance to oxaliplatin, which is a challenge given the limited number of therapeutic options in the treatment of this disease. While many mechanisms have been purported to explain the etiology of resistance to oxaliplatin in colorectal cancer, the role of intracellular signaling pathways that may be implicated in this phenomenon is not well-understood. **Methods:** We performed a functional genomic screen using a lentiviral overexpression system, in order to identify pathways that conferred a survival advantage to 2 patient-derived colorectal cancer cell lines treated with oxaliplatin in vitro. We classified 20 patient-derived colorectal cancer xenografts as either sensitive or resistant to oxaliplatin based upon tumor growth inhibition, and performed affymetrix microarray analysis on a representative mouse for each xenograft. This gene expression data was used to perform gene set enrichment analysis (GSEA, Gene Pattern) to identify pathways associated with resistance in vivo. We validated the importance of the pathway we identified in vitro using GI50 curves and in vivo by pharmacologically inhibiting the pathway and measuring effect on tumor volume in the absence and presence of oxaliplatin. **Results:** From our functional genomic screen, we found upregulation of the Wnt pathway in oxaliplatin-resistant, patient-derived colorectal cancer cell lines. GSEA identified Wnt pathway upregulation in oxaliplatin-resistant tumors treated with oxaliplatin. Activation of the Wnt pathway conferred oxaliplatin-resistance to patient-derived colorectal cancer cell lines in vitro. And finally, treatment of a patient-derived colorectal cancer xenograft with the Wnt inhibitor niclosamide was able to resensitize the tumor to oxaliplatin in vivo. **Conclusions:** Our study shows that functional genomic screening approaches can be utilized to identify novel targets that can be used to overcome resistance to therapy, and suggests that Wnt pathway inhibition may be able to resensitize colorectal cancer to oxaliplatin.

**3612 General Poster Session (Board #75), Sat, 8:00 AM-11:45 AM**

**Surveillance for asymptomatic recurrence in resected stage III colon cancer (CC): Does it result in a more favorable outcome?** *Presenting Author: Martin Smoragiewicz, British Columbia Cancer Agency, Vancouver, BC, Canada*

**Background:** Evidence supports a modest survival benefit for intensive post-treatment surveillance following potentially curative resection of CC. However, no studies so far included only patients with stage III CC, who have the highest risk of recurrence. **Methods:** Medical records of patients who initiated adjuvant chemotherapy (AC) with either 5-FU or capecitabine plus oxaliplatin for stage III CC between 2007 and 2011 at the BC Cancer Agency were reviewed. Kaplan-Meier and log rank test were generated to investigate whether diagnosis of recurrence based on symptoms was associated with worse OS. OS1 was considered from date of recurrence to date of death or last FU. OS2 was considered time from surgery (sg) to date of death or last follow-up (FU). **Results:** Of635 pts who received oxaliplatin-based AC for stage III colon cancer, 176 patients (27.7%) have recurred and 118 (18.6%) have died at a median FU of 57.9 months. Recurrence was detected based on CEA elevation (G1) in 72 (41.1%) pts, abnormal imaging (G1) in 77 (44%) and symptoms (G2) in 26 (14.9%). Median time from sg to recurrence was shorter in G1 as compared to G2 (18.5 vs 25.7 months, p=0.003, HR 0.501). Median OS1 was significantly prolonged in G1 as compared to G2 (26.7 vs 6.5 months, p<0.001, HR 0.393). However, median OS2 was not statistically different between G1 and G2 (49.8 vs 40.1, p=0.327, HR 0.776). Patients with surveillance detected recurrence underwent significantly more potentially curative metastasectomy than patients with recurrence detected due to symptoms (33% vs 8%, p= 0.014). **Conclusions:** In our population-based study, patients who were symptomatic at the time of recurrence were diagnosed later than those detected by abnormal CEA or imaging and had shorter OS1. However, OS2 was similar in both groups adjusting for the effect of lead time bias. Surveillance for asymptomatic recurrence may still provide an opportunity for curative metastasectomy but the overall survival impact is unclear.

**3613 General Poster Session (Board #76), Sat, 8:00 AM-11:45 AM**

**Association between body mass index and all-cause mortality in colorectal cancer patients: A meta-analysis of prospective cohort studies.** *Presenting Author: Junga Lee, Yonsei University, Seoul, South Korea*

**Background:** Studies have reported conflicting results on association between body mass index (BMI) and colorectal cancer-specific mortality and all-cause mortality in colorectal cancer patients. **Methods:** We performed a meta-analysis of 13 prospective cohort studies to identify the association between BMI (pre-diagnosis BMI or post-diagnosis BMI) and mortality outcome measures. Random-effects meta-analyses were performed to determine the risk ratio (RR) and 95% confidence interval (CIs). The analysis included 52,278 patients followed up over a period ranging from 4.9 to 20 years (median: 9.9 years). **Results:** We found that pre-diagnosis underweight was associated with increased all-cause mortality (RR: 1.62, 95% CI: 1.18-2.23, $p<0.01$) and obesity (BMI $\geq$ 30 kg/m$^2$) was associated with increased colorectal cancer-specific mortality (RR: 1.20, 95% CI: 1.07-1.36, $p<0.01$) and all-cause mortality (RR: 1.24, 95% CI: 1.12-1.38, $p<0.01$). On the other hand, post-diagnosis underweight (RR: 1.33, 95% CI: 1.19-1.47, $p<0.01$) and class II/III obesity (BMI $\geq$ 35 kg/m$^2$; RR: 1.13, 95%CI: 1.03-1.14, $p<0.01$) were associated with significantly increased all-cause mortality. When subgroup analysis according to gender was conducted, post-diagnosis obesity was associated with increased all-cause mortality (RR: 1.131, 95% CI: 1.054-1.213, $p<0.01$) in women only. **Conclusions:** Being obese prior to diagnosis of CRC was associated with CRC specific mortality and all-cause mortality, while being underweight and obesity after diagnosis was associated with increased all-cause mortality. Maintaining a normal body weight should be recommended to all individuals including colorectal cancer patients. This study was supported by National Research Foundation of Korea (2013 K2A1A2054437).

**3614 General Poster Session (Board #77), Sat, 8:00 AM-11:45 AM**

**Timing of adjuvant therapy in stage II-III colorectal cancer.** *Presenting Author: Lucas Vieira dos Santos, Instituto de Ensino e Pesquisa São Lucas, São Paulo, Brazil*

**Background:** Delay in commencing adjuvant therapy for colorectal cancer seems to impair survival in some retrospective studies. This is a large, bi-institutional retrospective study evaluating the impact of chemotherapy delay in survival. **Methods:** The interval between the primary surgery and the start of adjuvant chemotherapy was calculated. Survival was estimated using Kaplan-Meier method and the impact of multiple prognostic factors on survival by Cox Regression. **Results:** By the end of 2012, 2143 colorectal patients treated by surgery were identified from a retrospective database in two Brazilian institutions. Only stage II and III colorectal patients were selected, comprising 1963 patients, and 1318 patients received adjuvant chemotherapy (46% of patients started adjuvant chemotherapy within 6 weeks of surgery). The median follow up were 36 months. Patients starting chemotherapy within 6 weeks of surgery (vs. after 6 weeks) had longer overall survival (median not reached, HR 0.742, 95%CI 0.59-0.93, p=0.011). In the multivariate analysis, age, place of origin, stage, histological grade, emergency surgery, pre-operative therapy and radiotherapy were independent prognostic factors, but the interval between surgery and start of adjuvant therapy was not (HR 0.909, 95%CI 0.717-1.154, p=0.435). Sensitivity analysis using showed similar results. **Conclusions:** In this large retrospective study, the classic prognostic factors impacted on survival, and the timing of adjuvant therapy did not. Patients with delayed chemotherapy may harbor worst prognostic factors. Further investigation is warranted.

**3615 General Poster Session (Board #78), Sat, 8:00 AM-11:45 AM**

**IMPACT trial: Predictive factors for maintenance therapy with MGN1703 in patients with metastatic colorectal carcinoma.** *Presenting Author: Jorge Riera-Knorrenschild, Universitätsklinikum Giessen und Marburg, Marburg, Germany*

**Background:** The immunomodulator MGN1703, a TLR-9 agonist, has shown good safety profile in patients with metastatic solid tumors. The IMPACT trial was conducted to assess clinical efficacy, safety, and immunological effects of MGN1703 as maintenance therapy twice weekly. **Methods:** The international randomized (2:1) double-blind placebo-controlled phase 2 IMPACT trial in mCRC patients with disease control after 1st-line chemotherapy by FOLFOX/XELOX or FOLFIRI +/- bevacizumab. After randomization of 59 out of 129 planned patients (43 MGN1703, 16 placebo) the trial was prematurely closed due to slow recruitment. **Results:** A superior effect of MGN1703 compared to placebo was shown: HR for the primary endpoint PFS on maintenance was 0.55 (p=0.041) by local and 0.56 (p=0.070) by independent assessment. For PFS from start of induction therapy the HR was 0.50 (p=0.022) and 0.49 (p=0.030), respectively. Notably, at time of study closure 4 MGN1703 patients were still free of PD and continued in compassionate use. A possible predictive effect was identified by Cox regression analyses: HR of 0.07 (p<0.0001) for patients with normal CEA and 0.39 (p=0.005) for patients with an objective response. Evaluation of biological activity via cell populations and chemokine serum levels confirmed immune system activation in MGN1703 patients. Cox regression and ROC analyses identified of activated NKT-cells ($CD3^+/CD56^+/CD69^+$) at baseline as potentially predictive for a benefit from MGN1703 treatment (HR: 0.27, p=0.007). Study treatment was well tolerated: 32.6% vs. 18.8% of patients (MGN1703 vs. placebo) had drug-related AE and in only 1 patient per arm it was of grade 3 (MGN1703: sensory polyneuropathy, placebo: papular exanthema). Seven SAEs were reported of which only 1 was possible drug-related (moderate atypical pneumonia). **Conclusions:** Following induction chemotherapy, MGN1703 maintenance in mCRC patients is associated with improved PFS and an activation of the innate and adaptive immune system. Treatment was safe and well tolerated. There is preliminary evidence that CEA levels, tumor response, and activated NKT cells before start of MGN1703 therapy allow for identification of benefitting patients. Clinical trial information: NCT01208194.

**3616 General Poster Session (Board #79), Sat, 8:00 AM-11:45 AM**

**Improved disease-free survival with intraportal chemotherapy plus adjuvant chemotherapy (mFOLFOX6) as adjuvant treatment in colon cancer.** *Presenting Author: Wenju Chang, Fudan University, Shanghai, China*

**Background:** The optimal time from surgery to the start of chemotherapy in colon cancer is unknown. We evaluated the impact on survival of intraportal chemotherapy (IPC) administrated during surgery plus adjuvant chemotherapy (AC) as treatment for stage II and III colon cancer. **Methods:** Patients with stage II or stage III colon cancer were randomly assigned to receive IPC plus mFOLFOX6 (OCTREE) or mFOLFOX6 alone. The primary end point was disease-free survival (DFS). Secondary endpoints included metastasis-free survival (MFS), overall survival (OS) and safety. **Results:** The intent-to-treat population comprised 237 patients. After a median follow-up of 44 months, The 3-year DFS rate was 85.2% (95% CI 81.9 to 88.4) with OCTREE and 75.6% (95% CI 71.7 to 79.4) with mFOLFOX6 alone ($P = .030$). The hazard ratio (OCTREE versus mFOLFOX6) was 0.66 (95% CI, 0.43 to 0.90, $P = .016$). The 3-year MFS rates were 87.6% versus 78.0%, when compared OCTREE with mFOLFOX6, the hazard ratio was 0.59 (95% CI, 0.38 to 0.92, $P = .023$). Patients in OCTREE arm had decreased distant metastases events (12.7% versus 22.7%; $P = .044$) compared with those in mFOLFOX6 arm. Grade 3 hepatic toxicity was observed in 1.7% of patients receiving OCTREE within two weeks after surgery, and could be cured with medicine. Only one patient died as a result of any cause within 6 months of receiving chemotherapy, with no significant difference between regimens. **Conclusions:** Intraoperative intraportal chemotherapy combined with mFOLFOX6, reduced the occurrence of distant metastasis, and therefore improved DFS in patients with stage II and stage III colon cancer. Clinical trial information: NCT01972503.

**3617 General Poster Session (Board #80), Sat, 8:00 AM-11:45 AM**

**Randomized phase III trial of FOLFOX versus XELOX as adjuvant chemotherapy in patients with early-stage colorectal adenocarcinoma.** *Presenting Author: Dimitrios G. Pectasides, Hellenic Cooperative Oncology Group (HeCOG), Athens, Greece*

**Background:** The aim of the trial was to compare two active adjuvant chemotherapy regimens in patients with early stage colorectal cancer (CRC). **Methods:** Patients were assigned to oxaliplatin 85 mg/m$^2$ as a 2-h iv infusion (d1), given concurrently with leucovorin 200 mg/m$^2$, followed by 5-FU 400 mg/m$^2$ as an iv bolus (d1) and 5-FU 2400 mg/m$^2$ as a 46-h iv infusion (d1 & d2) every 14 d for 12 cycles (group A, FOLFOX6) or oxaliplatin 130 mg/m$^2$ as a 2-h iv infusion (d1) and capecitabine 1000 mg/m$^2$ per os (d1-14) every 21 d for 8 cycles (group B, XELOX). Primary endpoint was disease-free survival (DFS). Tumors were classified as MMR proficient (pMMR) or MMR deficient (dMMR) according to MLH1, PMS2, MSH2 and MSH6 protein expression. *KRAS* exon2 and *BRAF*V600E mutational status was also assessed. **Results:** Between 2005 and 2008, 439 patients were enrolled with 414 being eligible. Of the latter, 201 were randomized to FOLFOX and 213 to XELOX. Most common grade 3-4 toxicities were neutropenia (13.8% with FOLFOX vs 4.4% with XELOX, $p<0.0001$) and sensory neuropathy (3.2% with FOLFOX vs 2.1% with XELOX, $p=0.25$). Vomiting was more frequent in the XELOX group (1.6% vs 0%, $p=0.017$). After a median follow-up of 74.7 months, 3-year DFS was 79.8% (95% CI 76.5-83.4) in the FOLFOX group and 79.5% (95% CI 75.9-83.1) in the XELOX group ($p=0.78$). Three-year OS was 87.2% (95% CI 84.1-91.1) in the FOLFOX and 86.9% (95% CI 83.4-89.9) in the XELOX group ($p=0.84$). Overall, 34 of the 308 available tumors (11.0%) were dMMR, 104 of 306 (34.0%) *KRAS* mutant and 15 of 306 (4.9%) *BRAF* mutant. Multivariate analysis showed that primary site in the left colon, earlier TNM stage and the presence of anemia at diagnosis were associated with better DFS and overall survival (OS), while grade 1-2 tumors were associated with better OS. Finally, in the left colon only, dMMR tumors were associated with shorter OS ($N=208$, $p=0.016$ for interaction) and *KRAS*mutated tumors were associated with shorter DFS ($N=209$, $p=0.123$ for interaction). **Conclusions:** The FOLFOX and XELOX regimens did not differ significantly in their efficacy as adjuvant treatment in high-risk CRC patients. A significant interaction was found between primary site location and MMR status with respect to OS. Clinical trial information: ACTRN12610000509066.

**3618 General Poster Session (Board #81), Sat, 8:00 AM-11:45 AM**

**Molecular subtyping of colorectal cancer for identification of patients with a mesenchymal tumor type who might benefit from TGF-beta inhibition.** *Presenting Author: Ramon Salazar, Early Clinical Research Unit, Institut Català d'Oncologia, L´Hospitalet-Barcelona, Spain*

**Background:** Currently, most colorectal cancer (CRC) patients receive chemotherapy treatment, even though many patients do not benefit. Therefore, a better understanding of the biology is required to identify those patients who will benefit from chemotherapy and to find a more tailored therapy plan for all other patients. **Methods:** A molecular subtype classification (A-, B-, C-type) was developed using expression data of 188 stage I-IV CRC patients and validated in 543 stage II and III patients. Subtypes were correlated to clinical factors, prognosis and treatment benefit (stage III). To determine whether TGF-$\beta$ signaling is elevated, 78 patient biopsies were analyzed for TGF-beta (receptor) and phospho-SMAD2/3 expression. To analyze the effect of TGF-$\beta$ activation, we studied the effects of C-type-like cell lines under treatment with Cisplatin, Oxaliplatin or 5-FU. We analyzed the presence of subtypes in all stages (TCGA data, $n=218$), and investigate the stability of classification in multiple biopsies from the same tumor and in matching primary and liver metastases samples. **Results:** We developed a diagnostic test that allows the classification of colorectal cancer tumors into different intrinsic molecular subtypes. The heterogeneity of these subtypes is largely based on 3 biological hallmarks of the tumor. Especially C-type CRC is of clinical interest, as C-type patients have the worst outcome, a mesenchymal phenotype and show no benefit from chemotherapy treatment. The C-type subgroup has elevated TGF-$\beta$ signaling (*TGFB1*, $p=0.0012$; *TGFBR1*, $p=0.0005$) and increased p-SMAD2/3 staining in the tumor cells (1.9-fold, $p=0.0002$). In cell line experiments, up-regulation of TGF-$\beta$ signaling resulted in resistance against chemotherapy. We confirmed the presence of C-type tumors in stage IV CRC (16%) and currently investigate the stability of the subtype phenotype in 33 pairs of matching primary tumor and metastases. **Conclusions:** The molecular subtypes differ largely in prognosis and response to chemotherapy. A treatment strategy combining standard drugs with agents suppressing TGF-$\beta$ signaling might benefit C-type patients.

**3619 General Poster Session (Board #82), Sat, 8:00 AM-11:45 AM**

**Efficiency of biomarker screening for enriched metastatic colorectal cancer trials: The ATTACC program experience.** *Presenting Author: Van Karlyle Morris, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Incorporation of multiple enrichment biomarkers into prospective clinical trials for metastatic colorectal cancer (mCRC) has been proposed or initiated by NSABP, EORTC, NCI Colon Task Force, and UK MRC. The feasibility of large scale screening efforts in mCRC has not been previously assessed. **Methods:** Patients (pts) with 5-FU refractory mCRC at MD Anderson Cancer Center were offered screening in the Assessment of Targeted Therapies Against Colorectal Cancer (ATTACC) program to identify eligibility for companion phase I or II clinical trials with a therapy targeted to an aberration detected in the patient, based on FFPE testing by immunohistochemistry (IHC), 50-gene sequencing, and CpG island methylation phenotype (CIMP) assays. Ten unstained slides were required. **Results:** Between 8/2010 and 1/2014, 506 pts were enrolled. Median time from consent to results was 28 days (interquartile range 22-37 days). Outside tissue was obtained after a median of 6 days (4-10 days). IHC, sequencing, and CIMP results required a median of 10, 13, and 20 days, respectively (Table), with 95% yield. During this 40 month period, between 20 and 40% of pts were eligible on the basis of screened tumor biomarkers for at least one of the 18 companion studies. Given trial-specific eligibility, study logistics, and intermittent study openings, only 14% of pts enrolled on an enriched companion trial, representing an approximate 50% efficiency of enrolling eligible patients. 66% received alternate treatments off protocol, 16% enrolled on unenriched studies, and 4% received no further therapy due to a declining performance status. **Conclusions:** Even though dedicated screening infrastructures such as ATTACC represent an efficient strategy for enrichment studies, a majority of patients did not ultimately participate on a companion trial due to dropout of biomarker-eligible patients and a cumulative lack of trials targeting a majority of screened patients. Both of these hurdles need to be addressed to improve success of this strategy.

| Molecular aberration tested | Aberration present | Inadequate specimen |
|---|---|---|
| **KRAS mut** | 51% | 0.9% |
| **BRAF mut** | 8.7% | 0.0% |
| **PIK3CA mut** | 19% | 1.3% |
| **NRAS mut** | 6.6% | 2.2% |
| **CIMP high** | 37% | 4.0% |
| **PTEN loss** | 12% | 0.8% |

**3620 General Poster Session (Board #83), Sat, 8:00 AM-11:45 AM**

**Immune checkpoints expression in MSI versus MSS colorectal cancers and their potential therapeutic implications.** *Presenting Author: Nicolas Jose Llosa, The Johns Hopkins University School of Medicine, Baltimore, MD*

**Background:** Colorectal cancer (CRC) is divided into 2 groups based on genomic differences: chromosomal instability (80%), and microsatellite instability (MSI) (20%). MSI CRC is associated with a favorable prognosis independent of classic clinical prognostic factors. MSI CRC has been characterized by an intense immune infiltration which was assumed to be related to a high density of mutations creating numerous neoantigens. We compared the nature of inflammation in MSS and MSI CRC specimens to identify biomarkers which could guide therapeutic interventions. **Methods:** Pairs of CRC and normal tissues were enzymatically dissociated to isolate leukocytes by density gradient and their phenotypic characterization was done via multi-parameter flow cytometry (MFC). Immune infiltration was scored using immunohistochemistry (IHC) and *in situ* molecular analysis was performed via laser capture microdissection (LCM) and TaqMan quantitative RT-PCR. **Results:** IHC analysis of immune infiltrates in 15 CRC specimens delineated 3 distinct areas denominated intraepithelial lymphocytes (TIL), tumor stroma (TS) and invasive margin (IM). Scoring of $CD3^+$, $CD4^+$ and $CD8^+$ cells demonstrated that MSI specimens (n=8) were characterized by a higher infiltration of all three populations compared to MSS samples (n=7). Molecular analysis of the TIL (3 MSI versus 3 MSS) indicated that the tumor microenvironment of MSI CRC was characterized by a high expression of IFNg and genes associated with cytotoxic T cells (CTL) including *CD8A*, *TBX21*, *PERF*, *GZM*. Strikingly, MSI samples had a greater expression of IFN-g-driven immune checkpoints such as PD-1, PD-L1, IDO-1 and INOS suggesting that the high density of infiltrating CTL and IFNg stimulate mechanisms of adaptive immune resistance in MSI tumors. MFC analysis of TIL performed on fresh tumors confirmed the higher presence of IFNg-producing $PD1^{hi}$ $CD8^+$CTL in MSI samples (n=8). **Conclusions:** The genetic origin of CRC dictates the nature and intensity of inflammation. A strong IFNg -driven inflammatory response in MSI CRC patients triggered the expression of PD-L1 and IDO-1 which could be targeted to enhance clinical benefit and be predictive of response to immune checkpoint inhibitors.

**3621 General Poster Session (Board #84), Sat, 8:00 AM-11:45 AM**

**A marker-driven phase II trial of neoadjuvant chemotherapy in locally advanced colon cancer.** *Presenting Author: Anders Kristian Moeller Jakobsen, Department of Oncology, Vejle Hospital, Vejle, Denmark*

**Background:** The treatment of locally advanced colon cancer faces many challenges and new approaches are needed. Neoadjuvant chemotherapy has proven valuable in several tumors, but it has not been elucidated in colon cancer. One major reason has been the lack of validated methods for selection, but recent improvement in CT scanning has allowed for identification of high-risk patients in need of adjuvant chemotherapy. **Methods:** Patients with resectable colon cancer fulfilling the following criteria were offered inclusion; Histopathological verification of adenocarcinoma, T3 tumor on CT scan with extramural tumor invasion $>$ 5 mm or T4 tumor, age $\geq$ 18 years, PS $\leq$ 2, adequate hematology, and informed consent. Patients with KRAS, BRAF, or PIK3CA mutation or unknown mutational status received 3 cycles of capecitabine 2000 $mg/m^2$days 1-14 q3w and oxaliplatin 130 mg iv day 1 q3w. Wildtype patients received the same chemotherapy supplemented with panitumumab 9 mg/kg iv q3w. After the operation, patients fulfilling the international criteria for adjuvant chemotherapy received 5 cycles of the same chemotherapy without panitumumab. Patients not fulfilling the criteria (converted patients) were offered follow-up only. The primary endpoint was the fraction of converted patients. Secondary endpoints were 2-year disease free survival (DFS) and toxicity. The study was approved by the Regional Scientific Ethical Committee (S-20100014) and registered at ClinicalTrials.gov (NCT01918527). **Results:** The study included 77 patients. The conversion rate was 42% in the wildtype group compared to 51% in patients with a mutation. The objective response rate by CT scan was 45%. Three patients had complete pathological remission. The cumulative recurrence rate in converted vs. non-converted patients was 3% vs. 27% (p=0.003) translating into a 2-year DFS of 96% vs. 54% (p=0.004). Toxicity was manageable and 90% received $\geq$ two cycles of the three planned cycles of neoadjuvant chemotherapy. **Conclusions:** Neoadjuvant chemotherapy in colon cancer is feasible and the results suggest that a major part of the patients can be spared adjuvant chemotherapy. A randomized trial is warranted. Clinical trial information: NCT01918527.

**3622 General Poster Session (Board #85), Sat, 8:00 AM-11:45 AM**

**A new method to analyze adverse events longitudinally in oncology clinical trials.** *Presenting Author: Gita Thanarajasingam, Mayo Clinic, Rochester, MN*

**Background:** There are significant limitations to the current method for displaying treatment-related adverse events (AE) in clinical trials. Tables displaying grade 3 and 4 AEs do not capture toxicity profiles that evolve over time and do not provide clinically relevant information on when a given AE could arise, its probable duration and its severity at a given point in therapy. We developed a novel method of analysis to better capture and represent longitudinal AE data. **Methods:** Graphical and analytical routines were developed to analyze adverse events longitudinally. Mean symptom and toxicity values are plotted over time on a single axis for direct comparison. Butterfly plots compare adverse events by treatment arms longitudinally. Multiple longitudinal techniques (repeated measures modeling, profile analysis, area under the curve analysis, change from baseline, and time to event) are included. Heat maps, event charts and stream plots are produced for individual patient results over time. **Results:** The methodology was validated in two completed clinical trials in colorectal cancer treatment (N9741) and cancer control (979254). In N9741, a higher incidence and severity of diarrhea, nausea and vomiting in patients on IROX (irinotecan/oxaliplatin) versus FOLFOX (fluorouracil/oxaliplatin) was most pronounced in the first treatment cycle and declined sharply by cycle 2. An increased incidence of alopecia in this cohort was also most apparent upfront, from the first to the second cycle, as compared to a lower overall incidence of alopecia with a gradual rise from cycles 1 through 5 in patients on FOLFOX. In study 979254, a higher incidence of dry mouth in patients using venlafaxine 150 mg/d as compared with placebo was most prominent only later in therapy, at weeks 4 and 5 (incidence of 22% for placebo and 13% for venlafaxine 150 mg/d at week 1, p=0.25, versus, 2.2% and 49%, respectively, at week 5, p=0.0001). **Conclusions:** A new method of analyzing AEs in clinical trials that incorporates the dimension of time offers a more complete depiction of chemotherapy toxicity than current methods. Longitudinal analyses of toxicity over time can provide enhanced patient education and guide clinical management on a given chemotherapy strategy.

**3623 General Poster Session (Board #86), Sat, 8:00 AM-11:45 AM**

**Response rates to hepatic arterial infusion (HAI) pump therapy in patients with metastatic colorectal cancer liver metastases (mCRC LM) after progression on all standard chemotherapies.** *Presenting Author: Andrea Cercek, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** To evaluate the overall response rate of HAI with floxuridine (FUDR) in the refractory setting in patients with mCRC LM. **Methods:** After obtaining an IRB waiver a computerized search was performed for patients with mCRC treated with 5FU, oxaliplatin and irinotecan +/- EGFR and VEGF inhibitor from 2003-2012 . Charts were reviewed to ensure patients (pts); had received all standard therapies prior to HAI pump placement, all pts received HAI FUDR and that no new systemic targeted or cytotoxic therapies were used with HAI pump. Imaging was re-reviewed for confirmation of progression prior to HAI pump placement and for best response using RECIST 1.1 criteria. **Results:** 75 pts were identified; of these 23 had radiographic disease progression on all standard chemotherapies (5FU, irinotecan and oxaliplatin) prior to having a pump placed. Of the 23 evaluable pts, the median age was 53 (range 37-75). Six pts had low volume extrahepatic metastases at the time of pump placement. The overall response rate (ORR) was 8/23 (35%); 10/23 (43%) pts had stable disease (SD). The median duration of SD was 4 months (range 1-10). Median follow up, measured from the date of HAI initiation, was 24 months and median overall survival (OS) was 22 months (95% CI 13-16). The median hepatic progression free survival (hPFS) was 4.5 months [CI: 3.8-6.7]. Thirteen pts developed extrahepatic disease progression (including 5 pts with preexisting extrahepatic disease). The median overall PFS was 3.9 months [95% CI 2.24-5.33]. Median number of HAI treatments was 4 cycles (range 1-13). Six out of 23 (26%) pts required a 50-75% dose reduction by the second cycle due to elevated liver function tests and 18/23 (78%) required a dose reduction after the $3^{rd}$ cycle. No pts required stents or developed long term liver or biliary toxicity. **Conclusions:** In a cohort of 23 patients with mCRC LM, refractory to all standard agents, treatment with HAI FUDR resulted in an ORR by RECIST 1.1 of 35% and median OS of 22 months. Further studies focusing on locoregional therapy in patients with liver predominant disease are warranted. Studies to molecularly characterize these tumors are ongoing.

**3624 General Poster Session (Board #87), Sat, 8:00 AM-11:45 AM**

**Molecular evaluation of primary tumor (PT) and synchronous liver metastasis in colorectal cancer (srLmCRC) patients after cetuximab-based chemotherapy.** *Presenting Author: Daniela Adua, Medical Oncology Unit, S. Orsola-Malpighi Hospital, Bologna, Italy*

**Background:** Molecular heterogeneity among PT and LmCRC is not yet defined. Next Generation Sequencing (NGS) in clinical practice could increase the change of identifying multiple molecular driver alterations calling for therapy. This study evaluates mutations in PT and sLmCRC exon2 KRAS wt patients who underwent chemotherapy (CT) containing cetuximab. **Methods:** Genomic analysis was conducted in 7 sLmCRC pts: before CT on a PT biopsy, after CT on a PT surgical specimen and all srLmCRC. A total of 54 lesions were examined. DNA libraries were generated using the Ion AmpliSeq Colon and Lung Cancer Panel including 22 mutated genes (KRAS, EGFR, BRAF, PIK3CA, AKT1, ERBB2, PTEN, NRAS, STK11, MAP2K1, ALK, DDR2, CTNNB1, MET, TP53, SMAD4, FBXW7, FGFR3, NOTCH1, ERBB4 , FGFR1, FGFR2) and sequenced on a Ion PGM system **Results:** A partial response was achieved in all pts, with a median PFS of 11 months (4-15). Molecular analysis of genes correlated with target therapy is shown in the following table (K=KRAS; N=NRAS; P=PIK3AC; M=MET; m= -; wt= + ). Pt 1 showed heterogeneity in PT before and after CT with KRASm clonal selection and related expression of the mucinous pattern; in srLmCRC: 5/9 KRASm exon2, 1/9 PIK3CAm exon20, 2/9 KRASm exon2 and PIK3CA exon20. In pt 7 NRASm exon2 was identified in PT before and after CT; differences in srLmCRC: 3/5 no mutation, 1/5 NRASm exon2, 1/5 PIK3CAm exon20. The other cases showed rare mutations: SMAD4 (pt 2), TP53 (pts 2,5,6,7), FBXW7 (pt1). **Conclusions:** Our preliminary data suggest a potential role for NGS in the evaluation of biological drug resistance affecting future sequential treatments strategy

| | Pt 1 | | | | Pt 2 | | | | Pt 3 | | | | Pt 4 | | | | Pt 5 | | | | Pt 6 | | | | Pt 7 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CT regimen | Folfiri/Cet | | | | Folfiri/Cet | | | | Folfiri/Cet | | | | Folfoxiri/Cet | | | | Folfiri/Cet | | | | Folfiri/Cet | | | | Folfoxiri/Cet | | | |
| PFS (months) | 15 | | | | 4 | | | | 14 | | | | 14 | | | | 8 | | | | 11 | | | | 10 | | | |
| | K | N | P | M | K | N | P | M | K | N | P | M | K | N | P | M | K | N | P | M | K | N | P | M | K | N | P | M |
| PT pre-CT | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | + | - | + | - | - | - | - | - | + | - | - |
| PT post-CT | + | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | + | - | + | - | - | - | - | - | + | - | - |
| srLmCRC n.1 | + | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | + | - | + | - | - | - | - | - | + | - | - |
| srLmCRC n.2 | - | - | + | - | - | - | - | - | - | - | - | - | - | - | - | - | - | + | - | + | - | - | - | - | - | - | - | - |
| srLmCRC n.3 | + | - | - | - | | | | | - | - | - | - | - | - | - | - | | | | | - | - | - | - | - | - | + | - |
| srLmCRC n.4 | + | - | - | - | | | | | - | - | - | - | - | - | - | - | | | | | - | - | - | - | - | - | - | - |
| srLmCRC n.5 | + | - | - | - | | | | | - | - | - | - | - | - | - | - | | | | | - | - | - | - | - | - | - | - |
| srLmCRC n.6 | + | - | - | - | | | | | - | - | - | - | | | | | | | | | - | - | - | | | | | |
| srLmCRC n.7 | + | - | + | - | | | | | - | - | - | - | | | | | | | | | - | - | - | | | | | |
| srLmCRC n.8 | + | - | - | - | | | | | - | - | - | - | | | | | | | | | - | - | - | | | | | |
| srLmCRC n.9 | + | - | + | - | | | | | - | - | - | - | | | | | | | | | | | | | | | | |

**3625 General Poster Session (Board #88), Sat, 8:00 AM-11:45 AM**

**Programmed death 1 (PD-1) lymphocytes and ligand (PD-L1) in colorectal cancer and their relationship to microsatellite instability status.** *Presenting Author: Zoran Gatalica, Caris Life Sciences, Phoenix, AZ*

**Background:** PD-1 activation by its ligands (PD-L1 and PD-L2) inhibits T-cell activation and plays a role in cancer progression. PD-L1 is widely expressed in many cell types in tumor microenvironment. In contrast, expression of PD-1 is restricted to a small subset of T-lymphocytes. Inhibition of PD-1/PD-L1 interaction showed no benefit in a small number of colorectal cancers (CRC) studied in clinical trials. We investigated tumor infiltrating PD-1+ lymphocytes and PD-L1 expressing cells in CRC to gain insight in their role as biomarkers. **Methods:** 77 CRC cases (53 sporadic and 24 hereditary, including 23 Lynch syndrome and 1 FAP) were profiled (Caris Life Sciences) for the presence of PD-1 and PD-L1 expressing cells, mismatch repair proteins, DNA microsatellite instability (MSI) and select cancer genes sequences (NGS). Only intraepithelial PD-1+ lymphocytes (IEL) and aberrantly expressed PD-L1 on carcinoma cells were considered specific. **Results:** PD-1+ IEL were detected in 47% of sporadic CRC. Microsatellite stable (MSS) cancers were frequently (61%) negative for PD-1. Microsatellite instability-high (MSI-H, both Lynch syndrome and sporadic) were significantly ($p<0.03$) more frequently infiltrated with PD-1+ IEL than MSS (72% MSI-H vs. 39% MSS). Similarly, PD-L1+ cancer cells were more common in MSI-H (56%) than in MSS (21%, $p=0.007$), but the expression was patchy in all cases. Concurrent PD1+ IEL and PD-L1 cancer cells were seen in 30% of MSI-H and 5% of MSS cancers ($p=0.008$). **Conclusions:** Consideration of immune checkpoint therapies for colorectal cancer needs to consider the presence of PD-1 lymphocytes and cancer cell specific PD-L1 expression. PD-1+ IEL and PD-L1+ cancer cells are more frequent in MSI-H than in MSS colorectal cancers, which are rare in general CRC population.

**3626 General Poster Session (Board #89), Sat, 8:00 AM-11:45 AM**

**Prognostic impact of reduced lymph node yield in lymph-node negative rectal cancer specimens following neoadjuvant treatment.** *Presenting Author: Benjamin Garlipp, Otto von Guericke University Medical School, Magdeburg, Germany*

**Background:** Pathologic examination of at least 12 lymph nodes (LN) is required as per NCCN and ESMO guidelines to accurately identify pN0 rectal cancer. However, this may not apply to patients undergoing surgery following neoadjuvant treatment because LN may be rendered unrecognizable by preoperative chemoradiation. The prognostic impact of reduced LN yield in rectal cancer specimens following neoadjuvant treatment is unknown. **Methods:** Data from the prospective German multicenter Quality Assurance in Rectal Cancer observational trial were retrospectively analyzed. Patients undergoing radical surgery for rectal cancer between 01/01/2007 and 12/31/2009 who were staged to have pN0 disease were included. Propensity Score Analysis using factors potentially influencing the decision for or against neoadjuvant treatment was performed to compensate for bias inflicted by factors that affect both the decision on neoadjuvant treatment and survival. Cox regression including age, complicated surgery, pT stage, propensity score for neoadjuvant treatment, LN yield, and interaction between the latter two was then performed to identify factors independently influencing survival. **Results:** The full data set included 4,154 patients of whom 1,914 (46.1%) underwent neoadjuvant treatment. Significantly fewer LN were retrieved in neoadjuvantly treated patients (median, 13 vs. 15; $p<0.001$). Complete data were available for 1,394 patients. Only age ($p<0.001$), advanced pT stage ($p=0.001$ and $p<0.001$ for pT3 and pT4, respectively), and complicated surgery ($p<0.001$) were independently associated with survival. Neither number of LN, propensity for neoadjuvant treatment, nor interaction between these two were identified as factors independently affecting survival. Only when interaction between propensity for neoadjuvant treatment and LN number was removed from the model, number of LN retrieved was found to be an independent prognostic factor ($p=0.027$). **Conclusions:** Although neoadjuvant treatment reduces the number of LN retrieved in rectal cancer specimens, our data suggest that this has no influence on the prognostic impact of the number of LN examined in patients with pN0 rectal cancer.

**3627 General Poster Session (Board #90), Sat, 8:00 AM-11:45 AM**

**Comparative effectiveness of laparoscopy versus open colectomy among nonmetastatic colon cancer patients: An analysis using the National Cancer Data Base.** *Presenting Author: Zhiyuan Zheng, American Cancer Society, Atlanta, GA*

**Background:** Laparoscopy (LAC) has gained wide acceptance as a curative treatment for non-metastatic colon cancer after the publications of several major clinical trials in the last decade. However, there is limited data regarding the comparative effectiveness of LAC vs. open colectomy (OC) in routine clinical practice. The objective of the study is to compare short-term surgical outcomes between LAC and OC using a national hospital-based cancer registry dataset. **Methods:** The National Cancer Data Base was used to identify stage I-III colon cancer patients aged 18-84 between 2010 and 2011. An intent-to-treat analysis was conducted where converted cases were included in the LAC group. A propensity score matching (PS) method was used to create comparable LAC and OC groups. Patients were clustered at the hospital-level for multilevel regression analysis to investigate the associations between various clinical, demographic, and contextual variables (i.e. surgeon/hospital volume measurements, insurance types, and facility types) and short-term surgical outcomes (i.e. 30-day mortality, 30-day readmission, and length of hospital stay). Sensitivity analyses were conducted to examine the robustness of our findings by excluding converted colectomies (LAC completed only vs. OC), and including patients aged 85 and above at the time of diagnoses. **Results:** A total of 45,876 patients undergoing colectomy were included, 18,717 (41%) LAC and 27,159 (59%) OC. After PS, all variables were balanced and there were 18,189 patients in each of LAC and OC groups. Compared to OC, LAC showed consistent benefits in the 30-day mortality rate (OR = 0.51, 95%CI: 0.43---0.60, $p < 0.001$) and length of hospital stay (IRR = 0.82, 95%CI: 0.80---0.83, $p < 0.001$), but not the 30-day readmission rate (OR =0.93, 95%CI: 0.84---1.03, $p = 0.136$). These findings were not affected by either exclusion of converted cases nor inclusion of patients aged 85 and above. **Conclusions:** Compared to open colectomy, laparoscopic colectomy has lower 30 day mortality and shorter length of hospital stay in routine clinical practice.

**3628 General Poster Session (Board #91), Sat, 8:00 AM-11:45 AM**

**Association of adjuvant chemotherapy with clinical outcomes in patients treated with neoadjuvant chemoradiation for locally advanced rectal cancer.** *Presenting Author: Michael M. Vickers, Tom Baker Cancer Centre, Calgary, AB, Canada*

**Background:** Clinical trial data does not support the routine use of adjuvant chemotherapy (ACT) following neoadjuvant chemoradiation (nCRT) and surgery (Sx) in rectal cancer (Ca). Few studies have included oxaliplatin-based ACT or assessed the benefit in specific pathologic stage (Pstage) subgroups. **Methods:** Data from patients (pts) with locally advanced rectal Ca who received nCRT and had curative intent Sx from 2005 to 2012 were collected from Tom Baker Cancer Center, Cross Cancer Institute, BC Cancer Agency, Ottawa Hospital Cancer Centre and Dr. H. Bliss Murphy Cancer Centre. The effect of ACT on Time Free of Recurrence (TFR – death without recurrence censored), Disease Free Survival (DFS) and Overall Survival (OS) was assessed using cox proportional hazards model, controlling for age, sex, performance status (PS), circumferential resection margin (CRM), location of tumor, RT dose, Clinical stage (Cstage), Pstage. **Results:** 1172 pts were included, with a mean age of 61.6 (± 0.33) and a mean follow-up time of 3.8 years (± 0.05). 303 (25.9%) pts received oxaliplatin-based ACT, while 328 (28%) did not receive any ACT and these pts were more likely to be older (65.8 v 65 yrs, $p<0.0001$), have worse PS ($p=0.009$), receive lower doses of RT ($p=0.0003$) and have earlier Cstage ($p=0.004$) on univariate analysis compared with ACT pts. Univariate analyses for Pstage 0-II were non-significant (NS) for effect of ACT on TFR and DFS. See Table for all pts and Pstage III outcomes controlling for covariates above. Assessment of ACT in high risk v low risk stage II (as in colon Ca) was NS for TFR ($p=0.47$), DFS ($p=0.7$) and OS ($p=0.7$) adjusting for age, PS and CRM. **Conclusions:** ACT improved clinical outcomes in our retrospective database, however the benefits may be limited to those with Pstage III. Studies are needed to clarify if factors used to stratify stage II colon Ca into high vs. low risk may be applied to estimate recurrence risk in Pstage II rectal Ca.

| Population | TFR (95% CIs) | p-value | DFS (95% CIs) | p-value | OS (95% CIs) | p-value |
|---|---|---|---|---|---|---|
| **All pts** | 0.84 | 0.31 | 0.63 | 0.002 | 0.52 | 0.0004 |
| **ACT v no ACT** | (0.59 – 1.18) | | (0.47 –0.85) | | (0.36 – 0.75) | |
| **Pstage III** | 0.6 | 0.02 | 0.53 | 0.002 | 0.48 | 0.004 |
| **ACT v no ACT** | (0.39 – 0.93) | | (0.35 – 0.8) | | (0.29 – 0.79) | |

**3629 General Poster Session (Board #92), Sat, 8:00 AM-11:45 AM**

**Extended *RAS* analysis and subsequent anti-EGFR and anti-VEGF treatment (tx) in PEAK: A first-line phase 2 study of FOLFOX6 + panitumumab (pmab) or bevacizumab (bev) in metastatic colorectal cancer (mCRC).** *Presenting Author: Fernando Rivera, Hospital Universitario Marqués de Valdecilla, Santander, Spain*

**Background:** In PEAK, progression-free survival (PFS) was similar and overall survival (OS) was improved with pmab + FOLFOX6 relative to bev + FOLFOX6 in patients (pts) with WT *KRAS* exon 2 mCRC. In an extended *RAS* analysis (exons 2, 3, and 4 of *KRAS/NRAS*), this improvement was enhanced in pts with WT *RAS*. This analysis evaluates pts who received subsequent biologic therapy in PEAK. **Methods:** Kaplan-Meier medians for OS were estimated for pts receiving pmab/subsequent anti-VEGF tx and pts receiving bev/subsequent anti-EGFR tx. Analyses were performed on pts with WT *KRAS* exon 2 and WT *RAS* from an exploratory, updated analysis (03Jan2013). Results are from the time of randomization. **Results:** Demographic and baseline characteristics were generally similar with differences of < 20% between arms. Results are shown (Table). Prespecified analyses suggest that individual *RAS* exons that are WT favor the pmab arm and will be presented. **Conclusions:** In this exploratory analysis, the time and % of pts to biologic subsequent tx were similar between the arms. Median OS was observed to be longer for pts receiving pmab/subsequent anti-VEGF tx relative to pts receiving bev/subsequent anti-EGFR tx and the improvements were similar to that in the total populations of the WT *KRAS* exon 2 and WT *RAS* groups. Clinical trial information: NCT00819780.

| | Pmab + FOLFOX6 | Bev + FOLFOX6 | Pmab + FOLFOX6 subsequent anti-VEGF | Bev + FOLFOX6 subsequent anti-EGFR |
|---|---|---|---|---|
| **WT *KRAS* Exon 2, n** | 142 | 143 | 57 | 54 |
| **OS, events (%)** | 52 (37) | 78 (55) | 24 (42) | 36 (67) |
| **Median (95% CI), mos** | 34.2 (26.6 - NA) | 24.3 (21.0 - 29.2) | 34.2 (23.0 - 41.3) | 25.3 (22.1 - 29.2) |
| **Median (range) time to subsequent tx, mos** | | | | |
| **anti-EGFR** | | | | 12.0 (3 - 24) |
| **anti-VEGF** | | | 12.5 (2 - 38) | |
| **WT *RAS*, n** | 88 | 82 | 35 | 30 |
| **OS, events (%)** | 30 (34) | 40 (49) | 13 (37) | 15 (50) |
| **Median (95% CI), mos** | 41.3 (28.8 - 41.3) | 28.9 (23.9 - 31.3) | 41.3 (26.6 - 41.3) | 29.0 (26.0 - 34.4) |
| **Median (range) time to subsequent tx, mos** | | | | |
| **anti-EGFR** | | | | 15.4 (4 - 24) |
| **anti-VEGF** | | | 13.0 (2 - 38) | |

**3630 General Poster Session (Board #93), Sat, 8:00 AM-11:45 AM**

**Comparison of quantitative methods of assessing the hepatic burden of disease as predictors of overall survival at the initial diagnosis of stage IV colorectal cancer.** *Presenting Author: Michael Hayden Rosenthal, Dana-Farber Cancer Institute, Department of Imaging, Boston, MA*

**Background:** The metastatic tumor burden in the liver may be related to prognosis in patients with stage 4 colorectal cancer, but it is unclear if standard measurement techniques such as those used in the Response Evaluation Criteria for Solid Tumors (RECIST) will capture that prognostic information. Counting all liver lesions >= 1cm in size could offer a feasible alternative for whole-liver disease assessment. **Methods:** In this IRB-approved, HIPAA-compliant retrospective study, two board-certified radiologists independently reviewed the baseline imaging studies of 60 subjects with treatment-naïve stage 4 colorectal cancer. The hepatic tumor burden was assessed in two ways: by measuring the longest dimensions of the five largest measurable liver lesions, and by counting the number of lesions measuring at least 1 cm in size. Overall survival was assessed from diagnosis to death or censoring via the electronic medical record, which also references the social security death master file. No subject was lost to follow-up over a median of 1233 days. The sum of the longest dimensions of the five largest liver lesions (SLD5, in cm; RECIST 1.0 standard), the sum of the longest dimensions of the two largest liver lesions (SLD2, in cm; RECIST 1.1 standard), and the count of lesions measuring at least 1 cm in size were assessed as continuous predictors of overall survival using both univariate and multivariate Cox proportional hazards models. **Results:** Univariate analyses showed hazard rate ratios of 1.02 (CI 0.99-1.05), 1.01 (0.95-1.07), and 1.02 (CI 1.01 – 1.04) per unit change for the SLD5, SLD2, and count metrics, respectively ($p=0.33$, $p=0.77$, and $p=<0.001$). The multivariate model showed that only the count of liver lesions remained an independent predictor of survival with a hazard rate ratio of 1.02 per unit change (CI 1.01 – 1.04, $p<0.001$). **Conclusions:** In this cohort, the whole-liver count of lesions larger than 1 cm is superior to the RECIST 1.0 and 1.1 baseline assessments of sums of longest dimensions as a predictor of overall survival at the initial diagnosis of stage 4 colorectal cancer. Further research is necessary to validate this result in a larger cohort.

**3631 General Poster Session (Board #94), Sat, 8:00 AM-11:45 AM**

**Impact of preoperative treatments on the immune microenvironnement of colorectal liver metastases.** *Presenting Author: Frederic Bibeau, Pathology Department, Institut du Cancer de Montpelier, Montpellier, France*

**Background:** An adaptive $CD8^+/CD45^+$ immune response, is considered as a favorable prognostic factor in primary colorectal cancer (CRC). $FoxP3^+$regulatory T lymphocytes (Ly) inhibit this response. Such data are lacking in CRC liver metastases (LM), notably after preoperative treatments. We aim to analyze this subject. **Methods:** 105 CRC LM were selected as follows: chemotherapy alone (CT, n= 29), CT + anti-VEGF (bevacizumab) (n= 27), CT + anti-EGFR (cetuximab) (n= 20), surgery alone (control group, n= 29). LM were treated in first-line. Histologic response was assessed according to the Tumor Regression Grade (major response: MR, partial response: PR, no response: NR). Immune microenvironnement was evaluated as follows: intratumoral (IT), peritumoral (PT) , classified as minor or major and assessed by immunohistochemistry to characterize: i)T Ly: $CD8^+$ (cytotoxic) , CD $45^+$ (memory), $Tbet^+$ (T helper 1), $FoxP3^+$ (regulators) ii) macrophages: $CD68^+$, $CD163^+$. **Results:** A major immune infiltrate was more frequently associated with LM showing MR vs PR vs NR, with the following markers and locations: $CD8^+$ (IT; $p = 0.003$), $CD45^+$ (IT; $p = 0.011$), $Tbet^+$ (PT; $p= 0.015$), CD 68(IT; $p= 0.050$), CD163 (PT, IT; $p = 0.002$, $p = 0.023$). Conversely, a major $FoxP3^+$ IT infiltrate was more frequently associated with LM displaying NR vs PR vs MR ($p = 0.033$). Moreover, a major immune infiltrate was more frequently associated with treated LM than with untreated LM as folows: $CD8^+$ (IT; $p = 0.012$), $TBet^+$ (PT, IT; $p = 0.015$ $p= 0.023$), CD 68 (IT; $p = 0.048$), CD163 (IT; $p = 0.012$). Among treated LM, a major PT CD45 infiltrate was more frequently associated with CT+anti-EGFR than other treatments ($p = 0.036$), and a major IT CD45 infiltrate was more frequently associated with CT+anti-EGFR and chemotherapy alone than CT+anti-VEGF ( $p = 0.022$). **Conclusions:** Pre-operative treatments have an impact on CRC LM immune microenvironnement. Treated CRC LM with histologic response harbor a $CD8^+/CD45^+$ adaptive immune response, a stimulated T helper 1 pathway and a down regulation of Treg lymphocytes. The use of therapies targeting the immune microenvironnement can be suggested as an option in LM CRC. The prognostic impact of these results will be determined and presented.

**3632 General Poster Session (Board #95), Sat, 8:00 AM-11:45 AM**

**High-throughput exome array for identification of novel polymorphisms associated with clinical outcome in mCRC patients treated with first-line FOLFOXIRI/BEV versus FOLFIRI/BEV (TRIBE trial; NCT00719797).** *Presenting Author: Wu Zhang, USC Norris Comprehensive Cancer Center, Los Angeles, CA*

**Background:** TRIBE is a phase III randomized trial comparing FOLFOXIRI/Bev vs FOLFIRI/Bev as first-line treatment for metastatic colorectal cancer. In this post genomic area, whole exome sequence is emerging as an useful tool to identify novel snps to associated with clinical outcome. Here we tested the hypothesis that whole exome sequence may identifies snps to predict clinical outcome in mCRC patients enrolled in TRIBE study. **Methods:** Genomic DNA was extracted from peripheral blood of 503 pts. Arm A(FOLFIRI/BEV)(n=253); Arm B (FOLFOXIRI/BEV)(n=250), median age 60 years(29-75), Females(n=202) and males(n=301);Median follow up is 32.3 months. The Illumina HumanExome array with custom content was genotyped on 432 pts on Illumina HiSeq plateform. After applying genotyping quality control filters, 385 individuals and 241,812 single nucleotide polymorphisms (SNPs) remained in the analysis. Arm A included 163 pts with a mean age of 59.9 years (SD=9.14) and mean OS of 22.9 months while Arm B included 222 pts with mean age of 59.9 years and mean OS of 23.3 months. A Cox proportional hazard regression analysis was implemented to assess SNP associations with RR,PFS and OS after adjusting for sex, treatment arm, age at trial entry, number of metastases, ECOG, and mutation status for KRAS and BRAF. GenABEL was used for the statistical analysis. **Results:** Although our main effect analysis did not identify a genome-wide association ($P<5x10^{-8}$), our preliminary analysis did observe several promising associations between SNPs and OS. Our top association, rs10008360 on chromosome 4(VEGFR-2), with hazard ratio (HR) of 6.49 ($P=2.84x10^{-6}$). We observed four additional markers associated with OS ($P<1.0x10^{-4}$). Rare burden testing and pathway analyses are underway to determine additional biological candidates. Updated detailed analysis including response and PFS results will be presented at meeting. **Conclusions:** This is the first study identifies novel snps may predict which patient could benefit from bevacizumab-based therapy. These preliminary data warrants further validation clinical trials.

**3633 General Poster Session (Board #96), Sat, 8:00 AM-11:45 AM**

**Association of CpG island methylator phenotype (CIMP) with inferior progression-free survival with anti-EGFR monoclonal antibody therapy in metastatic colorectal cancer.** *Presenting Author: Michael Sangmin Lee, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Deranged epigenetic regulation is thought to play an important role in pathogenesis and behavior of metastatic colorectal cancer (mCRC). The CpG island methylator phenotype (CIMP) is associated with distinct tumor biology, which may have differential sensitivity to targeted drug therapy. We hypothesized that methylation status affects susceptibility to anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs). **Methods:** 195 mCRC patients initially tested as KRAS wild-type had tumor tissue successfully tested for CIMP status via bisulfite pyrosequencing and PCR amplification of MINT1, MINT2, and MINT31 loci and promoter sequences of p14, p16, and hMLH1. Next generation sequencing for KRAS, BRAF, and NRAS mutations was done. The duration of the first anti-EGFR mAb treatment and reason for cessation was retrospectively determined, and log-rank test was used for comparisons of progression-free survival (PFS). Cox regression analysis was performed. **Results:** 162 patients received therapy that included an anti-EGFR mAb: 24% CIMP-high (≥40% of tested sequences methylated), 40% CIMP-low, and 25% CIMP-none. Median PFS was 2.8 mo, 6.5 mo, and 6.5 mo respectively (p=0.0005 by log-rank test). On Cox regression analysis, CIMP-high was significantly associated with decreased PFS (HR 2.4, p=0.0002 on univariate analysis). CIMP-high status was associated with inferior PFS in the subgroup of patients known to be BRAF wild-type (p=0.03), and in the subgroup of known BRAF wild-type/NRAS wild-type patients (p=0.03). After excluding the 11 patients who received anti-EGFR mAb therapy first-line, CIMP-high status remained significantly associated with inferior PFS in the known BRAF wild-type and the known BRAF wild-type/NRAS wild-type subpopulations. **Conclusions:** CIMP-high methylation status is associated with shorter PFS on treatment with anti-EGFR mAb therapies, even among patients with BRAF and NRAS wild-type tumors.

**3634 General Poster Session (Board #97), Sat, 8:00 AM-11:45 AM**

**The safety and tolerability of veliparib (V) plus capecitabine (C) and radiation (RT) in subjects with locally advanced rectal cancer (LARC): Results of a phase 1b study.** *Presenting Author: Brian G. Czito, Duke University Medical Center, Durham, NC*

**Background:** Patients (pts) with LARC treated with neoadjuvant RT/C and then surgery have significant relapse rates with low rates of complete response. V is a potent, orally bioavailable PARP inhibitor that has been shown to enhance the efficacy of chemotherapy and RT in preclinical models. This study sought to establish the recommended phase 2 dose (RPTD) as well as to assess safety, pharmacokinetics (PK), and preliminary activity of V + RT/C in pts with LARC. **Methods:** Pts with stage II-III rectal cancer received RT (50.4Gy/1.8Gy/fraction) with C (825 mg/m$^2$BID) five days per week (W) for 5.5W. Dosing of V (BID, 20mg-400mg) continued from W1D2 to 2 days past RT. Pts underwent surgery 5-10W following RT. Assessments include identification of RPTD with the Exposure Adjusted Continual Reassessment Method, adverse events (AEs), PK, and pathological response: no disease present on pathologic review (ypCR), microscopic disease only (yCR), and tumor downstaging. **Results:** As of Dec 8, 2013, 18 pts have been enrolled, 12/6 male/female, median age 55 yrs; 1 pt discontinued due to an AE. The most common treatment-emergent AEs (>20% pts, n ≥ 4) were diarrhea (39%), nausea (39%), fatigue (33%), radiation skin injury (33%), dysuria (22%), and constipation (22%). One Grade 3/4 event of diarrhea and one post-operative event of anastomosis dehiscence were deemed at least possibly related to V. One dose limiting toxicity (DLT) occurred at 70mg BID V (radiation skin injury requiring dose interruption); 1 pt at 400 mg BID described ongoing intolerable nausea not meeting the criteria of a DLT. The RPTD is 400 mg V in combination with RT/C. PK results from 16 pts suggest that V PK was approximately dose proportional when administered with RT/C and that V had no effect on the PK of C. To date, 11/15 (73%) pts have been downstaged post-surgery; with 4/16 (25%) ypCR and 4/16 (25%) yCR. **Conclusions:** V at 400 mg in combination with RT/C has an acceptable safety profile, and the combination will move forward in an expanded cohort to better define toxicity and efficacy. Escalations of V resulted in approximately dose proportional increases in the V PK with no clear effect on C PK. Clinical trial information: NCT01589419.

**3635 General Poster Session (Board #98), Sat, 8:00 AM-11:45 AM**

**Extended follow-up following aggressive resection of locally recurrent rectal cancer.** *Presenting Author: Francis SW Zih, University of Toronto, Toronto, ON, Canada*

**Background:** The literature on resection of locally recurrent rectal cancer (LRRC) consists largely of case series based on retrospective data collection with median follow-up of less than 36 months. The goal of the present study was to determine outcomes after 5 to 10 yrs of follow-up in a group of patients managed with a consistent approach. **Methods:** We identified patients who underwent resection of LRRC between 06/1997 and 05/2005 from the prospective colorectal cancer databases in two cancer centers at the University of Toronto, Canada. Median follow-up time for the entire cohort (n=52) was 44 months; median follow-up in surviving patients (n=25) was 91 months. **Results:** All 52 patients (median age=60, 31 male) underwent grossly complete resection of their locoregional recurrence; 6 had synchronous distant metastases at the time of LRRC resection. The most common operative procedure for LRRC was a pelvic exenteration with sacrectomy (n=22). 24 patients had received adjuvant XRT for their primary tumor and 26 radionaïve patients received XRT prior to resection for recurrence. At last follow-up, 16 patients were alive with no evidence of disease; 9 alive with disease; 26 had died of disease; and 1 died of other causes. For the entire cohort (n=52), 5-yr and 8-yr Overall Survival (OS) were 49% and 46%, respectively; median OS was 60 months. M1 disease at the time of LRRC resection was associated with inferior OS (p=0.04). Predictors of improved OS included node negative primary cancer (p=0.02); receipt of systemic chemotherapy prior to LRRC resection (p=0.02); and R0 margin of resection on LRRC (p<0.0001). Sacrectomy (n=30) was not a prognostic factor. In patients with no distant metastases at the time of LRRC resection (M0, n=46), 5-yr and 8-yr re-recurrence-free survival were 35% and 31%, respectively. Patients who were clinically M0 at time of LRRC resection in whom R0 resection was achieved (n=36) had 5-yr and 8-yr OS of 65% and 61%, respectively; in that group, re-recurrence-free survival at 5 and 8 yrs were 45% and 39%, respectively. **Conclusions:** Margin negative resection of LRRC can result in extended survival beyond 5 yrs. Use of preoperative systemic chemotherapy and sacrectomy may be associated with improved results.

**3636^ General Poster Session (Board #99), Sat, 8:00 AM-11:45 AM**

**Phase I study of preoperative continuous 5-FU and sorafenib with external radiation therapy in locally advanced rectal adenocarcinoma.** *Presenting Author: Gopi Kesaria Prithviraj, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

**Background:** Preoperative treatment with fluoropyrimidine-based chemoradiotherapy is the standard of care in locally advanced rectal cancer (T3, T4 or N1). Sorafenib inhibits of ras/raf, PDFGR and VEGFR with synergistic activity with radiation (RT). This phase I study evaluated the safety and efficacy of sorafenib with infusional 5-FU and RT in patients with locally advanced rectal cancer. **Methods:** Patients with stage II or III rectal cancer, confirmed by endoscopic ultrasound (EUS) and CT scan, were recruited in 4 cohorts of 3 patients per dose level (DL), with an expansion cohort at the MTD. A 3+3 dose escalation design was used. RT was given in 25 fractions at 1.8Gy (45Gy) day 1-5 at all dose levels. Patients underwent surgery 6-10 weeks following neoadjuvant therapy. **Results:** 14 patients were enrolled at Moffitt Cancer Center, including 8 females and 6 males with a median age of 55 years (range: 40-72). After observing toxicity in the first cohort (2 patients with G2 and G3 skin toxicity and 1 patient with G2 mucositis) requiring dose interruptions, an amendment was made to change the schedule of chemotherapy and sorafenib to days 1-5 instead of daily. Following this, hypertension was the only G3 toxicity seen. 2 patients had G3 hypertension at 200mg adjusted dose(day1-5); 1 patient had G3 hypertension at the 400 mg PO BID dose level, and no grade IV toxicities were observed. No perioperative complications were seen. One patient is awaiting surgery. Due to patient refusal, 2 patients did not undergo surgery. *KRAS* status was available for 10 patients. The pCR rate was 36% and downstaging was observed in 81.8% of patients. The pCR was 50% in those with *KRAS* mutant tumors (2/4 pts). **Conclusions:** After changing the dosing schedule, this regimen was very well tolerated. The pCR and downstaging rate of the tumor is encouraging. Accrual to the expansion cohort is ongoing. Clinical trial information: NCT01376453.

**3637 General Poster Session (Board #100), Sat, 8:00 AM-11:45 AM**

**Molecular profiling of 6,892 colorectal cancer patients to identify potential treatment options.** *Presenting Author: Wafik S. El-Deiry, Penn State Hershey Cancer Institute, Hershey, PA*

**Background:** Colorectal cancer (CRC) especially with KRAS/BRAF mutation (MT) is aggressive and has limited treatment options when metastatic. We used a multiplatform molecular profiling (MP) approach to identify potential treatments not typically considered for CRC in order to improve the management of this disease. **Methods:** We evaluated6,892 CRCs referred to Caris Life Sciences by MP including sequencing (Sanger/NGS), protein expression (IHC) and gene amplification (CISH/FISH). **Results:** CRC metastases (mets) to liver, brain, ovary or lung (n=1507) showed expression of actionable markers including high TOPO1 (52%), low RRM1 (57%), TS (71%) and MGMT (39%), suggesting benefit from irinotecan, gemcitabine, 5FU/capecitabine and temozolomide. Brain mets had higher TOP2A (100% vs. 81%), while ovarian mets had lower TUBB3 (16% vs. 43%) than the other mets ($p<0.05$). Brain and lung mets had higher KRAS mutations (65% and 59%) than other mets (47%, $p=0.07$, $<0.01$), suggesting poor response to EGFR inhibitors (EGFRi). Additional analysis at other metastatic sites will be presented. BRAF-mutated CRC (n=455) showed coincident high IHC of RRM1 (56%), TS (53%) and low PDGFR (22%) compared with wild type, suggesting decreased response to gemcitabine, 5FU/capecitabine, or antiangiogenics. Mutation in other genes (APC, PTEN, HNF1A, ABL1, and RB1) may also suggest targeted therapies for these patients. KRAS-mutated CRC had higher cMET (47% vs. 36%) and lower MGMT (56% vs. 63%), suggesting cMETi and temozolomide. KRAS-mutated CRC also had high TUBB3 (42% vs. 33%) and low HER2 by IHC (0.5%) and FISH (3%), indicating less benefit from taxanes or HER2i ($p<0.05$). MP of CRC of ascending, descending colon or rectum showed KRAS mutations in 43%, 23%, 43%; PIK3CA in 29%, 25%, and 10% or BRAF in 27%, 18% and 3.3%, respectively. **Conclusions:** MP of 6,892 CRCs identified significant differences among tumors with BRAF/KRAS-MT and metastases, prompting unexpected treatment options. Agents uncommonly used in CRC metastases such as temozolomide are suggested, and etoposide or taxanes are suggested for brain or ovarian mets, respectively. Targeted therapies could be considered for KRAS or BRAF mutated tumors based on actionable targets revealed by MP.

**3638 General Poster Session (Board #101), Sat, 8:00 AM-11:45 AM**

**Axitinib in refractory colorectal metastatic cancer: A phase II study of increasing doses with dynamic contrast-enhanced ultrasonography monitory of the response.** *Presenting Author: Michel Ducreux, Paris Sud University, Le Kremlin Bicetre, France*

**Background:** Anti-angiogenic therapy plays a role in the treatment of colorectal cancer (CRC). We used monotherapy axitinib every other week given in refractory patients to evaluate the efficacy of this drug given at increasing doses and the role of Dynamic Contrast enhanced ultrasonography (DCE-US) to predict and measure its efficacy. **Methods:** Patients (pts) should have refractory metastatic CRC with at least one measurable lesion into the liver with DCE-US. They were given axitinib 5mg bid for one week followed by one week rest (Cycle 1) and then in case of good tolerance 7 mg bid for one week followed by one week rest (Cycle 2) and then 10 mg bid for one week followed by one week rest (Cycle 3). After 6 weeks of treatment a new CT-scan was performed to evaluate the efficacy of the treatment following RECIST criteria. If at least a stable disease was observed axitinib alone was continued at the same dose, if not addition of chemotherapy (CT) (Folfiri regimen) was allowed. DCE-US was performed on one liver metastasis at baseline D2, 7, 15, 21, 29, 35, 43. AUC, corresponding to the blood volume was calculated at each time point. **Results:** 25 pts (W: 10, M: 15; median age 60) are evaluable. Kras status: mutant 11, wild-type 9, unknown 5. 84% of the pts received more than 2 lines of CT before entry in the study. ECOG PS was 0 in 24% of the pts, 1 in 60%, 2 in 12% and 3 in 4%. Cycles received: 25 pts cycle 1, 24 pts cycle 2, 21 pts cycle 3. The only grade 3 toxicity frequently observed was hypertension (28%, 25%, 15% in cycle 1, 2, 3, respectively). No objective response was observed, stable disease was seen in 32% of the cases. Median overall survival was 5.8 months [IC 95%: 5.1 – 9.9], median overall progression free-survival was 1.5 months [IC 95%: 1.3 – 3.0]. A total of 169 DCE-US were analyzed. The median of AUC decreases by 55% from baseline to D43. AUC decreases by 53%, 1 % and 10 % after the first, second and third cycle, respectively. **Conclusions:** This study has shown that heavily pretreated patients patients who received axitinib monotherapy given every other week had a median overall survival of 5.8 months. DCE-US monitoring could help to detect the patients who get the greater benefit of the treatment. Clinical trial information: NCT01486251.

**3639 General Poster Session (Board #102), Sat, 8:00 AM-11:45 AM**

**The consistency of effect of ziv-aflibercept (Z) in the bevacizumab (B) pre-treated subgroup of patients (pts) in the velour trial stratified by first-line progression ≥ 9 months (mos) versus < 9 mos.** *Presenting Author: Paulo Marcelo Hoff, Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil*

**Background:** The addition of B to an oxaliplatin-based regimen in 1st line metastatic colorectal cancer (mCRC) pts has shown a median progression free survival (PFS) of 9.4 mos as seen in NO16966. In the ML18147 study, the benefit of B added to chemotherapy (CT) in 2nd line mCRC following 1st line CT + B combinations, was evaluated in pts pre-stratified by 1st line PFS ≤9 mos and >9 mos. We evaluated the consistency of the treatment effect of Z+FOLFIRI (F) vs placebo (P)+F according to the timing of progression from 1st line therapy (<9 mos *vs.* ≥9 mos) in the subgroup of pts treated with an oxaliplatin containing regimen and B in 1stline from VELOUR (NCT00561470). **Methods:** In VELOUR, 186 pts in the Z+F and 187 in the P+F groups were stratified to prior B. There were 17 pts (9 in Z+F and 8 in P+F arm) who experienced recurrence during or within 6 mos of completing adjuvant oxaliplatin-based therapy – (a population excluded from ML18147), who were excluded from this analysis. The prior B treated subgroup was analyzed by the timeframe of 1stline progression ([PFS] ≥9 vs <9 mos) in this post-hoc analysis. Hazard Ratio (HR) was adjusted on the baseline value of: Performance Status, prior B, age, hypertension, and number of metastatic organs. **Results:** Z+F had an overall survival (OS) benefit in B pre-treated pts both with 1st line PFS ≥9 mos and in pts with 1stline PFS < 9 mos, as shown by the median difference (MD) in OS (Table). A similar benefit was observed with PFS. **Conclusions:** In this post hoc analysis, pts benefited from Z+F therapy regardless of the timing of their 1st line progression <9 months *or* ≥9 months on a 1st line oxaliplatin + B containing regimen. Clinical trial information: NCT00561470.

| Prior B Subgroup | P+F [95% CI] N = 168 | Z+F [95% CI] N=161 | Median difference (mo) HR [95% CI] |
|---|---|---|---|
| **1st line PFS ≥9 mos** | | | |
| **Pts, n** | 92 | 86 | |
| **Median OS, mos** | 14.23 [11.6; 18.9] | 17.94 [14.5; 21.5] | 3.71 |
| **aHR** | | | 0.772 [0.52; 1.15] |
| **Median PFS, mos** | 4.24 [3.9; 5.5] | 7.26 [6.5; 8.7] | 3.02 |
| **aHR** | | | 0.588 [0.391; 0.89] |
| **1st line PFS <9 mos** | | | |
| **Pts, n** | 76 | 75 | |
| **Median OS, mos** | 7.11 [5.2; 10.3] | 9.92 [7.3; 11.4] | 2.81 |
| **aHR** | | | 0.825 [0.57; 1.18] |
| **Median PFS, mos** | 2.79 [2.5; 3.2] | 5.65 [3.9; 7.2] | 2.86 |
| **aHR** | | | 0.57 [0.39; 0.83] |

**3640 General Poster Session (Board #103), Sat, 8:00 AM-11:45 AM**

**mRNA expression levels of candidate genes and clinical outcome in mCRC patients treated with FOLFOXIRI plus bevacizumab (bev) or FOLFIRI plus bev in the TRIBE study.** *Presenting Author: Dongyun Yang, USC Norris Comprehensive Cancer Center, Los Angeles, CA*

**Background**: Phase III TRIBE trial demonstrated that first-line FOLFOXIRI plus bev improved PFS and RECIST response and, at adjusted analyses, OS as compared to FOLFIRI plus bev. Previous data suggested that higher *ERCC1* expression levels could be responsible for resistance to oxaliplatin-containing chemotherapy. Limited data are available up today for the predictive effect of the expression levels of major genes involved in tumoral angiogenesis. **Methods**: mRNA expression levels of *ERCC1*, *VEGF-A, -B, -C, VEGFR1, VEGFR2, ACVRL1, EGFL7* and *EPHB4* were measured using RT-PCR. Biomarker-adaptive threshold design by Jiang, Freilin and Simon (JNCI 2007) was used to identify which mRNA levels may predict subsets of patients who were more likely to benefit FOLFOXIRI + bev than FOLFIRI + bev. **Results**: Tissue samples adequate for expression analyses were available for 228 out of 503 randomized pts (45%). Pts with the tissue available had similar baseline characteristics as the whole cohort. Pts with high intratumoral *ERCC1* (>0.62) or high *VEGF C* (>0.211) were more likely to have longer PFS in FOLFOXIRI + bev (median=12.0 mths) than in FOLFIRI + bev (median=9.7 mths) (HR=0.46 and 0.24 for high *ERCC1* and *VEGF-C* expression level vs. HR=1.55 and 1.20 for low *ERCC1* and *VEGF-C* expression level; unadjusted *P* for interaction=0.0035 and 0.0037 for *ERCC1* and *VEGF-C*, respectively). *ERCC1* and *VEGF-C* expression levels also predicted similar differences in response and OS between two therapies. Applying recursive partitioning identified distinct signatures of genes predicting response (ranging from 20 to 76%, PFS (6-18 mths) and OS (18-49 mths). **Conclusions:** the findings suggested predictive roles for *ERCC1* and *VEGF-C* levels in patients receiving first-line FOLFOXIRI + bev vs in FOLFIRI + bev. Gene expression signature specific for response, PFS and OS may be important new biomarkers which warrant further validation.

**3641 General Poster Session (Board #104), Sat, 8:00 AM-11:45 AM**

**Comparison of survival and nodal staging in rectal cancer patients undergoing sentinel lymph node mapping versus conventional surgery.** *Presenting Author: Sukamal Saha, McLaren Regional Medical Center, Michigan State University, Flint, MI*

**Background:** Nodal metastasis (mets) is one of the most important prognostic factors in rectal cancer (RCa). Sentinel lymph node (SLN) mapping (M) identifies more nodal mets compared to conventional surgery (ConvSx). This identification may lead to upstaging and change in adjuvant treatment, thereby impacting survival. A retrospective study was undertaken comparing RCa patients (pts) undergoing total mesorectal excision (TME) with SLNM (Group A) vs. ConvSx without SLNM (Group B) for survival and nodal staging. **Methods:** SLNM was performed by using a blue dye injected subserosally for tumors above the peritoneal reflection, and trans-anally for tumors below the reflection, prior to TME. Data was collected for pts demographics, neoadjuvant and adjuvant therapy, TNM staging, SLN status, and 5 year overall survival. **Results:** Group A had 99 pts with an average (avg) age of 66 yrs (M:F = 57:42). Group B had 183 pts with an avg age of 63 yrs (M:F = 125:60). Avg number of LNs for Group A vs. Group B was 12 vs. 12.5. SLNM was successful in 87% of pts with an avg number of SLN per patient being 2.1. Overall nodal positivity was 24% vs. 33% for Group A vs. Group B, probably due to much higher use of neoadjuvant chemo-radiation in Group A (79%) vs. Group B (28%). For Group A pts the SLN was the only positive node in 33%. Overall 5 year survival for Group A vs. Group B was 57% vs. 40%. For both node -ve and node + pts, 5 year survival for all pts receiving neoadjuvant therapy for Group A was 50% vs. 22% for Group B, and not receiving neoadjuvant therapy was 71% vs. 48%, respectively. (See Table.) **Conclusions:** SLNM in RCa pts is highly feasible with better overall survival for both node positive and node negative patients when compared to pts who underwent ConvSx, irrespective of whether or not neoadjuvant therapy was received. SLNM may be performed during surgery for RCa pts.

**Comparison of five year survival: Group A vs. Group B.**

| | Node positive | | Node negative | |
|---|---|---|---|---|
| | Group A | Group B | Group A | Group B |
| T1 | N/A | 75.0% | 68.0% | 56.0% |
| T2 | 20% | 36% | 71.0% | 48.0% |
| T3 | 47% | 27% | 50.0% | 45.0% |
| T4 | 67% | 40% | 50% | 13.0% |

| | Group A | Group B |
|---|---|---|
| Neoadjuvant therapy | 50% | 22% |
| No neoadjuvant therapy | 71% | 48% |

**3642 General Poster Session (Board #105), Sat, 8:00 AM-11:45 AM**

**Effect of chemotherapy on the progress in colorectal cancer survival in the past two decades.** *Presenting Author: Irfan Jawed, Lawrence Memorial Hospital Oncology Center, Lawrence, KS*

**Background:** The past two decades have seen steady gains in the overall survival (OS) of colorectal cancer (CRC) patients. **Methods:** We reviewed 106 phase III and large phase II trials in CRC evaluating first and subsequent lines of therapy. Outcomes examined in the experimental (EA) and control arms (CA) included progression free survival (PFS), overall response rate (ORR), stable disease (SD), OS, and post protocol survival (PPS = OS - PFS). **Results:** The wealth of data provided significant correlations. The OS of EA has improved 0.76 mos/yr. Importantly OS of CA improved 0.55 mos/yr reflecting use of experimental therapies in CA in subsequent studies. A high correlation between gains in PFS and gains in OS in individual trials ($p<0.001$; slope=1.08) suggests within one trial PFS gains account for most OS gains. However, because PFS improved only 0.27 and 0.22 mos/yr, in EA and CA respectively, factors other than experimental and salvage therapies are needed to explain observed gains in OS over time. The discordance of OS/PFS gains over time point to important contributions from improved care and lead time bias suggested by: PPS gains of 0.43 and 0.32 mos/yr, in EA and CA respectively, accounting for large portion of OS gains despite OS improvement of only 0.11-0.13 mos/yr in 18 trials in second and subsequent lines insufficient to account for higher OS gains. As expected PFS correlates highly with OS, but importantly ORR had very high correlations with both PFS and OS. SD emerged as an adverse outcome, OS decreasing as SD rates increase. Examination of the effect on OS of the principal drugs showed oxaliplatin, irinotecan and bevacizumab contributed significantly while capecitabine and cetuximab/panitumumab did not. Capecitabine outcome not surprising for an oral substitute of an effective drug; while cetuximab/panitumumab results likely reflect the lack of efficacy/harm in patients harboring MT KRAS tumors. **Conclusions:** The OS of CRC patients enrolled in trials has improved gradually over the past two decades, with contributing factors including chemotherapy but importantly also likely lead time bias and better supportive care. Meaningful progress will require novel paradigms and much better salvage therapies.

**3643 General Poster Session (Board #106), Sat, 8:00 AM-11:45 AM**

**Surgical resection and intraoperative radiation therapy for locally recurrent rectal carcinoma.** *Presenting Author: David Furfaro, Harvard Medical School, Boston, MA*

**Background:** Surgical resection with intraoperative radiation therapy (IORT) has been used to treat locally recurrent rectosigmoid adenocarcinoma (LRRSA). We present the experience at Massachusetts General Hospital (MGH) with resection and IORT for LRRSA. **Methods:** We retrospectively evaluated patients with LRRSA referred for IORT. Charts were evaluated for TNM staging, treatment regimen, IORT, resection margins, complications, recurrences, and current status. For the purpose of this study, R0 resection was defined as margins > 1mm from tumor. We evaluated the prognostic impact of treatment and resection margins on local control (LC), 5-year overall survival (OS) and disease-free survival (DFS). **Results:** Between 1995 and 2010, 51 patients with LRRSA were referred for IORT. Pre-operative radiation therapy was delivered to 88.2% of patients—for 5.9% this was re-irradiation—and 27.5% received post-resection radiation. IORT was delivered to 42 patients. Neoadjuvant chemotherapy was given to 96.1% of patients, and 76.5% had adjuvant chemotherapy. The resection margins achieved, measured as R0, clear margins with tumor within 1 mm (R<1mm), R1 and R2, were 49.0%, 7.8%, 25.5%, and 17.6%, respectively. The overall 5-year LC, OS and DFS were 52.3%, 60.9% and 36.4% respectively. The patients who received resection and IORT vs resection alone did not have improved DFS (HR 1.07, $p=0.896$), LC (HR 1.40, $p=0.590$) or OS (HR 0.52, $p=0.247$). R0 resection predicted favorable LC (HR 0.34, $p=0.017$), DFS (HR 0.22, $p<0.001$) and OS (HR 0.32, $p=0.043$). Patients with R0 margins vs R<1mm had improved LC (HR 0.20, $p=0.024$) and DFS (HR 0.12, $p=0.004$). On multivariate regression, margins of R0 or R<1mm (vs. R1 or R2) improved OS (HR 0.31, $p=0.028$), patients with worse resection margin status had worse DFS (HR 5.19, $p<0.001$), and R0 resections improved LC (HR 0.34, $p=0.017$). **Conclusions:** For patients with LRRSA optimal 5-year DFS, LC and OS were achieved with a margin negative surgical resection. Patients with R<1mm resections had the same OS as patients with R0 resections, but had worse DFS and LC. IORT in addition to surgical resection did not improve DFS, LC, or OS; however, the results are limited due to small sample size and patient selection bias.

**3644 General Poster Session (Board #107), Sat, 8:00 AM-11:45 AM**

**Incidence of diabetes among patients with colorectal cancer.** *Presenting Author: Simron Singh, Odette Cancer Centre, Sunnybrook Health Sciences Centre; University of Toronto, Toronto, ON, Canada*

**Background:** Emerging data show an increasingly recognized risk of colorectal cancer (CRC) in patients with type 2 diabetes (DM) likely due to common biologic pathways. Few data are available on DM incidence among patients with CRC. Our objective was to determine whether patients with CRC have a higher incidence of DM compared to those without CRC. **Methods:** We conducted a population-based retrospective cohort study in Ontario, Canada, using administrative databases comparing the incidence of DM among all CRC patients identified in the Ontario Cancer registry from Jan 1, 2002 to Dec 31, 2011 with an age-matched control population without CRC. We used Cox proportional hazard to study the association. We modeled the effect of CRC on the cause-specific hazard of developing DM and censored subjects at the time of a competing event. Subgroup analysis was performed on patients receiving chemotherapy vs. not, metastatic disease vs. not and colon vs. rectal cancer. **Results:** We identified 39,707 persons with CRC and 198,535 controls. The mean age was 68 and 48.6% were female. We found an overall DM incidence of 8.7% over a mean follow up time of 4.8 years. On multivariable analysis, the effect of CRC on the instantaneous hazard of the DM incidence varied over time, and thus we estimated instantaneous hazard ratios (IHR) for years 1-5 of follow up. The risk of DM among CRC patients was significantly higher than controls for at least five years post CRC diagnosis. The overall DM incidence was higher in patients with no metastasis (10.6% vs 8.6%, $p<0.01$), and lower in patients who received chemotherapy (8.0% vs 9.0%, $p<0.01$). **Conclusions:** This is among the first study to report an increased DM incidence among CRC survivors. This association may be due to common risk factors rather than a treatment effect, as the risk remains elevated for at least five years post diagnosis. The hazard may be underestimated, as patients with advanced cancer may not be formally diagnosed with DM. These results strengthen our understanding of the common biologic pathway of both diseases and have major implications for survivorship care in patients with CRC.

| Years since CRC diagnosis | IHR (95% CI) of DM (CRC vs. no CRC) |
|---|---|
| 1 | 1.42 (1.37, 1.47) |
| 2 | 1.36 (1.32, 1.41) |
| 3 | 1.31 (1.26, 1.36) |
| 4 | 1.26 (1.21, 1.31) |
| 5 | 1.21 (1.16, 1.26) |

**3645 General Poster Session (Board #108), Sat, 8:00 AM-11:45 AM**

**Monitoring changes in circulating tumor DNA in gastrointestinal malignancies using a novel next-generation sequencing method.** *Presenting Author: Edward Samuel James, Yale School of Medicine, New Haven, CT*

**Background:** Circulating tumor DNA (ctDNA) is showing promise as a highly-specific cancer biomarker. We have developed an ultrasensitive ctDNA assay that can evaluate recurrent cancer-associated point mutations and insertions/deletions simultaneously in multiple genes without prior knowledge of the tumor's mutation profile. Here we report on use of this assay for non-invasively assessing tumor mutation status and for monitoring treatment response or disease progression in patients with gastrointestinal malignancies. **Methods:** Plasma samples were collected at multiple time points in a cohort of patients (pts) with colorectal, pancreatic, or bile duct malignancies in the locally advanced, metastatic and adjuvant settings. Mutation-prone regions of genes known to be commonly mutated in GI tumors were amplified by multiplexed PCR, and the resultant amplicons were subjected to next-generation ultra-deep sequencing. Application of novel techniques to suppress sequencer and PCR errors allowed mutations to be identified and quantified with a sensitivity of approximately 1 variant in 5,000 molecules. **Results:** 75 plasma samples from 17 pts were analyzed for the presence of tumor-derived mutations. We found plasma DNA mutations in the following genes: KRAS (7 pts), TP-53 (2 pts), and PIK3CA (1 pt). Among the 8 pts whose tumors were profiled by an independent clinical lab, our plasma results showed perfect concordance of mutation status and type. Testing of serial samples revealed that ctDNA levels changed appropriately with therapy or with disease progression. Examples include one case that showed a dramatic decrease in ctDNA after initiation of first-line chemotherapy, a second case that had rising levels upon development of liver metastases, and a third case that showed reversal of a rising trend upon switching to a different chemotherapeutic regimen. **Conclusions:** We present here a novel NGS-based method for identifying and measuring mutant ctDNA. Results from this cohort of patients with GI malignancies indicate that this approach may find clinical utility for non-invasive assessment of tumor mutation status and for monitoring of recurrence, progression, or therapeutic response.

**3646 General Poster Session (Board #109), Sat, 8:00 AM-11:45 AM**

**A phase II study of 5-FU/l-LV/oxaliplatin (mFOLFOX6) in patients with metastatic or unresectable small bowel adenocarcinoma.** *Presenting Author: Norisuke Nakayama, Kanagawa Cancer Center, Yokohama, Japan*

**Background:** Several prospective and retrospective studies have suggested that chemotherapy prolongs survival in patients with metastatic or recurrent small bowel adenocarcinoma (SBA). However, there is no standard chemotherapyregimen for this disease. The aim of this study was to evaluate the efficacy and safety of mFOLFOX6 as a first-line therapy in patients with SBA. **Methods:** This study was designed as a multi-center, single-arm, open-label phase II study. Eligibility criteria included a histologically proved diagnosis of adenocarcinoma, age 20–80 years, and an Eastern Cooperative Oncology Group performance status (PS) of 0–2. The mFOLFOX6 treatment comprised oxaliplatin (85 mg/m$^2$) and l-leucovorin (200 mg/m$^2$) administered intravenously over a two hour period on day one, followed by a bolus of 5-FU bolus (400 mg/m$^2$) and a 46 hour infusion of 5-FU (2400 mg/m$^2$) every two weeks. The primary endpoint was one year progression-free survival (PFS). The secondary endpoints included overall response rate (ORR), overall survival (OS), PFS, and safety. **Results:** Between April 2010 and November 2012, 24 patients were enrolled from 12 institutions. Median age: 63 years (range, 31–79); male/female ratio: 18/6; PS 0: 17 (71%); PS 1: 7 (29%); locally advanced/metastatic disease: 2/22; primary tumor site: duodenum (58%) and jejunum (42%). The median follow-up time was 14.7 months (3.7-40.3). The one-year PFS was 23.3%. The ORR was 45% (9/20). The median PFS and OS were 5.9 months (95% CI, 3.0–10.2) and 17.3 months (95% CI, 11.7–19.0), respectively. The common grade 3 or 4 toxicities were neutropenia (38%), anemia/peripheral neuropathy (25%), stricture (17%), fatigue/anorexia/bilirubin increase (8%), and diarrhea (4%). There were no treatment-related deaths. **Conclusions:** This phase II study showed a good efficacy with an acceptable safety profile. The mFOLFOX6 regimen is moderately active and well tolerated as a first-line treatment for SBA. Clinical trial information: UMIN000002797.

**3647 General Poster Session (Board #110), Sat, 8:00 AM-11:45 AM**

**Molecular profiling of small-bowel adenocarcinomas.** *Presenting Author: Rebecca Anne Feldman-Moreno, Caris Life Sciences, Phoenix, AZ*

**Background:** Small-bowel adenocarcinoma (SBA) is a rare malignancy with limited knowledge of the molecular mechanisms, or clinical evidence-based guidelines for therapy. We conducted a comprehensive analysis of biomarkers with therapeutic relevance for SBA. **Methods:** We examined the biomarker profiles of 266 SBA cases. Multiplatform biomarker panel included a combination of sequencing (Sanger, NGS), protein expression (IHC) and gene amplification (CISH /FISH). **Results:** Several biomarkers have been identified by IHC evaluation in ~250 patients: high TOP2A (74%) and low TUBB3 (81%), low ERCC1 (71%), low RRM1 (69%) and low TS (63%)- favorable for chemotherapy drugs such as doxorubicin, taxanes, oxaliplatin, gemcitabine and capecitabine, respectively. A minority of cases were found to express other favorable chemotherapy response biomarkers: low MGMT (alkylating agents, 30%), high SPARC (nab-paclitaxel, 36%) and high TOPO1 (irinotecan, 39%). SBA demonstrated a high prevalence of multidrug resistance gene expression: MRP1 and BCRP (83%) and PGP (51%). Unexpectedly, a number of cases showed genomic alterations associated with activated oncogenic signaling: EGFR (13% or 12/96), TOP2A (12% or 4/33), HER2 (7% or 9/130) and cMET (1.4% or 1/71). Two patients demonstrated co-amplification of TOP2A and HER2, suggesting these patients may benefit from anthracyclines. Evaluation of mutational hotspots demonstrated a high incidence of oncogenic/tumor suppressor mutations in 60% (47/78) of patients. We discovered that mutations in TP53 (51%) and KRAS (46%) were most common. Other genes with notable alterations included: APC (22%), SMAD4 (20%), BRAF (9%), CTNNB1 (7%) and PTEN (5%). Recent data suggest favorable responses to cetuximab in SBA; these results and high frequency of KRAS mutations in our series indicate that KRAS testing may be recommended in SBA. **Conclusions:** Our data demonstrate the potential utility of a wide range of traditional chemotherapies for SBA, targeted therapies utilized for other cancer types as well as therapies under clinical investigation. SBA exhibits biologically similar tumorigenesis as large-bowel adenocarcinoma, therefore similar treatment guidelines and biomarker testing strategies should be considered.

**TPS3648^ General Poster Session (Board #111A), Sat, 8:00 AM-11:45 AM**

**Strategic 1-multi-line therapy trial in unresectable wild-type RAS metastatic colorectal cancer: A gercor randomized open-label phase III study.** *Presenting Author: Benoist Chibaudel, Hôpital Saint-Antoine, Paris, France*

**Background:** Several strategies using chemotherapy and molecular targeted drugs are available for the treatment of unresectable metastatic colorectal cancer. Recent and ongoing randomized trials evaluate chemotherapy with bevacizumab or epidermal growth factor receptor (EGFR) inhibitors, but the prior and/or subsequent lines are not fixed and the imbalanced cross-overs will not allow to interpret overall survival. This STRATEGIC-1 trial is a study designed to determine the best sequence of therapy and to define subset populations that will benefit most from one sequence. **Methods:** This is an ongoing randomized, two-arm, phase III study comparing two multi-line therapeutic strategies in patients wild-type RAS unresectable metastatic colorectal adenocarcinoma, ECOG PS 0-2 and age $\geq$ 18years. Randomization is stratified by center, GERCOR prognostic score (using PS and LDH level), prior use of oxaliplatin in adjuvant setting and the extent of metastatic disease. Patients (n=474) are randomized (1:1) to either (arm A) FOLFIRI/cetuximab, followed by an oxaliplatin-based chemotherapy with bevacizumab or (arm B) OPTIMOX/bevacizumab, followed by an irinotecan-based chemotherapy with bevacizumab, followed by anti-EGFR mab (cetuximab or panitumumab) with or without irinotecan. The primary endpoint is Duration of Disease Control (DDC). The sample size was planned for testing the primary variable DDC with a two-sided 5% $\alpha$ type one error and a 10% $\beta$ type two error (Software: EAST 5.3) and a planned interim analysis. A 33% reduction in the risk of event (HR 0.67) was assumed under $H_1$ in the arm B. Secondary endpoints include OS, HR-QoL, TFS, ORR and PFS per sequence, salvage surgery rate, safety and correlations between biomarkers and clinical outcome. CRC tissue (primary or met.) and blood collection are mandatory for biomarker analyses. Enrolment began in October 2013. Clinical trial information: NCT01910610.

**TPS3649 General Poster Session (Board #111B), Sat, 8:00 AM-11:45 AM**

**A randomized phase II study (B2151005) of the intravenous phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) inhibitor PF-05212384 plus irinotecan versus cetuximab plus irinotecan in patients with wild-type *KRAS* metastatic colorectal cancer (mCRC).** *Presenting Author: Josep Tabernero, Vall d'Hebron University Hospital, Barcelona, Spain*

**Background:** The combination of cetuximab plus irinotecan is considered a standard of care regimen for third-line treatment of patients with wild-type *KRAS* metastatic colorectal cancer (mCRC). However, the combination of cetuximab plus irinotecan provides limited tumor control and is associated with skin rash, diarrhea, and neutropenia. Thus, the need for more efficacious and better tolerated regimens remains high. Signaling through the phosphatidylinositol 3-kinase (PI3K) pathway is associated with resistance to a variety of antitumor agents. This association has been described in pre-clinical studies for cytotoxic chemotherapeutic agents with different mechanisms of action, including taxanes and DNA-damaging agents. In the clinic, activation of the PI3K pathway in tumors has been correlated with decreased response to therapy and worse clinical outcomes. Preliminary data from the phase I study B1271002 indicate that the combination of the intravenous PI3K/mammalian target of rapamycin (mTOR) inhibitor PF-05212384 and irinotecan is well tolerated and shows promising antitumor activity in patients with mCRC, suggesting the need to further explore this regimen. **Methods:** This trial was designed to investigate whether the combination of PF-05212384 plus irinotecan is superior to the combination of cetuximab plus irinotecan in prolonging progression-free survival in patients with wild-type *KRAS* mCRC. Additionally, the study includes a lead-in cohort to determine the safety of this combination in Japanese patients. The study is being conducted in men and women with wild-type *KRAS* mCRC whose disease has progressed following treatment with irinotecan, oxaliplatin and fluoropyrimidine therapy in the metastatic setting. Eligible patients will be randomly assigned to either treatment arm. This global trial is open to enrollment and has recruited its first patients. Clinical trial information: NCT01925274.

**TPS3650 General Poster Session (Board #112A), Sat, 8:00 AM-11:45 AM**

**A phase II trial of maintenance ADAPT therapy targeting colon cancer stem cells in patients with metastatic colorectal cancer.** *Presenting Author: Edward H. Lin, Seattle Cancer Care Alliance, Seattle, WA*

**Background:** Presence of cancer stem cells (CSC) appears to be the chief cause of drug resistance to cytotoxic or targeted chemotherapy. Experimental models suggest that these resistant cancer cells undergo dormancy transition that is best targeted with a stemness modulator in its activation window through a strategy that we call ADAPT: Activating (CSC) from Dormancy And Potentiate for Targeting. In vitro and in vivo data suggest that 5FU activates while celecoxib inhibits and depletes these putative colorectal CSC. We retrospectively administer three year ADAPT therapy in unresectable metastatic colorectal cancer (MCRC) patients using capecitabine and celecoxib +/- radiation following maximal responses (complete (CR) and partial response (PR) and stable disease (SD)) to first-line combination chemotherapy. ADAPT therapy led to 30% CR and additional 10% surgical CR whose median survival reached 92.7 months in patients with unresectable MCRC. (Lin et al AACR 2010 LB-254). **Methods:** Fred Hutch Cancer Research Center institutional review board (IRB) approved this prospective phase II ADAPT study funded by Gateway for Cancer Cure in October 2013. The primary endpoint is to determine the rate of CR at three years. The secondary objectives are to determine progression free survival, overall survival, and relapse free survival (if CR) based on intent to treat analysis. Forty-three unresectable MCRC patients except those with brain or bone metastases or severe bowel obstruction will be enrolled and patients must have achieved maximal response (CR, PR, or SD) to first-line chemotherapy before prior to three-year ADAPT protocol +/-radiation. Patient must not be allergic to NSAIDs or sulfonamide and aspirin is not allowed. Eight patients have been enrolled to date and trial will be terminated if less than one complete response (including surgical CR) in the first 20 MCRC patients. Translational "omics" endpoints using UW Oncoplex assay and RareCyte technology are being explored. Clinical trial information: NCT01729923.

**TPS3651 General Poster Session (Board #112B), Sat, 8:00 AM-11:45 AM**

**Regorafenib as a single agent for first-line treatment of frail and/or unfit for polychemotherapy patients with metastatic colorectal cancer (mCRC): A study of the Spanish Cooperative Group for digestive tumor therapy (TTD).** *Presenting Author: Enrique Grande, Hospital Universitario Ramon y Cajal, Medical Oncology Department, Madrid, Spain*

**Background:** More than half of the mCRC are diagnosed in patients over 70 years. Around 15-20% of patients diagnosed of mCRC do not qualify to receive polychemotherapy as first-line systemic therapy due to age and/or comorbidities. The optimal treatment strategy for this group of patients has not been adequately defined. Regorafenib is a multikinase inhibitor that has shown benefit in overall and progression free survival (PFS) over placebo in patients with mCRC who have failed to all approved standard therapies (*Grothey et al. 2013*). This trial will assess the efficacy and safety of regorafenib as a single agent in the first-line setting of frail and/or unfit mCRC patients who are ineligible to receive polychemotherapy. **Methods:** This is a phase II, single-arm, open-label study conducted in patients with mCRC who are considered frail and/or unfit to receive polychemotherapy. Patients should meet at least one of the following criteria: Dependence in activities of daily living owing to the presence of comorbidities other than those resulting from the deterioration caused by the neoplastic disease and/or presence of three or more of the following entities: congestive heart failure, other chronic cardiovascular diseases, chronic obstructive pulmonary disease, cerebrovascular disease, peripheral neuropathy, chronic kidney failure, hypertension, diabetes mellitus, systemic vasculitis, or severe arthritis; presence of geriatric syndromes such as age $>$ 85 years, fecal or urinary incontinence, spontaneous bone fractures, mild and moderate dementia, or patients who fall repeatedly. Patients will receive regorafenib 160 mg PO, three weeks on/one week off in a four-week cycle. The primary endpoint is PFS rate at six months. There are 46 patients who needed to demonstrate that the treatment is effective if PFS rate at six months is higher than 55% and to reject the null hypothesis (PFS rate at six months $<$ 35%), considering an alpha error of 0.05 and a power of 80%. Elderly and unfit for chemotherapy mCRC remains a clinical unmet need in the daily clinical practice. Regorafenib is an active and promising agent that could fill up this gap. Clinical trial information: NCT01875380.

**TPS3652 General Poster Session (Board #113A), Sat, 8:00 AM-11:45 AM**

**STEAM: A randomized, open-label, phase 2 trial of sequential and concurrent FOLFOXIRI-bevacizumab (BEV) versus FOLFOX-BEV for the first-line (1L) treatment (tx) of patients (pts) with metastatic colorectal cancer (mCRC).** *Presenting Author: Johanna C. Bendell, The Sarah Cannon Research Institute, Nashville, TN*

**Background:** Recent randomized trials investigating 5-fluorouracil [5-FU]/leucovorin [LV]/oxaliplatin/irinotecan (FOLFOXIRI) with bevacizumab (BEV) for the first-line (1L) treatment (tx) of metastatic colorectal cancer (mCRC) patients (pts) showed improved progression-free survival (PFS) and overall response rate (ORR) vs. 5-FU/LV/irinotecan (FOLFIRI) with BEV (Falcone et al, ASCO 2013) and improved PFS, ORR, and resection rate of metastases vs. 5-FU/LV/oxaliplatin (FOLFOX) with BEV (Bridgewater et al, ESMO 2013). Toxicity may be a limitation of the regimen; alternating tx with FOLFOX and FOLFIRI (sequential FOLFOXIRI) may improve the tolerability of treating 1L pts with all three agents. The efficacy and safety of FOLFOXIRI-BEV have yet to be investigated in the US, and the impact of maintenance and of BEV tx beyond disease progression (PD) following FOLFOXIRI-BEV is unknown. **Methods:** The STEAM study (NCT01765582) is a randomized, open-label, US-based, phase 2 trial investigating sequential or concurrent FOLFOXIRI-BEV vs. FOLFOX-BEV and maintenance tx in pts with previously untreated mCRC. Key eligibility criteria include unresectable mCRC and age 18–75 years. Pts are randomized 1:1:1 to concurrent FOLFOXIRI-BEV, sequential FOLFOXIRI-BEV (alternating FOLFOX and FOLFIRI q4w), or FOLFOX-BEV q2w during a four to six month induction phase (BEV 5 mg/kg in each arm). After induction, pts receive 5-FU/LV + BEV (5 mg/kg) q2w or capecitabine + BEV (7.5 mg/kg) q3w as maintenance tx until PD. After PD, pts receive second-line (2L) 5-FU–based chemotherapy (physician's choice) with BEV (dose equivalent of 2.5 mg/kg/week) until 2L PD. Pts are stratified by extent of metastatic disease (liver-limited vs non–liver-limited), primary tumor location (right- vs left-sided), and study center. Primary objectives are to evaluate 1L ORR (concurrent FOLFOXIRI-BEV vs FOLFOX-BEV), 1L PFS (concurrent and sequential FOLFOXIRI-BEV vs FOLFOX-BEV), and safety. Secondary objectives include resection rate, rate of conversion to resectable disease, time to 2L PFS, and overall survival (concurrent and sequential FOLFOXIRI-BEV vs FOLFOX-BEV). The study has enrolled 109 of a planned 280 pts to date. Clinical trial information: NCT01765582.

**TPS3653 General Poster Session (Board #113B), Sat, 8:00 AM-11:45 AM**

**Bevacizumab and combination chemotherapy in rectal cancer until surgery (BACCHUS): A phase II, multicenter, open-label, randomized study of neoadjuvant chemotherapy alone without radiation in patients with MRI-defined high-risk cancer of the rectum not threatening the circumferential margin.** *Presenting Author: Mark Harrison, Mount Vernon Hospital, Northwood, United Kingdom*

**Background:** In locally advanced rectal cancer (LARC), local recurrence is uncommon with good quality total mesorectal excision (TME) allowing preoperative chemo-radiotherapy (PCRT) to be omitted. The risk of developing metastases can be partly predicted using magnetic resonance imaging (MRI). PCRT does not benefit all patients with LARC, and is associated with long-term morbidity. Chemotherapy (Cty) may reduce the chance of local recurrence, but compliance to postoperative adjuvant Cty is poor, and its efficacy following CRT has been questioned. Neoadjuvant Cty is being examined in primary colon and rectal cancer (FOXTROT). BACCHUS will examine the efficacy and safety of intensified systemic Cty for LARC prior to TME. **Methods:** This is a multi-centre, randomized phase II trial. Eligible pts must have histologically confirmed LARC, distal part of the tumour 4-12 cm from anal verge, no metastases, poor prognostic features on pelvic MRI, WHO performance status 0-1. Pts receive folinic acid + fluorouracil + oxaliplatin (FOLFOX) + bevacizumab or FOLFOX + irinotecan (FOLFOXIRI) + bevacizumab, given in two weekly cycles for up to six cycles prior to TME. MRI and positron emission tomography–computed tomography (PET/CT) are repeated prior to cycle four. Pts stop treatment if they fail to respond (defined as $\geq$30% decrease in Standardised Uptake Value compared to baseline PET/CT). The primary endpoint is pathological complete response (pCR) rate. Secondary endpoints are response rate (RECIST v1.1), circumferential resection margin-negative resection rate, T and N stage downstaging, progression-free, disease-free and overall survival, local control, one-year colostomy rate, acute toxicity, compliance to chemotherapy, tumour regression grade, and tumour cell density. Thirty pts in each arm are required to detect an improvement from 5-20% pCR rate for each regimen compared to RT alone (80% power, $\alpha$=0.05, assuming 10% non-evaluable rate). A regimen will be considered successful if at least 4/27 pCRs are observed. Clinical trial information: NCT01650428.

**TPS3654 General Poster Session (Board #114A), Sat, 8:00 AM-11:45 AM**

**Randomized phase II study of panitumumab (Pmab) plus irinotecan (CPT-11) versus cetuximab (Cmab) plus CPT-11 in patients with KRAS wild-type (WT) metastatic colorectal cancer (mCRC) following treatment with fluoropyrimidine, CPT-11, and oxaliplatin (L-OHP) chemotherapy: WJOG6510G.** *Presenting Author: Daisuke Sakai, Osaka University Graduate School of Medicine, Osaka, Japan*

**Background:** Pmab and Cmab are known to be effective in KRAS WT mCRC. Recent study showed that Pmab and Cmab monotherapy were comparable in patients with KRAS WT mCRC previously treated with fluoropyrimidine-, L-OHP-, and CPT-11- based regimens. However, it is not clear whether their combination therapy with CPT-11 confers similar benefit. **Methods:** This randomized phase II study of Pmab + CPT-11 or Cmab + CPT-11 recruits patients with mCRC with KRAS WT from 45 sites in Japan. Primary objective is progression free survival (PFS), with a non-inferiority margin of 1.3 (80% CI). Median PFS with both arms is assumed to be 6.0 months. Secondary objectives are overall survival, response rate, disease control rate, and safety. Eligibility: Patients with proven colorectal adenocarcinoma with KRAS (exon 2) WT; unresectable metastatic disease; failed prior regimens containing CPT-11 and L-OHP and fluoropyrimidine; age>=20years; ECOG performance status 0-2; evaluable disease, as defined by the RECIST criteria v1.1; adequate hematologic, renal, hepatic and metabolic function; expected survival>=90 days; written informed consent obtained from the patient. Patients are randomized after stratification by site; PS; refractory or intolerance for L-OHP; previous use of bevacizumab to receive either arm A) Cmab (400 mg/m2 followed by 250 mg/m2 weekly) + CPT-11 (150mg/m2 every 2 weeks) or arm B) Pmab (6 mg/kg every 2 weeks) + CPT-11 (same dose as arm A). Status: Opened to accrual December 2011, at 31 Jan 2014 93/120 patients have been enrolled. Clinical trial information: UMIN000006643.

**TPS3655 General Poster Session (Board #114B), Sat, 8:00 AM-11:45 AM**

**Two phase III studies comparing 6 months of either mFOLFOX6 or XELOX with 3 months of the same regimen as adjuvant chemotherapy in patients with completely resected stage III colon cancer (ACHIEVE) or high-risk stage II colon cancer (ACHIEVE-2).** *Presenting Author: Takayuki Yoshino, National Cancer Center Hospital East, Chiba, Japan*

**Background:** The International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration was established to prospectively combine/analyze data from several randomized trials conducted around the world to test whether three months of oxaliplatin-based adjuvant therapy (FOLFOX4/ mFOLFOX6 or XELOX) is non-inferior for disease-free survival (DFS) to six months of the same therapy in patients with stage III or high-risk stage II colon cancer. ACHIEVE (JFMC47-1202-C3) and ACHIEVE-2 (JFMC48-1301-C4) are in progress as part of the IDEA project. **Methods:** The ACHIEVE and ACHIEVE-2 trials, conducted by the Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC), are open-label, randomized, phase III, multicenter studies in Japanese patients with completely resected stage III or high-risk stage II colon cancer, respectively. Main eligibility criteria are adenocarcinoma of the colon; ECOG performance status of 0-1; age 20 years or older; registration within eight weeks of curative resection; starting oxaliplatin-based chemotherapy within two weeks after registration; and adequate organ function. Allocation is done centrally with a 1:1 ratio using randomization stratified by the primary site, number of lymph nodes involved, regimen, age, and participating center for stage III, or by depth of invasion, number of lymph nodes examined, regimen, age, and participating center for high-risk stage II. The primary endpoint is to evaluate whether treatment for three months is not inferior to six months in terms of relapse-free survival (RFS), which is defined as time to colon cancer recurrence or death from any cause. Main secondary endpoints include DFS, overall survival (OS) and adverse events. The target sample size is 1,200 patients for stage III and 500 patients for high-risk stage II. As of February 2014, 992 patients have been randomized for stage III. Enrollment for high-risk stage II starts in February 2014. Study ID: UMIN 000008543 for ACHIEVE and UMIN 000013036 for ACHIEVE-2. Clinical trial information: UMIN 000008543 and UMIN 000013036.

**TPS3656 General Poster Session (Board #115A), Sat, 8:00 AM-11:45 AM**

**Biopsy-driven study to identify biomarkers predictive of clinical response to second-line regorafenib in patients with metastatic colorectal cancer.** *Presenting Author: Petr Kavan, Department of Oncology, McGill University and the Segal Cancer Center, Sir Mortimer B. Davis, Jewish General Hospital, Montreal, QC, Canada*

**Background**: Biopsy-driven trials offer unique opportunities for discovery and validation of molecular signatures. We began a Phase II investigator-initiated study (IIS) to identify biomarkers (BMs) predictive of response to regorafenib in patients with metastatic colorectal cancer (mCRC) (QCROC-06; NCT01949194). Regorafenib is an oral multikinase inhibitor that targets angiogenic, stromal and oncogenic kinases. Results from the CORRECT trial suggest that some patients benefit more than others from single-agent regorafenib, but the trial was not designed to study these differences (Grothey et al. The Lancet 381: 303-312, 2012). **Methods**: Patients with mCRC and at least one liver metastasis available for biopsy, who have failed first-line treatment, are eligible for this study of second-line treatment with single-agent regorafenib. The primary objective is to identify BMs in blood or tissue. Secondary objectives include progression free survival, response rate and safety. Patients are accrued at four Canadian centers to collect 42 evaluable pre-treatment biopsies. Two patients have been enrolled so far. The trial is part of a portfolio of sequential biopsy-driven IIS. Patients are primarily recruited after participating in QCROC-01, a prospective study to identify BMs of resistance to first-line therapy. A biopsy taken at resistance to first-line treatment serves as the entry biopsy for QCROC-06. Another biopsy at disease progression is optional. Genomic material is isolated from all biopsies, and blood is collected regularly for analysis of VEGF polymorphism and circulating tumor DNA. BMs will be identified using targeted and global profiling approaches. We assume a maximum of 10 BMs, and an overall type 1 error of 5%, and that a disease control rate of 74% will be achieved. With 80% power, this sample size allows us to detect BM(s) if the proportion of patients with the BM(s) is $\leq$ 26% in non-responders and $\geq$ 84% in responders. Bioinformatics analysis will correlate findings with response to regorafenib. The trial is supported by Bayer HealthCare. Clinical trial information: NCT01949194.

**TPS3657 General Poster Session (Board #115B), Sat, 8:00 AM-11:45 AM**

**Randomized phase Ib/II study of PF-05212384 plus 5-fluorouracil-leucovorin-irinotecan (FOLFIRI) versus bevacizumab plus FOLFIRI in metastatic colorectal cancer (B2151007; NCT01937715).** *Presenting Author: Zev A. Wainberg, David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA*

**Background:** Despite recent advances in cytotoxic chemotherapies and targeted agents, metastatic colorectal cancer (mCRC) continues to be an area of great unmet medical need. Patients with mCRC are typically treated with a fluoropyrimidine plus oxaliplatin or irinotecan, with or without an anti-angiogenic agent or monoclonal antibody to epidermal growth factor receptor. Although these regimens are considered standard of care, they are only moderately effective, and more-active regimens are needed. Signaling through the phosphatidylinositol 3-kinase (PI3K) pathway is associated with resistance to chemotherapies with different mechanisms of action, including taxanes and DNA-damaging agents, in nonclinical models. In the clinic, PI3K pathway activation in tumors has been correlated with decreased response to therapy and worse clinical outcomes. The combination of PF-05212384 (intravenous PI3K/mammalian target of rapamycin inhibitor) and irinotecan was additive in preclinical mCRC models and showed preliminary antitumor activity with acceptable tolerability in a phase I study (B1271002; NCT01347866) in patients with cancer, including mCRC, warranting further exploration of irinotecan-based combination regimens. **Methods:** This global study includes a dose escalation, phase Ib portion to evaluate dose limiting toxicities (primary endpoint) and determine the recommended phase II dose of PF-05212384 combined with FOLFIRI. A separate lead-in cohort to confirm the safety of the PF-05212384/FOLFIRI combination will be conducted at clinical sites in Japan. Then, a randomized phase II portion will investigate whether PF-05212384 plus FOLFIRI is superior to bevacizumab plus FOLFIRI in prolonging progression-free survival (primary endpoint) in patients with mutated or wild-type *KRAS* mCRC and disease progression on a first-line oxaliplatin-containing regimen or with progression within six months of an oxaliplatin-containing regimen in the adjuvant setting. Secondary endpoints include safety, overall survival, and biomarker correlations associated with the PI3K pathway. This trial is now recruiting. Clinical trial information: NCT01937715.

**TPS3658 General Poster Session (Board #116A), Sat, 8:00 AM-11:45 AM**

**A randomized, double-blind, placebo-controlled, multicenter, binational, phase II trial of immunotherapy with L-BLP25 (tecemotide) in patients with colorectal carcinoma following R0/R1 hepatic metastasectomy.** *Presenting Author: Stefan Kasper, Department of Medical Oncology, West German Cancer Center, University Hospital Essen, Essen, Germany*

**Background:** Surgical resection is the only potentially curative treatment for colorectal cancer (CRC) metastases. The five-year survival rate following R0 resection of liver mets is 28-39% and recurrence occurs in approximately 70%. Adjuvant chemotherapy does not significantly improve clinical outcomes. The primary endpoint of the L-BLP25 In Colorectal Cancer trial (LICC) is to test if tecemotide, an active MUC1-specific cancer immunotherapy, increases recurrence-free survival (RFS) time over placebo in CRC patients (pts) after R0/R1 resection of hepatic mets. **Methods:** This is a binational, phase II, multicenter, randomized, double-blind, placebo controlled trial with a sample size of 159 pts from 23 centers in pts with stage IV CRC limited to liver mets. Pts must have had a complete resection of the primary tumor with curative intent and a R0/R1 resection of all syn/metachronous mets. Eligible pts are randomized 2:1 to receive either tecemotide or placebo. Pts in the tecemotide arm receive a single dose of 300 mg/m$^2$ cyclophosphamide (CPA) three days before the first tecemotide dose, then primary treatment with tecemotide 930 $\mu$g weekly for eight weeks, followed by maintenance doses at six-week (year one and two) and 12-week (year three) intervals or until recurrence. In the control arm CPA is replaced by saline solution and tecemotide by placebo. Primary objective of the trial is RFS time. Secondary objectives include overall survival (OS), safety, tolerance, and RFS/OS in MUC1-positive cancers. Exploratory immune response analyses are independently run in a project supported by the German Ministry of Education and Research. The study started in Q3 2011. Recruitment is estimated to be completed by Q3 2014 and follow-up by Q3 2018. Interim analyses have not been planned and endpoint assessment is estimated for Q3 2017. Independent medical and radiological review will guarantee data quality. By Jan 24, 2014, 23 centers have been initiated and 81 pts recruited. Two SUSARS have been reported by Jan 2014. No practical issues have been identified during setup and early conduct of the study. Updated recruitment figures will be presented at the meeting. Clinical trial information: NCT01462513.

**TPS3659 General Poster Session (Board #116B), Sat, 8:00 AM-11:45 AM**

**Regorafenib assessment guided by metabolic imaging in refractory advanced colorectal cancer (aCRC): REGARD-C study.** *Presenting Author: Alain Hendlisz, Institut Jules Bordet, Brussells, Belgium*

**Background:** Regorafenib, an oral multi-tyrosine kinase inhibitor that shares with sorafenib several targets on tumor angiogenesis, oncogenesis, and tumor microenvironment, was recently approved for patients (pts) with pretreated advanced colorectal cancer (aCRC). The drug improves the pts' outcome, but with significant toxicities, underscoring the need to identify those who will not benefit. A previous study (SoMore trial) showed that early FDGPET-based metabolic response assessment (MRA) may adequately discriminate pts with chemorefractory aCRC unlikely to benefit from a sorafenib-capecitabine combination. RegARd-C aims to explore early MRA in pts treated with regorafenib as a clinical tool to spare pts from needless toxicity from a drug that gives them little or no benefit and as a translational tool to guide comprehensive genomic and epigenetic research on the determinants of drug resistance. **Methods:** RegARd-C's (EUDRACT 2012-005655-16) is a multi-centric prospective study. Its primary objective is to identify in a population of pts with pretreated aCRC, those who will not benefit from regorafenib given at 160 mg/day, three weeks/4. Baseline PET is repeated at D14 of the first treatment course. MRA results are blinded for the investigators. Tumor tissues, optionally obtained from a PET-measurable lesion, and blood samples (at baseline; after the first chemotherapy course; and every two months) are collected. Overall survival (OS) is the primary endpoint and will be correlated with metabolic parameters, and genetic, epigenetic and molecular aberrations assessed from tumor biopsies and blood samples using gene expression and methylation profiling, RNA and exome sequencing. As the study is exploratory, no formal hypothesis was formulated. We arbitrarily decided to have a sample size of 105 evaluable pts with 70 pts as a derivation set and 35 pts as a validation set. Taking into account an expected 20-25% drop-out rate, between 124 and 140 pts will be accrued.This sample size is, however, sufficient to validate the hypothesis generated by the SoMore study, which found a prognostic impact of homogeneous metabolic response on OS, with an estimated HR of 0.59. RegARd-C has accrued 76 pts since August 2013. Clinical trial information: NCT01929616.

**TPS3660 General Poster Session (Board #117A), Sat, 8:00 AM-11:45 AM**

**The NCIC CTG and AGITG CO.23 trial: A phase III randomized study of BBI608 plus best supportive care (BSC) versus placebo (PBO) plus BSC in patients (Pts) with pretreated advanced colorectal carcinoma (CRC).** *Presenting Author: Derek J. Jonker, The Ottawa Hospital Research Institute, Ottawa, ON, Canada*

**Background:** BBI608 is an orally-administered first-in-class cancer stemness inhibitor which blocks cancer stem cell (CSC) self-renewal and induces cell death in CSCs as well as non-stem cancer cells by inhibition of the Stat3, $\beta$-catenin and Nanog pathways. Encouraging signs of anticancer activity, particularly in colorectal carcinoma (CRC), were observed in a phase I dose escalation study: disease control in 8/12 (67%) evaluable patients (pts); median progression free survival (PFS) equals 14 weeks; median overall survival (OS) equals 47 weeks (Langleben *et al. J Clin Oncol* 2013; 31 suppl; abstr 2542). Similar activity in CRC pts was observed in a subsequent phase I/II extension study. On the basis of these data, a phase III trial was designed and is being conducted by the National Cancer Institute of Canada (NCIC) Clinical Trials Group and the Australasian Gastrointestinal Trials Group under special protocol assessment with the FDA. **Methods:** This randomized, double-blind, placebo (PBO)-controlled study (ClinicalTrials.gov NCT01830621) will assess the efficacy and safety of BBI608+best supportive care (BSC) versus PBO+BSC in pts with metastatic or advanced, unresectable, refractory CRC (target n=650). Pts have no remaining approved therapies available, having failed standard chemotherapy based regimens containing a fluoropyrimidine, irinotecan and oxaliplatin (and an EGFR inhibitor, if *KRAS* wild type). Pts are randomized in a 1:1 ratio to receive BBI608 480 mg or matching PBO twice daily continuously. Treatment will continue until disease progression, death, intolerable toxicity, or patient/investigator decision to stop. Primary endpoint is OS; secondary endpoints include disease control rate, PFS, safety, and quality of life. Analysis will be according to randomized group stratified by Eastern Cooperative Oncology Group performance status (0 vs. 1), *KRAS* status (wild type vs. mutant), prior anti-vascular endothelial growth factor therapy (yes vs .no), and time from diagnosis of metastatic disease to randomization ($<$18 vs. $\geq$18 months). In addition blood, plasma, and archival tissue will be assessed for pharmacokinetic and biomarker analyses and health utility will be measured. As of February 2014, 130 pts were randomized and recruitment is ongoing in Canada, Australia, New Zealand and Japan. Clinical trial information: NCT01830621.

**TPS3661 General Poster Session (Board #117B), Sat, 8:00 AM-11:45 AM**

**ONC-2012-001: A single-arm phase II study of tivantinib (ARQ 197) plus cetuximab in EGFR inhibitor-resistant *MET* high patients (pts) with locally advanced or metastatic colorectal cancer (CRC) with wild-type *KRAS*.** *Presenting Author: Lorenza Rimassa, Humanitas Cancer Center, Humanitas Clinical and Research Hospital, Rozzano, Italy*

**Background:** *MET* overexpression has been identified in 30-70% colorectal cancer (CRC) and activation of this pathway can be associated to resistance to cetuximab (Krumbach R et al, *Eur J Cancer* 41:1231-43, 2011). Tivantinib (ARQ 197) is a non-adenosine triphosphate (ATP)-competitive, oral inhibitor of the *MET* receptor tyrosine kinase. The ARQ 197-A-U252 phase I/II trial in wild-type *KRAS* metastatic CRC (mCRC) demonstrated that tivantinib in combination with irinotecan and cetuximab is well tolerated and showed encouraging antitumor activity, particularly in *MET*-high patients (pts) (Eng C et al, *J Clin Oncol* 31, 2013; suppl, abstr 3508). Additionally in the last years, the potential role of epidermal growth factor receptor inhibitors beyond progression in mCRC has been evaluated. Adding tivantinib to cetuximab is based on a strong rationale to improve outcome in cetuximab resistant *MET*-high mCRC pts. **Methods:** Enrollment in this single-arm, Simon 2-stage, phase II study (ONC-2012-001) has begun. Eligible pts have: MET-high (at immunohistochemistry), surgically unresectable, locally advanced or metastatic CRC; received $>$1 prior systemic therapy for advanced or metastatic disease; progressed on or after a cetuximab or panitumumab containing regimen after a best response of at least stable disease and within three months before enrollment; Eastern Cooperative Oncology Group performance score $<$ 2; adequate bone marrow, liver and kidney functions. Pts receive tivantinib 240 mg p.o. twice daily plus cetuximab 500 mg i.v. every two weeks and are evaluated by CT or MRI scan at eight-week intervals. The primary endpoint is objective response rate. Secondary endpoints include progression-free survival, overall survival and safety. Treatment continues until disease progression or unacceptable toxicity. Pts discontinued from study treatment will be followed for survival. As of January 28, 2014, four of the planned first-stage 21 pts have been enrolled. This trial is expected to complete enrollment by the end of 2014. Clinical trial information: NCT01892527.

**TPS3662 General Poster Session (Board #118A), Sat, 8:00 AM-11:45 AM**

**Randomized phase II study of regorafenib followed by cetuximab versus reverse sequence for wild-type *KRAS* metastatic colorectal cancer previously treated with fluoropyrimidine, oxaliplatin, and irinotecan (REVERCE).** *Presenting Author: Kohei Shitara, National Cancer Center Hospital East, Kashiwa, Japan*

**Background:** Regorafenib (RE) and cetuximab (CE) are both effective treatments for patients (pts) with metastatic colorectal cancer (mCRC) with the current standard sequence as CE followed by RE. For optimal continuum of care for mCRC pts, it is important to compare efficacy and safety of different sequential treatments. Furthermore, several possible biomarkers including oncogenic mutations and serum protein have been identified for both RE and CE treatment so far. The objective of this study is to evaluate the efficacy and safety of sequential treatment of RE followed by CE as compared with CE followed by RE. Exploratory objective is to investigate several biomarkers with an aim of producing findings that may be useful in elucidating the mechanism of resistance to each agent and contribute to future individualized therapy. **Methods:** This multicenter randomized phase II trial will enroll pts with *KRAS* wild-type mCRC after failure of chemotherapy including fluoropyrimidine, oxaliplatin, and irinotecan (UMIN000011294). Pts will be randomized (1:1; stratified by prior use of bevacizumab and intent to use irinotecan in combination with CE) to receive sequential treatment with RE followed by CE $\pm$ irinotecan or reverse sequence (CE $\pm$ irinotecan followed by RE). Primary endpoint is overall survival (OS). Secondary endpoints include time to sequential treatment failure (TTF), progression-free survival (PFS) of sequential treatment, anti-tumor effects (response rate, disease control rate) of RE or CE, safety, and patients reported outcome of quality of life (QOL). Exploratory endpoint is to investigate possible biomarkers including oncogenic mutations from circulating cell free DNA by liquid biopsy with serial measurement and multiple serum proteins related to epidermal growth factor receptor or vascular endothelial growth factor pathway change over time at several point of sequential treatment. To evaluate the similarity of OS between both arms (HR between 0.8 and 1.25), the sample size was planned as 180 subjects in total to observe 132 deaths with 1.5-year enrollment and subsequent 1.5-year follow-up periods. As of 21 Jan 2014, eight pts have been enrolled. Clinical trial information: UMIN000011294.

**TPS3663 General Poster Session (Board #118B), Sat, 8:00 AM-11:45 AM**

**A phase III study of the impact of a physical activity program on disease-free survival in patients with high-risk stage II or stage III colon cancer: A randomized controlled trial (NCIC CTG CO.21).** *Presenting Author: Christopher M. Booth, Division of Cancer Care & Epidemiology, Cancer Research Institute, Queen's University, Kingston, ON, Canada*

**Background:** Observational studies indicate that physical activity (PA) is associated with colon-cancer specific survival. The National Cancer Institute of Canada Clinical Trial Group CO.21 (CHALLENGE) trial is designed to determine the effects of a structured physical activity (PA) intervention on disease-free survival in high-risk stage II or III colon cancer survivors who have completed adjuvant chemotherapy within the previous 2-6 months. **Methods:** Phase III randomized controlled trial. Target sample size of 962 patients is powered to detect a Hazard Ratio of 0.75 for disease-free survival (DFS). Trial participants are stratified by centre, disease stage, body mass index, and performance prior to randomization to a structured PA intervention or general health education materials. The PA intervention consists of a behavioural support program and supervised PA sessions delivered over a three-year period, beginning with regular face-to-face sessions and tapering to less frequent face-to-face or telephone sessions. The goal of the PA program is to increase weekly PA by 10 METhours/week. The PA program is delivered by physical activity consultants trained in exercise physiology and behavior change. Outcomes:The primary endpoint is DFS. Important secondary endpoints include multiple patient-reported outcomes (including those that address fatigue), objective physical functioning, biologic correlative markers (including assessment of the insulin pathway), and an economic analysis. Data is also being collected on motivational outcomes and behavior change that will inform program delivery. Current Enrollment:The study is open at 20 centers in Canada and 26 centers in Australia and will open in other countries in 2014. Accrual as of February 3, 2014 includes 311 registered and 262 randomized patients. Summary: Cancer survivors and cancer care professionals are interested in the potential role of PA to improve disease-free survival and quality of life. A randomized controlled trial is needed to provide compelling evidence to justify changes in health care policies and practice. Clinical trial information: NCT00819208.

**TPS3664 General Poster Session (Board #119A), Sat, 8:00 AM-11:45 AM**

**Phase II randomized study of induction FOLFOXIRI plus bevacizumab (bev) followed by maintenance with bev alone or bev plus metronomic chemotherapy (metroCT) in metastatic colorectal cancer (mCRC): The MOMA trial.** *Presenting Author: Lisa Salvatore, U.O. Oncologia Medica 2, Azienda Ospedaliero-Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy*

**Background:** FOLFOXIRI plus bevacizumab (bev) followed by 5-FU plus bev is an efficacious option for first line tx of metastatic colorectal cancer (mCRC) patients (pts) (TRIBE study). CAIRO-3 trial demonstrated that maintenance with standard doses of capecitabine plus bev provides a significant second progression (PFS2) advantage, as compared to observation alone, although at the cost of some toxicities that limited the rate of reintroduction of CAPOX. Metronomic chemotherapy (metroCT) may represent an alternative and better tolerated strategy for targeting tumor angiogenesis and preclinical evidences show that it may synergize with bev in order to maximize the antiangiogenic effect. On the basis of such premises we are conducting the MOMA study to explore maintenance tx with bev alone or bev plus metroCT following a four-months induction phase with FOLFOXIRI plus bev. **Methods:** This is a multi-center, phase II randomized study. Pts with unresectable mCRC, untreated for the metastatic disease, are randomized to receive 8 cycles of induction FOLFOXIRI plus bv, followed by bev (7.5 mg/Kg every three weeks) until the evidence of disease progression (PD), or the same induction regimen followed by bev in combination with metronomic capecitabine and oral cyclophosphamide (Cape: 500 mg/tid, CTX: 50 mg/die) continuously, until PD. The primary end-point is first-line PFS. FOLFOXIRI plus bev is reintroduced in pts undergoing PD during maintenance. Secondary end-points are response rate, resection rate, duration of response, time to strategy failure, time to second PD, overall survival, safety profile and the evaluation of potential surrogate markers of bev and metroCT efficacy (including pharmacodynamic, pharmacokinetic, and pharmacogenetic parameters). According to Rubinstein and Korn's design, estimating a first-line PFS with CT plus bev of 11 months, to detect a hazard ratio of 0.75 in favour of the experimental arm, with a power of 80% and a type-I error of 15%, 173 events are required. From May 2012 to Jan 2014, 117 pts have been so far enrolled in 13 Italian centers and the study is still recruiting. Supported by ARCO Foundation. Clinical trial information: 2011-006332-23.

**TPS3665 General Poster Session (Board #119B), Sat, 8:00 AM-11:45 AM**

**E7208: A randomized phase II trial of irinotecan and cetuximab (IC) versus IC plus ramucirumab (ICR) in second-line therapy of KRAS wild-type colorectal cancer (CRC).** *Presenting Author: Howard S. Hochster, Department of Medical Oncology, Yale University School of Medicine, New Haven, CT*

**Background:** Anti-angiogenic therapy for CRC has been accepted as standard therapy with approval of bevacizumab (bev) in both first-line and second-line settings. At the time this study was started, the benefit of continuing an anti-angiogenic in second line therapy was unproven. Ramucirumab (RAM, IMC 1121b) is a humanized antibody directed against the VEGF-R2 receptor, which may prove to have different activity compared to anti-VEGF antibody (bev). Additionally, while combining the anti-EGFR antibody, cetuximab (CMAB), with bev in first-line unselected patients was not effective, it is unknown whether the same may be true with RAM plus CMAB in a second-line setting for KRAS-selected patients. **Methods:** The study was designed as a randomized phase II trial with 147 patients assigned to IC = Irinotecan (I) 180 mg/m2 IV plus CMAB 500 mg/m2 IV q2w versus ICR = IC plus RAM 8 mg/kg IV q2w. Eligibility included prior treatment on one prior oxaliplatin and bev-containing regimen and progression within 42 days of last bev, PS 0-1, KRAS codon 12,13 wild-type and standard other chemo and bev criteria. Doses were modified for neutropenia, diarrhea, mucositis, rash and grade 3 other toxicities. The study was activated 10/8/10. After the first 35 patients were enrolled, accrual was held 6/24/12 for toxicity analysis per protocol. More grade 3 events of mucositis, diarrhea, neutropenia and perforation events (including peri-rectal abscesses) were seen in the ICR arm. The study has been modified to reflect the actual doses received, and will reopen with modified ICR (mICR) = I 150 mg/m2, CMAB 400 mg/m2 and RAM 6 mg/kg IV q2w. An additional 100 pts will be accrued to the revised study, giving 85% power to detect improved median PFS from 4.5 to 7.65 months. New eligibility criteria include any progression from 1$^{st}$ line chemo (on or off), normal albumin, no bowel perforation or obstruction in last 6 months. The revision was approved by CTEP in December 2013 and will re-open to accrual in March 2014, with SWOG participation. Clinical trial information: NCT01079780.

**TPS3666 General Poster Session (Board #120A), Sat, 8:00 AM-11:45 AM**

**UCGI 25: A multicentric randomized phase II trial evaluating dual targeting of the epidermal growth factor (EGFR) using the combination of cetuximab and afatinib versus cetuximab alone in patients (pts) wih chemotherapy refractory wtRAS metastatic colorectal cancer (mCRC).** *Presenting Author: Hélène Senellart, Institut de Cancerologie de l'Ouest-site René Gauducheau, Nantes, France*

**Background:** A previous study assessing erlotinib-cetuximab combo in chemo- refractory wt KRAS mCRC (Weickhardt AJ, et al J Clin Oncol 201;30:1505-12) has shown encouraging data (ORR=41 %, PFS=5.6 months). Afatinib is an Erb-B family blocker that irreversibly blocks signaling from all relevant Erb-B family homo and heterodimers. **Methods:** We conduct a randomized phase II study to determine the benefit of afatinib plus cetuximab versus cetuximab alone in patients with wtRAS metastatic CRC after oxaliplatin and irinotecan failure.Key eligibility criteria: pts with mCRC expressing wt KRAS/NRAS status; ECOG status 0 or 1; no disease progression with previous anti-EGFR targeted therapy; failure with a prior regimen containing irinotecan or oxaliplatin for metastatic disease; pts must have previously received a thymidylate inhibitor at any point for treatment of CRC; Pts are randomized 2:1 to receive oral afatinib (40 mg/qd) in combo with i.v. cetuximab (500mg/m$^2$ q 2 weeks) or cetuximab alone (500mg/m$^2$ q2 weeks). Dose adjustments are permitted according to the occurrence of drug related Adverse Events (AE). Pts receive treatment until PD or unacceptable AE. Pts randomized in the cetuximab arm have the opportunity to crossover to the combo arm after disease progression. The primary endpoint is the 6-month PFS rate. Secondary endpoints include ORR, median PFS, OS, safety and tolerability. Target enrolment is 75 pts. Completion of pt recruitment and data analyses are awaited. this study is promoted by UNICANCER GI. Clinical trial information: NCT01919879.

**TPS3667 General Poster Session (Board #120B), Sat, 8:00 AM-11:45 AM**

**A phase IB/II study of neoadjuvant chemoradiotherapy with CRLX101 and capecitabine for locally advanced rectal cancer.** *Presenting Author: Michael Joseph Eblan, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC*

**Background:** Neoadjuvant chemoradiotherapy followed by surgical resection is the standard of care for locally advanced rectal cancer. There is strong interest in the development of novel agents and strategies to further improve the therapeutic ratio of chemoradiotherapy. One innovative approach is to incorporate nanoparticle (NP) therapeutics, which are known to preferentially accumulate in tumors. CRLX101 is a NP formulation of camptothecin (CPT), a potent nanotherapeutic shown to be safe in phase I clinical evaluation. In addition to inhibiting Topo-1, CRLX101 demonstrates durable suppression of HIF-1$\alpha$, a regulator of the tumor survival pathway that was previously considered un-druggable. It has also been implicated in resistance to radiotherapy. Preclinically, CRLX101 has been shown to be a potent radiosensitizer. The purpose of this study is to evaluate whether the addition of CRLX101 to capecitabine and radiotherapy can improve pathologic complete response (pCR) and clinical outcomes for rectal cancer. **Methods:** This ongoing open label, single-arm multicenter Phase Ib/II study is designed to identify the maximum tolerated dose (MTD) using a 3+3 dose escalation design. The MTD will be assigned as the recommended Phase II dose (RP2D). In Phase II, we will evaluate the efficacy of RP2D and further characterize the safety of CRLX101 when combined with CRT prior to surgery in patients with locally advanced rectal carcinoma (stage cT3-4N0 or cT1-4N+). Patients in the Phase Ib study with resectable disease and treated at the RP2D will be included in the Phase II study population. Target accrual is 53 evaluable patients in the Phase II trial, using a Simon two-stage design, with a primary endpoint of pCR. Secondary objectives include evaluation of pathologic response, disease free survival (DFS) and overall survival (OS). We hypothesize that our proposed regimen is safe, and will improve the rate of pCR as compared to 15-25% pCR rate of historical controls. If the results are consistent with a pCR rate of at least 35%, the treatment regimen will be considered worthy of further investigation. The study was initiated in December, 2013. Clinical trial information: NCT02010567.

**4000 Oral Abstract Session, Mon, 1:15 PM-4:15 PM**

**A randomized double-blind phase 2 study of ruxolitinib (RUX) or placebo (PBO) with capecitabine (CAPE) as second-line therapy in patients (pts) with metastatic pancreatic cancer (mPC).** *Presenting Author: Herbert Hurwitz, Duke University Medical Center, Durham, NC*

**Background:** Local and systemic inflammation (INFL) are hallmarks of cancer, including PC, that adversely impact prognosis. Given the role of JAK-STAT signaling in cancer INFL, the efficacy and safety of RUX, a JAK1/JAK2 inhibitor, given with CAPE in pts with mPC refractory to initial therapy was explored. **Methods:** Pts with adequate performance status and organ function who progressed after gemcitabine treatment were included. RUX + CAPE was well tolerated in a 9 pt safety run-in. Subsequently, 127 pts were randomized to CAPE 1000 mg/m$^2$ BID days 1–14 with either RUX 15 mg BID or PBO on days 1–21 of a 21-day cycle. The primary endpoint was OS; secondary endpoints included PFS and ORR. To detect a HR $\leq$0.6 with 2-sided $\alpha$=0.2 and $\beta$<0.2, final analysis was planned to occur after 97 deaths. Subgroup analyses were prespecified to explore treatment heterogeneity and a hypothesis that RUX would preferentially benefit pts with evidence of INFL. **Results:** In the randomized population, OS and PFS favored RUX (Table). Confirmed ORR was 7.8% for RUX and 0% for PBO. In a prespecified subgroup of pts with INFL, as measured by serum C-reactive protein (CRP > group median of 13 mg/L), OS significantly favored RUX over PBO (Table). In this subgroup, 3 and 6 month survival was 48% and 42% with RUX vs 29% and 11% with PBO, respectively. In pts with CRP $\leq$13 mg/L, significant benefits in OS or PFS were not observed (HR = 0.89 and 0.82, respectively). OS benefit was also seen in pts classified by modified Glasgow Prognostic Score (mGPS), a measure of INFL in cancer (HRs 0.91, 0.71, 0.49 for mGPS 0, 1, 2, respectively). The combination of RUX and CAPE was generally well tolerated. Grade 3 or 4 (G3/4) adverse events occurred in 75% and 82% of RUX and PBO pts, respectively. G3/4 neutropenia and thrombocytopenia were uncommon in RUX pts (1.7% and 0%, respectively). G3/4 anemia occurred more frequently on RUX (15.3%) than PBO (1.7%). **Conclusions:** RUX may improve OS and PFS in mPC pts with INFL characterized by elevated CRP or mGPS of 1 or 2. Clinical trial information: NCT01423604.

| HR (95% CI) | RUX | PBO |
|---|---|---|
| Randomized, n | 64 | 63 |
| OS | 0.79 (0.53–1.18) p=0.25 | |
| PFS | 0.75 (0.52–1.10) p=0.28 | |
| CRP >13 mg/L, n | 31 | 29 |
| OS | 0.47 (0.26–0.85) p=0.01 | |
| PFS | 0.62 (0.35–1.1) p=0.20 | |

**4001^ Oral Abstract Session, Mon, 1:15 PM-4:15 PM**

**Impact of chemoradiotherapy (CRT) on local control and time without treatment in patients with locally advanced pancreatic cancer (LAPC) included in the international phase III LAP 07 study.** *Presenting Author: Florence Huguet, Hopital Tenon, Paris, France*

**Background:** In the LAP07 multicenter randomized study, administration of CRT in patients with LAPC controlled with induction chemotherapy (CT) was not superior to continuing CT alone in terms of overall survival. However, whether CRT should have an impact on locoregional tumor control remains unknown. **Methods:** LAPC patients were first randomized to gemcitabine or gemcitabine plus erlotinib. Patients with controlled disease after 4 months of CT were then randomized to two additional months of CT or CRT 54 Gy and concurrent capecitabine. A quality control for radiotherapy was done using validation by a dummy run and assessment of treated patients. Primary objective was overall survival (OS) in patients who acceded to the second randomization. Survivals were estimated using the Kaplan-Meier method and compared using the log-rank test. **Results:** Among the 442 included patients, 269 patients had tumor control after 4 months of induction CT and were randomized to either the CRT arm (n=133) or the CT arm (n=136). The OS was not significantly different between the two arms (15.2 vs 16.5 months, p=0.8). At the time of analysis, 238 patients had a tumor progression, which was locoregional in 96 patients (50.5%) and metastatic in 97 patients (49.5%). In the CRT arm, patients had significantly less local tumor progression compared to the CT arm (34% vs 65%, p<0.0001). Median time without treatment (i.e. reintroduction of chemotherapy) was longer in the CRT arm compared to the CT arm (159 vs 96 days, respectively, p=0.05). **Conclusions:** Even though the OS was not improved in the CRT arm, patients with non-progressive LAPC after 4 months of induction CT had a longer time without treatment in the CRT arm with significantly less local tumor progression which could translate into a better quality of life. Clinical trial information: NCT00634725.

**4002 Oral Abstract Session, Mon, 1:15 PM-4:15 PM**

**ABC-03: A randomized phase II trial of cediranib (AZD2171) or placebo in combination with cisplatin/gemcitabine (CisGem) chemotherapy for patients (pts) with advanced biliary tract cancer (ABC).** *Presenting Author: Juan W. Valle, University of Manchester, Manchester Academic Health Science Centre; Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, United Kingdom*

**Background:** ABCs exhibit increased VEGF expression, correlating with metastatic disease. Combining cediranib (which inhibits VEGFR1, 2 and 3 tyrosine kinase and VEGF-induced signaling in endothelial cells) with CisGem may improve outcome. **Methods:** Pts with histo-/cytologically confirmed ABC, aged $\geq$18 yrs, ECOG PS 0-1 and adequate bone marrow, liver and renal function were randomized to receive Cis (25mg/m$^2$) followed by Gem (1000mg/m$^2$) on days 1 and 8 of a 21-day cycle (up to 8 cycles), plus either cediranib (20mg once daily [OD]) or placebo (OD), until disease progression (PD). Tumor assessment was performed 12-weekly until PD. The target hazard ratio (HR) for progression-free survival (PFS, primary endpoint) was 0.64, requiring 136 pts (for 92 PFS events, 80% power, alpha=0.2, two-sided, ITT analysis). **Results:** 124 pts were enrolled (62 per arm, Apr-11 to Sep-12, study closed early due to cessation of cediranib development). Pt characteristics (cediranib vs. placebo): median age 68.0 vs. 64.5 years; 45% vs. 55% female; 19% locally advanced and 81% metastatic vs. 13% and 87%; bile duct, gall bladder, ampulla (%): 61, 32, 6 vs. 63, 31, 6; prior adjuvant chemotherapy: 3% vs. 2%; ECOG PS 0, 1: 44, 56 vs. 45, 55%. The most common grade 3-4 non-haematological adverse events (AEs) were hypertension, diarrhea and fatigue; 50% and 45% of cediranib and placebo pts experienced grade 3-4 haematological AEs, predominantly neutropenia (40 vs. 39%). Response rate (RECIST, in evaluable pts): cediranib (23/55 [43%] vs. placebo 10/53 [19%], p=0.01. With a median follow-up of 11.9 mo, PFS was not different (median (95%-CI)): 7.7 (6.3 – 9.3) vs. 7.4 (5.7 – 8.6) mo, HR (80% CI) 0.99 (0.78 – 1.26), p=0.95; with a trend for longer OS in the cediranib arm, median (95% CI): 14.1 (10.2 – 16.0) vs. 11.9 (9.2 – 13.4) mo, HR (95% CI) 0.76 (0.50 – 1.14), p=0.19. ELISA was performed for 15 potential plasma biomarkers of which Angiopoietin-2 (HR 0.65 (0.44 to 0.97) p=0.006) and Fibroblast Growth Factor-b (HR 0.83 (0.68 to 1.00) p=0.009) were the most significant. **Conclusions:** Cediranib appears to improve response rate but not PFS; effect on OS may warrant further studies. Clinical trial information: NCT00939848.

**4003 Oral Abstract Session, Mon, 1:15 PM-4:15 PM**

**Phase III study of apatinib in advanced gastric cancer: A randomized, double-blind, placebo-controlled trial.** *Presenting Author: Shukui Qin, PLA Cancer Center of Nanjing Bayi Hospital, Nanjing, China*

**Background:** Molecular targeted therapy has made great progress in the treatment of gastric cancer. This paper reports the outcome of a phase III clinical study of apatinib, as an oral small molecular of VEGFR-2 tyrosine kinase inhibitor, in the treatment of patients with advanced gastric cancer who prior failure to second-line chemotherapy. This study may provide a new treatment options and leading a new hope for these patients. **Methods:** This is a multicenter, randomized, double-blind, placebo-controlled phase 3 trial. Apatinib or matching placebo, 850 mg, po, qd, 28 days as one cycle. Primary outcomes were overall survival. Study randomization was centralized and stratified according to the number of metastatic sites ($\leq$2 or >2). Planned to enroll 270 cases: 180 of apatinib and 90 of placebo. This trial was registered with ClinicalTrials.gov, number NCT01512745. **Results:** The patient baseline characteristics were similar in two arms in regards to age, historical of the disease, gender, ECOG scores, number of metastatic sites, pathological grading, clinical stage and therapy history(P>0.05). As the efficacy, median overall survival (mOS) was significantly prolonger in the apatinib group compare with in the placebo group (195 days versus 140 days ; HR= 0.71; 95% CI (0.54~0.94); p< 0.016). Median progression-free survival (mPFS) was also prolonged in the apatinib group compared with the placebo group (78 days versus 53 days, HR= 0.44, 95%CI (0.33~0.61), *P*<0.0001). The objective response rates (ORR) of apatinib group and placebo group were 2.84% and 0.00% respectively. As the safety, Treatment of apatinib group was generally well tolerated. Most of the adverse reaction could be managed by dose interruptions or reductions. Grade 3/4 adverse reactions that occurred in more than 2% of patients were hypertension, hand-and-foot syndrome, proteinuria, fatigue, anorexia, elevated aminotransferase. **Conclusions:** This study further confirmed the efficacy and safety of apatinib in the patients with advanced gastric cancer. 850 mg, qd is the recommended dose for clinical use. Clinical trial information: NCT01512745.

**4004 Oral Abstract Session, Mon, 1:15 PM-4:15 PM**

**Ramucirumab (RAM) plus FOLFOX as front-line therapy (Rx) for advanced gastric or esophageal adenocarcinoma (GE-AC): Randomized, double-blind, multicenter phase 2 trial.** *Presenting Author: Harry H. Yoon, Mayo Clinic, Rochester, MN*

**Background:** RAM, an anti-VEGFR2 monoclonal antibody, improved overall survival (OS) in 2 phase 3 trials in patients (pts) with previously treated gastric/gastroesophageal junction (GEJ) AC. We report the first assessment of RAM as 1st-line Rx for GE-AC. **Methods:** Pts with untreated metastatic or locally advanced unresectable GE-AC (PS ≤1) were randomized 1:1 to mFOLFOX6 plus RAM (8 mg/kg IV) v placebo (PL), q14d. Primary endpoint was progression-free survival (PFS), with 80% power to detect HR 0.71 ($\alpha$ =.3). Secondary endpoints included OS, response rate (RR), disease control rate (DCR), and safety. **Results:** 168 pts (RAM 84 v PL 84) enrolled at 47 US sites, 04/11 – 08/12. Pt characteristics: age (65 v 60); male (75% v 73%); gastric (23% v 24%), GEJ (31% v 27%), esophageal (46% v 49%); metastatic (95% v 94%). Median PFS 6.4 v 6.7 m (HR 0.98 [95% CI 0.69 – 1.37]; p =.89) and OS 11.7 v 11.5 m (HR 1.08 [0.73-1.58]). Subgroup analyses by primary tumor location: for esophageal, median PFS was 5.6 v 6.1 m (HR 1.30); for gastric/GEJ, PFS was 8.7 v 7.1 m (HR 0.77 [0.48 – 1.24]; p =.28) and OS 14.6 v 12.5 m. PFS rate at 3 m was higher in RAM v PL (89% v 75%, p =.020), but not at 6, 9, or 12 m. RR (CR, PR) 45% v 46%. DCR (SD, CR, PR) 85% v 67% (p =.008). Most common grade ≥3 adverse events (AEs): neutropenia (27% v 36%), fatigue (18% v 15%), neuropathy (9% v 11%). Grade ≥3 AEs of special interest were uncommon, except hypertension. Median cycles of OX were similar among arms (8.5 v 9.5), but cycles of 5FU or RAM/PL (both 9 v 11) were lower in RAM arm. Rx discontinuation for non-progressive disease (PD) was more common in RAM: pt/physician decision (27% v 10%), AEs (21% v 6%). In exploratory analyses that censored PFS at Rx discontinuation for non-PD, HR for PFS favored RAM arm (HR 0.76; p =.194), mainly in gastric/GEJ pts (PFS 9.3 v 7.6 m; HR 0.53 [0.29 – 0.97]; p =.036). **Conclusions:** Addition of RAM to FOLFOX did not improve median PFS but showed PFS difference at 3 m and improved DCR. Longer PFS in RAM v PL was observed in gastric/GEJ cancer pts. A higher non-PD discontinuation rate and lower drug exposure in RAM arm may have impacted PFS assessment. These data are critical for clinical development of RAM in gastric cancer. Clinical trial information: NCT01246960.

**4005 Oral Abstract Session, Mon, 1:15 PM-4:15 PM**

**RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab (RAM) plus paclitaxel (PTX) versus placebo (PL) plus PTX in the treatment of metastatic gastroesophageal junction and gastric adenocarcinoma (mGC) following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy—Efficacy analysis in Japanese and Western patients.** *Presenting Author: Shuichi Hironaka, Clinical Trial Promotion Department, Chiba Cancer Center, Chiba, Japan*

**Background:** RAINBOW, a global phase III trial, demonstrated significant improvements in overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) in patients (pts) with mGC receiving RAM, a human IgG1 VEGF-receptor-2 targeted antibody, plus PTX compared with PL plus PTX. In global trials for mGC, regional differences in survival outcomes have been reported. Here, we analyzed clinical outcomes of Japanese (JP) pts and Western (Europe, US, Australia) pts. **Methods:** Eligibility included Eastern Cooperative Oncology Group performance status ≤1, adequate organ function, and disease progression during or within 4 months of the last dose of first-line therapy. OS and PFS were compared using a stratified log-rank test. ORR was analyzed using a Cochran-Mantel-Haenszel test. **Results:** Of 665 patients randomized worldwide, 140 were JP pts and 398 were Western pts. Efficacy results are shown in the Table. **Conclusions:** Benefit was seen in PFS, ORR, and the 6-mos OS rate in the JP population, which was consistent with the Western population. Prolonged post-progression survival in JP pts may be due to higher use of post-discontinuation treatment (PDT) and may have masked the potential OS benefit. Clinical trial information: NCT01170663.

| | Japanese | | Western | |
|---|---|---|---|---|
| | RAM+PTX n=68 | PL+PTX n=72 | RAM+PTX n=198 | PL+PTX n=200 |
| mPFS, mos | 5.6 | 2.8 | 4.2 | 2.8 |
| HR, 95% CI | 0.503 (0.348-0.728) P=0.0002 | | 0.631 (0.506-0.786) P<0.0001 | |
| mOS, mos | 11.4 | 11.5 | 8.6 | 5.9 |
| HR, 95% CI | 0.880 (0.603-1.284) P=0.5113 | | 0.726 (0.580-0.909) P=0.0050 | |
| 6-mos OS, % | 94.1 | 71.4 | 66.0 | 49.0 |
| 12-mos OS, % | 47.1 | 48.6 | 34.8 | 21.7 |
| Post-progression survival (mOS – mPFS), mos | 5.8 | 8.7 | 4.4 | 3.1 |
| ORR, % | 41 | 19 | 27 | 13 |
| Odds ratio, 95% CI | 3.29 (1.46-7.44) P=0.0035 | | 2.51 (1.49-4.23) P=0.0004 | |
| PDT, % | 75 | 75 | 38 | 36 |
| Pts w/o PDT, n | 17 | 18 | 122 | 128 |
| mOS, mos | 9.6 | 4.3 | 5.6 | 4.1 |
| HR, 95% CI | 0.338 (0.124-0.922) P=0.0298 | | 0.685 (0.518-0.906) P=0.0076 | |

Abbreviations: CI, confidence interval; HR, hazard ratio; m, median; mos, months; PDT, postdiscontinuation therapy.

**4006^ Oral Abstract Session, Mon, 1:15 PM-4:15 PM**

**STORM: A phase III randomized, double-blind, placebo-controlled trial of adjuvant sorafenib after resection or ablation to prevent recurrence of hepatocellular carcinoma (HCC)** *Presenting Author: Jordi Bruix, BCLC Group, Liver Unit, Hospital Clinic, University of Barcelona, Barcelona, Spain*

**Background:** Sorafenib is a multikinase inhibitor with proven efficacy in unresectable HCC. We evaluated the efficacy and safety of adjuvant sorafenib for HCC. **Methods:** Patients who had undergone surgical resection or local ablation with curative intent and had an intermediate or high recurrence risk were eligible. Main inclusion criteria were Child-Pugh score 5–7, ECOG PS 0, and no residual disease confirmed by CT or MRI. Exclusion criteria included recurrent HCC, ascites, extrahepatic spread, macrovascular invasion, and prior systemic therapy for HCC. Patients were stratified by curative treatment, geographic region, recurrence risk, and Child-Pugh status and randomized 1:1 to treatment with sorafenib 400 mg orally twice a day or placebo for a maximum of 4 yrs. The primary endpoint was recurrence-free survival (RFS) by independent review. Secondary endpoints included time to recurrence (TTR) and overall survival (OS). **Results:** A total of 1114 patients were randomized (n=556 sorafenib; n=558 placebo). Baseline characteristics were balanced between groups. Median age was 59 yrs, 62% were Asian, 81% had resection, 97% were Child-Pugh A, and 46% had high recurrence risk. The analysis was based on a total of 464 RFS events. No differences in RFS, TTR, and OS were observed (Table). The sorafenib group had a shorter median treatment duration (12.5 vs 22.2 mos) and lower mean daily dose (578 vs 778 mg). Discontinuation rates with sorafenib were higher due to treatment-emergent adverse events (TEAE) (24% vs 7%) and consent withdrawal (17% vs 6%). Most common grade (Gr) 3–4 sorafenib TEAEs occurring more frequently vs placebo were hand-foot skin reaction (28%), hypertension (7%), and diarrhea (6%). **Conclusions:**The primary endpoint of the trial was not met. Adverse events are consistent with the known sorafenib safety profile and no new safety findings were observed. Clinical trial information: NCT00692770.

| | Sorafenib | Placebo | Hazard Ratio (95% CI) | P* |
|---|---|---|---|---|
| **Median, mos** | | | | |
| **RFS** | 33.4 | 33.8 | 0.940 (0.780 – 1.134) | 0.26 |
| **TTR** | 38.6 | 35.8 | 0.891 (0.735 – 1.081) | 0.12 |
| **OS** | NR | NR | 0.995 (0.761 – 1.300) | 0.48 |
| **TEAE, %** | | | | |
| **All Gr** | 98 | 90 | | |
| **Serious** | 40 | 42 | | |
| **Gr 3–4** | 69 | 47 | | |
| **Gr 5** | 3 | 2 | | |
| **Drug-related, all Gr** | 94 | 46 | | |
| **Serious** | 9 | 3 | | |
| **Gr 5** | <1 | <1 | | |

*One sided; NR, not reached.

**4007 Oral Abstract Session, Mon, 1:15 PM-4:15 PM**

**RTOG 0436: A phase III trial evaluating the addition of cetuximab to paclitaxel, cisplatin, and radiation for patients with esophageal cancer treated without surgery.** *Presenting Author: David H. Ilson, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** RTOG 0436 is a randomized Ph III trial evaluating cetuximab added to concurrent chemoradiation for patients (pts) undergoing non-operative management of esophageal carcinoma (EC). **Methods:** Pts with biopsy proven squamous cell or adenocarcinoma of the esophagus (T1N1M0; T2-4 AnyN M0; Any T/N M1a) were randomized to weekly concurrent cisplatin (50 mg/m2), paclitaxel (25 mg/m2) for 6 weeks and daily radiation 50.4 Gy/1.8 Gy fractions ± weekly cetuximab (400 mg/m2 day 1 then weekly 250 mg/m2) for 6 weeks. Pts were stratified by histology, tumor size (< 5 cm vs > 5cm) and the status of celiac lymph nodal involvement. Overall survival (OS) was the primary endpoint, with a planned accrual of 420 pts to detect an increase in 2-year OS from 41% to 53%; 80% power and 1-sided 0.025 alpha. An interim analysis of cCR was planned for the first 150 of each histology. **Results:** The study accrued 344 pts from 2008-2013 and 328 were eligible. Based on interim analyses, the study stopped accruing adeno pts in 5/2012 and SCC pts in 1/2013. Pts were well matched for pretreatment characteristics: 80% T3/4 disease, 66% N1, and 19% celiac nodes. Grade 3/4/5 treatment (tx) related AEs were 45%, 22%, 4% in Arm 1 (cetuximab) and 49%, 17%, 1% in Arm 2 (no cetuximab). A cCR rate of 56% was observed in Arm 1 vs 59% in Arm 2 [p=0.72]. No differences were seen in cCR between tx arms for either histology. The 12 and 24 mo OS rates for cCR pts were 79% and 58% vs 53% and 30% for those with residual disease [p<0.0001]. Median follow-up for all pts is 15.4 mos. The 12 and 24 mo OS (95% CI) for Arm 1 is 64% (56%, 71%) and 44% (36%, 52%) vs 65% (57%, 72%) and 42% (34%, 50%) for Arm 2 [p=0.70]. Adeno pts (n=203) had a 12 and 24 mo OS of 65% and 43% for Arm 1 vs 64% and 41% for Arm 2 [p=0.37]. The 12 and 24 mo OS for the 125 SCC pts was 62% and 46% for Arm 1 vs 67% and 43% for Arm 2 [p=0.97]. **Conclusions:** Cetuximab added to chemoradiation did not improve OS. There were no differences in cCR rates by tx arm. These results add to the growing body of literature indicating no benefit for current EGFR targeted agents in the tx of unselected patients with EC. Supported by RTOG CA21661 and CCOP CA3742 NCI grants and Bristol Myers Squibb. Clinical trial information: NCT00655876.

**4008 Oral Abstract Session, Mon, 1:15 PM-4:15 PM**

**Phase III trial to compare capecitabine/cisplatin (XP) versus XP plus concurrent capecitabine-radiotherapy in gastric cancer (GC): The final report on the ARTIST trial.** *Presenting Author: Jeeyun Lee, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

**Background:** The adjuvant chemoradiation therapy in stomach cancer (ARTIST) trial is the first study to investigate the efficacy of postoperative chemoradiation therapy as adjuvant treatment in gastric cancer patients with curative resection and extended D2 lymph node dissection. In this study, we report on the final analysis of the disease free survival (DFS) and survival (OS). **Methods:** XP arm received six cycles of XP (capecitabine 2000 mg/m$^2$ per day on days 1 to 14 and cisplatin 60 mg/m$^2$ on day 1, repeated every 3 weeks) chemotherapy. XP/XRT/XP arm received two cycles of XP followed by 45 Gy radiotherapy (capecitabine 1650 mg/m$^2$/d for 5 weeks) and two cycles of XP. Preplanned subgroup analyses on Lauren classification and lymph node status were performed. EGFR, HER2 and MET overexpression were studied in this patient cohort and correaltive analyses with DFS and OS were performed. **Results:** Of 458 patients, 228 patients were randomized to the XP arm and 230 patients were randomized to the XP/XRT/XP arm. At final analysis, the addition of radiotherapy to XP chemotherapy did not significantly prolong DFS (HR 1.352, 95% CI 0.952 - 1.922; P=0.0922). In the intestinal subtype, however, DFS on the XP/XRT/XP arm was significantly prolonged when compared with XP alone (HR 2.883, 95% CI, 1.36 - 6.111, P=0.0057). In contrast, the addition of RT to XP in diffuse type GC did not considerably prolong DFS (HR 1.161, 95% CI, 0.753-1.791; P=0.4985). In accordance with the results from the first report, the DFS was superior in XP/XRT/XP then XP alone in LN(+) group. Currently, biomarker analyses including HER1, HER2, MET are being carried out. The correlative analyses between these markers and DFS/OS will be presented. **Conclusions:** Overall, the ARTIST trial was a negative trial with no significant difference in DFS between XP alone and XP/XRT/XP. However, XP/XRT/XP significantly prolonged DFS in intestinal type by Lauren classification when compared to XP alone. After a longer follow up duration, XP/XRT/XP seemed to benefit LN(+) GC patients. Hence, a subsequent ARTIST-II (TS-1 alone, TS-1/oxaliplatin, TS-1/oxaliplatin/RT) is enrolling patients with pathologic LN(+) GC. Clinical trial information: 00323830.

**4009 Poster Highlights Session (Board #27), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**A randomized phase III study in advanced esophageal cancer (OC) to compare the quality of life (QoL) and palliation of dysphagia in patients treated with radiotherapy (RT) or chemoradiotherapy (CRT) TROG 03.01 NCIC CTG ES.2.** *Presenting Author: Michael Gordon Penniment, Royal Adelaide Hospital, Adelaide, Australia*

**Background:** RT is known to relieve dysphagia of advanced oesophageal cancer, there is no data from randomised phase III trials determining response, toxicity, or role of palliative CRT. Aims 1) to establish effective and least toxic treatment for symptom relief of advanced OC 2) determine effects of common cancer treatments on QoL and end of life care 3) establish an evidence base for patient decision making regarding the optimal management for incurable OC. **Methods:** 220 patients were randomised to receive a course of palliative RT [35 Gy in 15 fractions, (n=115) or 30 Gy in 10 fractions (n=105) in Canada and UK], or concomitant CRT with Cisplatin and 5FU (D1-4) (n=111). Dysphagia was measured using the Mellow score, toxicity using CTCAE v2, and QoL using EORTC QLQ30 and oesophagus module (OES-18). The primary end point was the proportion of patients with improved dysphagia as measured at week 9 and maintained until week 13. **Results:** The patients receiving radiotherapy alone showed a dysphagia response (at any point) of 67.89% compared to chemotherapy response in 73.87%, this was not a significant difference (p=0.343). There was increased toxicity in patients receiving CRT, with worse bowel conditions (nausea (p=0.0019) and vomiting (p=0.0072)). The median survival was 210 days for CRT and 203 days for RT alone. The baseline parameters of both groups were well matched at randomisation and although the results of the trial showed equally poor survival prognosis in both arms, there were some patients (n=21) still alive at 2 years post treatment. **Conclusions:** Although the CRT group had slightly better dysphagia response and median survival, the bowel toxicity was worse. Further analysis of QoL, toxicity and durable palliative response will be published. This multicentre trial, conducted in the UK, Canada, Australia and New Zealand reflects practice in several countries RT alone remains an excellent tool for palliation of patients with advanced OC and should remain the standard of care. Clinical trial information: NCT00193882.

**4010 Poster Highlights Session (Board #28), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Can induction chemotherapy improve dysphagia in locally advanced esophageal/GEJ cancer?** *Presenting Author: Elizabeth Won, Memorial Sloan-Kettering Cancer Center, New York, NY*

**Background:** Dysphagia is one of the most common presenting symptoms in esophageal cancer (EC) and can lead to significant nutritional decline, which is associated with increased toxicity and poor outcomes. Invasive feeding tubes (FT) or endoscopic stents are frequently used to improve nutrition in this setting. We evaluated the role of induction chemotherapy prior to concurrent chemoradiation as presurgical treatment in improving dysphagia. **Methods:** Retrospective analysis of 4 prospective studies conducted at MSKCC with induction chemotherapy followed by concurrent chemoRT and surgery in locally advanced esophageal/GEJ cancer. Regimens included cisplatin/paclitaxel, cisplatin/irinotecan, and cisplatin/irinotecan/bevacizumab. Dysphagia was graded prospectively using a validated dysphagia scale. Response of dysphagia and nutritional status to induction chemotherapy was evaluated. **Results:** Of 161 patients (pts) undergoing induction chemotherapy, [median age 59(21-76), KPS 90 (70-100), 77% adenocarcinoma], 121 (76%) had dysphagia, with 59(37%) with grade 2 dysphagia or higher (20% Stage II, 80% Stage III). 6(4%) required EGD dilatation/stent and none required FT placement prior to treatment. 22% pts had>10% body weight loss prior to treatment and average weight loss in all pts was 4.3kg. After induction chemotherapy, 103 (65%) had improvement in dysphagia. This was associated with a weight gain in 42% of pts. Only 7(4%) had worsening dysphagia after induction chemotherapy: 4/7 required FT (2% of all pts), 2/7 EGD intervention (1% of all pts). 6/7 of these pts with worsening dysphagia had poor short term outcomes: 2/7 progressive disease, 3/7 unresectable, 1/7 post-operative death. **Conclusions:** Induction chemotherapy prior to concurrent chemoradiation for locally advanced esophageal cancer can effectively improve swallowing and nutritional status, while mitigating need for feeding tubes or stents in patients with significant dysphagia. Post-induction dysphagia may be prognostic and merits further investigation. Research supported by Foundation 14.

**4011 Poster Highlights Session (Board #29), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Impact of external-beam radiation therapy on outcomes among patients with resected gastric cancer: A multi-institutional analysis.** *Presenting Author: Aslam Ejaz, The Johns Hopkins University School of Medicine, Baltimore, MD*

**Background:** Use of perioperative chemotherapy (CTx) alone versus chemoradiation therapy (cXRT) in the treatment of resectable gastric cancer remains varied. We sought to define the utilization and effect of CTx alone versus cXRT on patients having undergone curative-intent resection for gastric cancer. **Methods:** Using the multi-institutional U.S. Gastric Cancer Collaborative database, we identified 505 patients between 2000 and 2012 with gastric cancer who received perioperative therapy in addition to curative-intent resection. The impact of perioperative therapy on survival was analyzed by the use of propensity-score matching of clinicopathologic factors among patients who received CTx alone versus cXRT. **Results:** Median patient age was 62 years and the majority of patients were male (58%). Surgical resection involved either partial gastrectomy (54%) or total gastrectomy (46%). On pathology, median tumor size was 5.0 cm; most patients had a T3 (37%) or T4 (36%) lesion and lymph node metastasis (74%). Margin status was R0 in most patients (89%). 211 (42%) patients received perioperative CTx alone whereas the remaining 294 (58%) patients received 5-FU based cXRT. Factors associated with receipt of cXRT were younger age (OR 0.98), T3 tumors (OR 1.52), and lymph node metastasis (OR 2.03) (all P < .05). Recurrence occurred in 214 (39%) patients. At a median follow-up of 28 months, median overall survival (OS) was 33.4 months and 5-year survival was 36.7%. Factors associated with worse OS included tumor size (HR 1.1), T-stage (HR 1.5), and lymph node metastasis (HR 1.58) (all P<0.05). In contrast, receipt of cXRT was associated with improved long-term OS (CTx alone: 21 months vs. cXRT 45 months; p<0.001). In the propensity-matched multivariate model that adjusted for tumor size, T-stage, and nodal status, cXRT remained associated with an improved long-term disease-free (HR 0.43) and overall (HR 0.41) survival (both P<0.001). **Conclusions:** XRT was utilized in 58% of patients undergoing curative-intent resection for gastric cancer. Using propensity-matched analysis, cXRT was an independent factor associated with improved recurrence-free and overall survival.

**4012 Poster Highlights Session (Board #30), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Lymph node yield and survival in gastric carcinoma.** *Presenting Author: Jennifer E. Samples, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

**Background:** Although the extent of lymph node (LN) dissection in gastric cancer remains controversial, it is recommended that at least15 LN be examined for accurate staging. Existing data suggest that many gastrectomies performed in the US do not achieve this benchmark. This study examines trends in LN yield over time in patients undergoing curative surgery for gastric cancer and the relationship between LN yield and survival. **Methods:** Under IRB waiver, all National Cancer Database patients who underwent total, distal or proximal gastrectomy for gastric cancer from 1998-2011 were examined. Patients with metastatic disease or for whom treatment was indicated to be palliative were excluded from this study. Wilcoxan rank-sum test was used to compare LN yield. Cox proportional hazards models were used to compare overall survival. **Results:** 73,674 patients met inclusion criteria. 7,938 (10.8%) had neoadjuvant therapy. Patients who received neoadjuvant therapy had higher median LN yield than patients who did not (12 vs. 9, $p<0.001$). Median LN yield improved over time (8 in 1998 vs. 11 in 2011, $p<0.001$), as did the proportion of patients with LN yield >15 (21% in 1998 vs. 36% in 2011, $p<0.001$). Median overall survival (OS) was positively associated with LN yield in node-positive and node-negative patients. See Table. These survival differences persisted after adjustment for patient demographics and comorbidity. **Conclusions:** Slow improvement in LN yield has been seen on a population level over the past two decades, although nearly two thirds of all patients undergoing curative resection still have fewer than 15 LN examined. Higher LN yield is associated with better OS in patients with resectable gastric carcinoma. Based on these results, continued effort is needed to improve surgical quality in patients undergoing curative resection for gastric cancer.

| | | 0-15 LN | 16-25 LN | 26+ LN | 0-15 LN (ref) | 16-25 LN | | 26+ LN | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Median survival (months) | | | aHR | aHR | CI | aHR | CI |
| **T1-2N0** | 21079 | 75 | 109 | 121 | 1.0 | 0.75 | 0.67-0.81 | 0.71 | 0.63-0.81 |
| **T-2N1** | 11283 | 29 | 43 | 67 | 1.0 | 0.83 | 0.77-0.89 | 0.63 | 0.57-0.71 |
| **T3N0** | 5814 | 31 | 56 | 69 | 1.0 | 0.73 | 0.64-0.82 | 0.65 | 0.53-0.79 |
| **T3N1** | 10462 | 17 | 26 | 37 | 1.0 | 0.79 | 0.74-0.85 | 0.59 | 0.53-0.66 |
| **T1-2N2-3** | 3305 | 17 | 22 | 37 | 1.0 | 0.77 | 0.69-0.86 | 0.51 | 0.43-0.60 |
| **T3N2-3** | 6176 | 12 | 16 | 19 | 1.0 | 0.75 | 0.69-0.81 | 0.66 | 0.59-0.74 |

**4014 Poster Highlights Session (Board #32), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Toxicity, surgical complications, and short-term mortality in a randomized trial of neoadjuvant cisplatin/5FU versus epirubicin/cisplatin and capecitabine prior to resection of lower esophageal/gastroesophageal junction (GOJ) adenocarcinoma (MRC OEO5, ISRCTN01852072, CRUK 02/010).** *Presenting Author: David Cunningham, Royal Marsden Hospital, Sutton, United Kingdom*

**Background:** Randomized trials have shown that neoadjuvant approaches improve survival following esophagectomy. Data on toxicities from the different approaches are often not reported in detail. **Methods:** OEO5 is a Cancer Research UK funded multi-centre, phase III randomized clinical trial for resectable (T1/2 N1 M0 to T3/4 N0/1 M0) adenocarcinoma of the lower esophagus and Type I/II GOJ. Patients were randomly allocated (1:1) to 2 cycles of cisplatin/5FU (CF) or 4 cycles of epirubicin/cisplatin and capecitabine (ECX) pre-operatively followed by esophagectomy with 2-field lymphadenectomy. The Independent Data Monitoring Committee and Trial Steering Committee agreed to release data on treatment related toxicities and deaths up to 90 days post-surgery. Overall survival is the primary outcome measure but is not yet mature; events having accrued more slowly than expected. **Results:** Between 2005 and 2011, 897 patients (median age 62 years (range 27-81), 90% male, 63% T3 N1, WHO PS 0-1) were randomly allocated to CF (451) or ECX (446). CF: 96% received 2 cycles, ECX: 81% received 4 cycles. Any grade 3/4 toxicity (CF 30%, ECX 47%, $p<0.001$), (CF v ECX: neutropenia 16% v 23%, diarrhoea 1% v 8% and plantar palmar erythema 0% v 9%). Median time (days) from randomisation (day 1 of last chemo cycle) to surgery (CF 72 (45), ECX 128(58)). Surgical data were available on 878 (CF 446, ECX 432) patients, with 84% reported as having resection and reconstruction. Post-operative complications reported in CF 54% and ECX 59% (life threatening complications CF 7% vs ECX 9%). No differences were seen in anastomotic leak rates (clinical 11%, radiologic only 5%), thromboembolic complications (4%) or deaths within 30 days of operation (2% both arms), or within 90 days (CF 4%, ECX 5%). **Conclusions:** Four cycles of ECX compared to 2 cycles of CF increased chemotherapy related toxicity, but did not affect resection rates, surgical complications or 90 day mortality. Clinical trial information: ISRCTN01852072.

**4015 Poster Highlights Session (Board #33), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Association of a DNA damage response deficiency (DDRD) assay and prognosis in early-stage esophageal adenocarcinoma.** *Presenting Author: Richard C. Turkington, Centre for Cancer Research and Cell Biology, Queen's University Belfast, Belfast, United Kingdom*

**Background:** The incidence of esophageal adenocarcinoma (EAC) has increased 6-fold in the last 30 years and in early stage EAC 5-year survival remains poor at 25-35%. Neoadjuvant therapy confers a significant improvement in outcomes but the optimal approach for individual patients remains unclear. We assessed a 44 gene DNA Damage Response Deficient (DDRD) assay, previously developed to detect loss of the Fanconi Anaemia (FA)/BRCA pathway in breast cancer, as a predictor of prognosis following DNA damaging chemotherapy in EAC. **Methods:** This study was conducted using 63 formalin fixed paraffin embedded (FFPE) pre-treatment endoscopic biopsy specimens from early stage EAC patients treated with cisplatin-based neoadjuvant chemotherapy followed by surgical resection between 2004 and 2010 at the NI Cancer Centre. EAC biopsies were profiled using the Xcel array, a cDNA microarray-based technology optimized for archival FFPE tissue (Almac/Affymetrix), and scored for the DDRD assay. The association between the DDRD score and prognosis was assessed by Kaplan-Meier analysis and Cox Proportional Hazards regression. **Results:** Sufficient quality RNA for analysis was obtained for 62 out of 63 samples (98.4%). A total of 13 samples (21%) were characterised as DDRD positive with the remaining 49 samples (79%) DDRD negative. With a median follow up of 65 months, DDRD assay positivity demonstrated a statistically significant association with disease-free (HR 0.33; 95% CI 0.13-0.87; $p=0.024$) and overall survival (HR 0.32; 95% CI 0.12-0.82; $p=0.017$; median DDRD+ve 94.3 months vs DDRD-ve 32.2 months). The assay was not predictive of survival in patients who did not receive chemotherapy. **Conclusions:** The DDRD assay is the first array-based biomarker using pre-treatment FFPE biopsies to be validated as predictive of prognosis following DNA damaging chemotherapy in early stage EAC.

**Multivariable analysis of disease-free survival.**

| | Hazard ratio | Lower 95% CI | Upper 95% CI | p value |
|---|---|---|---|---|
| **DDRD-positive** | 0.310 | 0.110 | 0.877 | 0.027 |
| **Surgical T stage 2 vs 0 & 1** | 0.343 | 0.078 | 1.519 | 0.159 |
| **Surgical T stage 3+ vs 0 & 1** | 0.470 | 0.126 | 1.751 | 0.261 |
| **N stage 1 vs 0** | 4.793 | 1.590 | 14.447 | 0.005 |
| **N stage 2 & 3 vs 0** | 7.822 | 2.777 | 22.034 | <0.001 |

**4016 Poster Highlights Session (Board #34), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Epidermal growth factor receptor copy number gain (EGFR CNG) and response to gefitinib in esophageal cancer (EC): Results of a biomarker analysis of a phase III trial of gefitinib versus placebo (TRANS-COG).** *Presenting Author: Russell D. Petty, University of Aberdeen, Aberdeen, Scotland*

**Background:** The Cancer Oesophagus Gefitinib (COG) trial randomised (1:1) 450 patients(pts) with advanced EC who had progressed after 1-2 lines of chemotherapy to gefitinib (G) or placebo (P). Improved disease control rates- DCR= RECIST CR+PR+SD at 8 weeks (P 15.6%, G 24.1%, $p = 0.016$), improved patient reported outcomes, and progression free survival (HR = 0.80, 95%CI 0.66, 0.96, $p = 0.020$) were seen with G-indicative of rapid and durable responses that were observed in a subset. We hypothesised that EGFR CNG in ECs would identify a subgroup responsive to G. **Methods:** EGFR CNG was determined by FISH on FFPE tumour specimens(all subject to central pathology review) and performed blind to treatment allocation and outcome. Disomy, low and high trisomy and low polysomy were classified as negative (No CNG) and high polysomy and amplification as positive(CNG). Primary endpoint was OS for G versus P in EGFR CNG and no CNG groups. Secondary endpoints were PFS, DCR and HRQL and outcomes in EGFR amplified patients only. **Results:** EGFR FISH results were available for 295 patients. Clinical features were not different from the COG trial . EGFR CNG was found in 46/295 (15.6%). There was no significant correlation with EGFR CNG and any clinical features which were also balanced in G and P groups. In EGFR CNG Pts OS was improved with G compared to P (HR=0.53 95%CI 0.28, 0.98 $p=0.042$), with survival for G vs P 71 vs 64% ,38 vs 14% , 25 vs 5% and 13 vs 0% at 3 ,6, 9, and 12 months respectively. There was no difference in OS for G vs P in EGFR No CNG pts (HR=0.892 95%CI 0.69, 1.16 $p=0.395$). For PFS EGFR CNG pts, HR=0.58, 95%CI 0.30, 1.07 $p=0.080$ for G vs P and HR=0.83 95% CI 0.64, 1.07,$p=0.144$ for EGFR No CNG pts. DCR was improved for G in EGFR CNG pts(42 vs 13%, $p=0.035$), and less so for EGFR No CNG (24 vs 14 %, $p=0.053$). EGFR amplification(6%) pts gained greatest benefit from G ( OS, HR=0.19 95%CI 0.05, 0.65 $p=0.007$). **Conclusions:** EGFR CNG identified a subgroup of EC who benefit from Gefitinib as a second line treatment and is a useful predictive biomarker for the first stratified treatment approach in this setting and also a subgroup that may be responsive to other anti-EGFR therapies. Clinical trial information: ISRCTN32435732.

**4017 Poster Highlights Session (Board #35), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Tumor profiling of 1,306 gastric and esophageal carcinomas and different treatment options.** *Presenting Author: John Thomas Miura, Medical College of Wisconsin, Milwaukee, WI*

**Background:** NCCN guidelines state that chemotherapies for esophageal and gastric carcinomas may be used interchangeably. We interrogated biomarkers from a large cohort of gastroesophageal cancer patients to identify similar and different alterations with therapeutic implications for gastric and esophageal cancers. **Methods:** 666 gastric adenocarcinoma (GA) and 640 esophageal (553 adenocarcinoma, or EA, and 87 others) cases were evaluated by a combination of sequencing (Sanger, NGS), protein expression (IHC) and gene amplification (CISH/FISH). **Results:** In the complete cohort of 1306 patients, 30 of 45 (66%) genes tested had mutations, with the highest rates seen in TP53 (54%), APC (10%), SMAD4 (5.9%), KRAS (5.9%) and PIK3CA (5.1%). Elevated IHC of TOP2A was seen in 76% of cases, TOPO1 in 51% and SPARC in 25%; decreased IHC of ERCC1 was seen in 65%, RRM1 in 62%, TS in 61% and MGMT in 45%, indicating benefit from epirubicin, irinotecan, nab-paclitaxel, platinums, gemcitabine, 5FU/capecitabine and temozolomide, respectively. In the HER2-positive cases, additional alterations were seen including low TS (50%), ERCC1 (63%), RRM1 (55%) and high TOPO1 (53%), indicating potential benefit from combining trastuzumab with 5FU/capecitabine, cisplatin, gemcitabine and irinotecan, respectively. When comparing EA to GA, select biomarkers showed a differential pattern between cancer types (Table), suggesting potential variability in efficacy of available therapeutic agents. **Conclusions:** A multiplatform biomarker analysis identified common actionable targets in gastric and esophageal cancer as well as significant biomarker differences in EA and GA. This indicates the potential clinical impact of molecular profiling and highlights the need for separation of the two cancer entities for therapeutics.

**Biomarker comparison of gastric (GA) and esophageal adenocarcinoma (EA).**

| Target biomarker | Associated therapeutic agent | EA (%) | GA (%) | p-value |
|---|---|---|---|---|
| **IHC** | | | | |
| **HER2** | trastuzumab | 13 | 4.6 | <0.01 |
| **SPARC** | nab-paclitaxel | 34 | 15 | <0.01 |
| **TOP2A** | epirubicin | 86 | 67 | <0.01 |
| **TOPO1** | irinotecan | 55 | 46 | 0.01 |
| **FISH** | | | | |
| **HER2** | trastuzumab | 22 | 9 | <0.01 |
| **EGFR** | cetuximab | 33 | 16 | <0.01 |
| **SEQ** | | | | |
| **KRAS** | cetuximab* | 3.8 | 8.4 | <0.01 |
| **PIK3CA** | mTOR inhibitors | 2.4 | 7.8 | 0.04 |

*Lack of benefit.

**4018 Poster Highlights Session (Board #36), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Genetic variants in tumor immune checkpoints as prognostic markers in patients (pts) with localized advanced gastric cancer (AGC).** *Presenting Author: Yu Sunakawa, USC Norris Comprehensive Cancer Center, Los Angeles, CA*

**Background:** Multiple tumor immune checkpoint receptors and ligands, some of which are selectively upregulated in various types of tumors, play a role as an antitumor immune suppressor. The potential use of immune-based therapy in gastrointestinal cancers is just being realized. We examined the prognostic impact of single nucleotide polymorphisms (SNPs) in genes encoding for immune checkpoints on clinical outcome in pts with localized AGC from U.S. and Japan (JPN). **Methods:** Genomic DNA was extracted from blood or tissues of 161 Japanese pts (median age 68; median follow-up 4 yrs) for evaluation set and 105 U.S. pts (median age 59; median follow-up 3.3 yrs) for validation set, with localized AGC treated with surgery alone or plus adjuvant therapy (stage Ib-IV; AJCC-6$^{th}$). Thirty-six functional SNPs in genes of immune checkpoints (*PDCD1, CD274, CD73, IDO1, CTLA4, LAG3, ADORA2A,* and *FOXP3*) were analyzed by PCR-based direct sequencing for association with disease-free survival (DFS) / time to recurrence (TTR) and overall survival (OS). **Results:** The univariate analysis showed 4 SNPs were significantly associated with DFS and OS in JPN cohort. *IDO1* rs9657182 remained significant upon multivariate analysis. Any C allele of *PDCD1* rs10204525 in U.S. cohort was associated with worse TTR and OS compared to T/T genotype (2.1 vs 7.0 y; HR 2.01; p=0.03, 4.1 vs 7.3 y; HR 2.46; p=0.02, respectively) as well as worse DFS and OS in JPN cohort (HR 1.61; p=0.03, HR 1.79; p=0.01, respectively) in univariate analysis. Interestingly, pts with any T allele of *CD73* rs6922 in U.S. cohort had shorter OS compared to those with G/G genotype (HR 2.48; p=0.03) but longer OS in JPN cohort (HR 0.58; p=0.04) in uni- and multivariate analyses, there was no association with TTR/DFS in both cohorts. This different impact on OS reached statistical significance (p=0.002). **Conclusions:** Our results showed for the first time that tumor immune checkpoint SNPs may serve as a prognostic marker in pts with localized AGC and that there may be an ethnic difference in the impact on clinical outcome by genetic variants in immune checkpoints. Our data suggest that clinical trials using drugs targeting immune checkpoints should be stratified by ethnicity.

**4019 Poster Highlights Session (Board #37), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Apatinib in Chinese patients with advanced hepatocellular carcinoma: A phase II randomized, open-label trial.** *Presenting Author: Shukui Qin, Nanjing Bayi Hospital, Nanjing, China*

**Background:** Advanced hepatocellular carcinoma (HCC) is the third most common cause of cancer death in worldwide. Apatinib is a novel oral multi-kinase inhibitor of the vascular endothelial growth factor receptor-2 . Here report the results of phase II clinical study of apatinib as first- line treatment in chinese patients with advanced HCC. **Methods:** This was a multicenter, randomized, open-label, dose-finding, phase II trial. Treatment naive Patients with advanced HCC had Child-Pugh liver function class A were randomized to receive apatinib 850 mg/qd or 750 mg/qd. The efficacy was assessed at the end of each 8 weeks period. Primary endpoint was time to progression (TTP). Secondary endpoint included overall survival (OS), objective response rate (ORR), disease control rate (DCR), the level of $\alpha$-fetoprotein (AFP) and safety. According to oncology clinical trial Simon two-stage design, thirty-six patients were enrolled into stage 1 and 85 patients were enrolled into stage 2 (extension phase) of the trial. The trial was registered with ClinicalTrial.gov, NO. NCT01192971. **Results:** From 2010.07-2012.03 Total 121 patients were enrolled. The patient baseline characteristics of two treatment groups were similar with regards to disease status, ECOG scores, number of metastatic sites, pathological grading and prior therapy (P>0.05). For efficacy, median time to progression of the 850 mg group and the 750 mg group was 4.2 months and 3.3 months respectively. The median overall survival of the two groups was 9.7 months and 9.8 months respectively. The DCR was 48.57% for 850 mg qd group and 37.25% for 750 mg qd, respectively. Apatinib has been well tolerable in patients, most of the adverse event could be managed by dose interruptions or reductions. There was no significant favorable safety profile between two groups, above 2% of patients were elevated aminotransferase, thrombocytopenia, elevated bilirubin, hypertension, leukocytopenia, hand-and-foot syndrome, fatigue. **Conclusions:** Results of this uncontrolled phase II study indicated that apatinib has potential survival benefit in patients with advance HCC. 850 mg/qd or 750 mg/qd was recommended dose for further clinical study. Clinical trial information: NCT01192971.

**4020 Poster Highlights Session (Board #38), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**E2208: Randomized phase II study of paclitaxel with or without the anti-IGF-IR antibody cixutumumab (IMC-A12) as second-line treatment for patients with metastatic esophageal or GE junction cancer.** *Presenting Author: Steven J. Cohen, Fox Chase Cancer Center, Philadelphia, PA*

**Background:** Paclitaxel has activity in previously treated metastatic esophagus/GE junction cancer. Given activation of IGFR signaling in these patients (pts), we performed a randomized phase II study of paclitaxel ± cixutumumab (anti-IGF1R). **Methods:** Pts with metastatic measurable adenocarcinoma or squamous cell carcinoma of esophagus/GE junction who had progressed on one line of systemic therapy (recurrence within 6 months of adjuvant permitted) were randomized 1:1 to receive paclitaxel, 80 mg/m2 IV days 1,8,15 Q28 alone (Arm A) or with cixutumumab, 10 mg/kg days 1,15 Q28 (Arm B). CT imaging Q2 cycles. Key eligibility: ECOG PS 0-2, no prior taxane, fasting glucose ≤ 160 mg/dL, HgbA1C ≤ 7%. Primary endpoint PFS. Secondary endpoints OS, RR, toxicity. 90 pts would provide 90% power to detect a PFS difference of 3.5 m in experimental arm vs. 2m in control. **Results:** 94 pts were enrolled between 9/2010 and 10/2012 and 87 were evaluable for efficacy (43 Arm A, 44 Arm B). Pt characteristics were balanced between arms: median age 62 (range 40-89), 78% male, 94% Caucasian, 82% adenoca, 16% squamous ca, 54% GE junction, 18% lower esophageal, PS 0/1=39%/56%. Median number of cycles=2 on both arms. Most common grade 3/4 non-heme tox (%) Arm A(fatigue=8, hyperglycemia=5,hypophosphatemia=5), Arm B (hyperglycemia=11, muscle weakness=5, mucositis=5). Grade 3/4 heme tox (%ArmA/B):anemia 10/9, neutropenia 8/18, plts 0/2. 2 deaths in Arm A and 1 in Arm B were judged possibly related to therapy. Median PFS for all patients was 2.6 (90% CL [2.0-3.5]) months. Median PFS for Arms A and B were 2.6 (90% CL [1.8-4.1]) and 2.3 (90% CL [2.0-3.6]) months, respectively (p=0.72). Median OS for all patients was 6.4 (90% CL, 5.0-7.9) months. Median OS for Arms A and B were 6.5 (90% CL, 4.6-9.5) and 6.4 (90% CL, 4.9-8.0) months, respectively (p=0.92). The RR (CR+PR) for Arm A and B were 12% [90% CI: 5%, 23%] and 14% [90% CI: 6%, 25%], respectively. **Conclusions:** The addition of cixutumumab to paclitaxel in second-line therapy of metastatic esophageal/GE junction cancer was well tolerated but did not improve clinical outcome. Clinical trial information: NCT01142388.

**4021 Poster Highlights Session (Board #40), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**A phase II randomized, placebo controlled study to evaluate the efficacy of the combination of gemcitabine, erlotinib, and metformin in patients with locally advanced or metastatic pancreatic cancer.** *Presenting Author: Johanna Wilmink, Academic Medical Center, Amsterdam, Netherlands*

**Background:** In addition to clinical data from retrospective observational studies, there is a strong preclinical rationale for a beneficial effect of metformin in cancer treatment. Therefore we conducted a randomized phase II, placebo controlled study to assess the clinical effects of metformin in pancreatic cancer. **Methods:** Patients with locally advanced or metastatic pancreatic cancer were randomly assigned to gemcitabine at 1000 mg/m$^2$ on day 1, 8 and 15 q 4 weeks plus erlotinib 100 mg once daily in combination with metformin or placebo. Metformin was administered at a dose of 500 mg twice daily during the first week. If tolerated well, the dose was increased to 1000 mg twice daily. Patients were stratified according to stage of disease and the presence of diabetes. The primary endpoint was survival at 6 months. Secondary endpoints were overall survival (OS), progression free survival (PFS), objective response rate-(ORR), toxicity profile, pharmacodynamics, and biomarker research. Results: A total of 121 patients were included. Baseline characteristics were well balanced. Median follow-up is 23.6 months (95%CI: 17.5-29.6). Survival at 6 months was 55% (95% CI: 42-68) for the metformin arm versus 66% (95% CI: 54-78) for the placebo arm (p=0.23). Median OS and PFS were 6.8 (95%CI: 5.3-8.3)and 4.4 (95%CI: 2.0-6.7) months for the metformin arm versus 7.6 (95%CI: 6.3-9.0) and 5.4 (95%CI: 4.7-6.1) months for the placebo arm (p=0. 62 and p=0.45), respectively. The objective response rate was 9% in both groups. The addition of metformin was well tolerated with no significant differences in grade ≥3 toxicity between treatment arms. Baseline insulin and glucose levels were not predictive for outcome. Conclusion: The addition of metformin to gemcitabine and erlotinib does not improve the outcome of patients with locally advanced or metastatic pancreatic cancer. Additional data on predictive biomarkers, including IGF1 and IGF binding protein-3 and pharmacodynamics will be presented at the meeting. Clinical trial information: NCT01210911.

**4022 Poster Highlights Session (Board #41), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**PANCREOX: A randomized phase 3 study of 5FU/LV with or without oxaliplatin for second-line advanced pancreatic cancer (APC) in patients (pts) who have received gemcitabine (GEM)-based chemotherapy (CT).** *Presenting Author: Sharlene Gill, British Columbia Cancer Agency, Vancouver, BC, Canada*

**Background**: There is no current standard of care for APC after 1st line GEM. The CONKO3 study (ASCO 2008) reported a survival benefit with 2nd line oxaliplatin-5FU (OFF), but has not yet been validated. PANCREOX was initiated to evaluate the benefit of mFOLFOX6 vs infusional 5FU/LV in this setting. **Methods**: Pts with APC previously treated with GEM and ECOG PS <=2 were eligible. 108 pts were randomized. PFS was the primary endpoint in this Canadian, multicentre, open-label study. Secondary outcomes included OS and quality of life. Pts received mFOLFOX6 or infusional 5FU/LV until progression. **Results**: Pt characteristics, efficacy and quality of life results are shown in the Table. Duration of 1st line GEM was similar. More pts withdrew due to adverse events (AEs) in the mFOLFOX6 arm (20.4% vs 1.9%) and due to progression in the 5FU/LV arm (74.1% vs 50.0%). No difference was observed in PFS (median 3.1 vs 2.9 mos, p=0.99). OS was inferior in pts assigned to mFOLFOX6 (median 6.1 vs 9.9 mos, p=0.02). Use of post-progression therapy was significantly higher in the 5FU/LV arm (25% vs 6.8%, p<0.05). Increased toxicity was observed with the addition of oxaliplatin in 2nd line APC with grade 3/4 possibly-related AEs occurring in 63% of mFOLFOX6 pts and 11% of 5FU/LV pts. No treatment related deaths. **Conclusions**: No benefit was observed with the addition of oxaliplatin to infusional 5FU/LV in GEM-treated 2nd line APC. PFS was similar and OS was inferior with mFOLFOX6. Given the proven benefit of FOLFIRINOX in untreated APC (ACCORD 11), these results suggest that the opportunity for use of oxaliplatin-based CT would be primarily in the 1st-line setting. Funding: Sanofi Canada. Clinical trial information: NCT01121848.

| Variables | Statistic | mFOLFOX6 n=54 | 5FU/LV n=54 | HR (95% CI) | P |
|---|---|---|---|---|---|
| **Age** | Median (y) | 65 | 67 | | 0.36 |
| **Duration of advanced disease** | Median (mos) | 7.9 | 5.7 | | 0.20 |
| **Stage (%)** | | | | | |
| **Locally advanced** | | 7.4 | 5.6 | | 0.70 |
| **Metastatic** | | 92.6 | 94.4 | | |
| **ECOG (%)** | | | | | |
| **0** | | 13.0 | 18.9 | | 0.22 |
| **1** | | 75.9 | 75.5 | | |
| **2** | | 11.1 | 5.7 | | |
| **PFS** | Median (mos) | 3.1 | 2.9 | 1.00 (0.66-1.53) | 0.99 |
| **OS** | Median (mos) | 6.1 | 9.9 | 1.78 (1.08-2.93) | 0.02 |
| **ORR** | (%) | 13.2 | 8.5 | | 0.36 |
| **EORTC-QLQ-C30** | Time to definite deterioration > 10 pts (days) | 65 | 92 | 1.47 (0.74-29.4 | 0.27 |

**4023 Poster Highlights Session (Board #42), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Phase IB trial of cisplatin (C), gemcitabine (G), and veliparib (V) in patients with known or potential BRCA or PALB2-mutated pancreas adenocarcinoma (PC).** *Presenting Author: Eileen Mary O'Reilly, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** 5% to 8% PC have *BRCA 1,2* mutations; higher in Ashkenazi Jewish with PC (10-15%). Pre-clinical data demonstrates that DNA-damaging drugs (C) and poly-ADP ribose polymerase inhibitors (PARPi) have significant activity in BRCA mut PC models. This trial evaluates the optimal dose of V with fixed doses of C and G in PC. **Methods:** Primary endpoints: Determination of dose-limiting toxicity (DLT) and Recommended Phase II Dose (RP2D), safety (NCI CTCAE 4.0). Secondary endpoints: RECIST 1.1 response rate (RR), duration of response, progression-free survival, overall survival and correlatives involving tumor biopsies to evaluate mechanisms of sensitivity, resistance to platinum and PARPi. Eligibility: Untreated BRCA, PALB2 mut PC or strong personal/family history of pancreas or BRCA-related malignancy; measurable stage III/IV PC; ECOG 0-1. Treatment Plan: C 25mg/m$^2$ IV, G 600mg/m$^2$ IV, both d3, 10, q 3 weeks and V PO BID day 1- X. **Results:** Between 02/12– 10/13, N= 33 screened, 17 enrolled. Male = 10, Female = 7. Median age = 60 years (range 42- 72). BRCA = 9. Non-BRCA = 8. Four dose levels of V evaluated; 2 DLT's at V 80 mg PO BID continuous dosing (Table). Grade 3-4 toxicities: Anemia, neutropenia, thrombocytopenia, fatigue. 1 fatal bowel perforation tumor/diverticulitis*. For N= 9 BRCA patients: 5 (56%) partial responses (PR), 4 (44%) stable disease. For N= 8 non-BRCA: 5 stable, 2 progression. N= 5 BRCA patients continue on study and 7 of 9 BRCA patients are alive. Tissue analyses on BRCA subset will be presented. **Conclusions:** The RP2D of veliparib is 80 mg PO BID day 1-12 q 3 weeks with fixed dose C + G. Main grade 3-4 toxicities are hematologic, fatigue. The combination of C, G + V shows high activity in BRCA mut PC. A randomized phase II trial evaluating C, G +/- V is underway in BRCA/PALB2 mut PC (NCT01585805). Funding and acknowledgements: National Cancer Institute CTEP, Lustgarten Foundation, AbbVie. Clinical trial information: NCT01585805.

| Veliparib PO BID | N | DLT | BRCA subgroup |
|---|---|---|---|
| **20 mg, day 1-12** | 3 | - | N= 2, 1 PR, 1 SD* |
| **40 mg, day 1-12** | 3 | - | N= 1, 1 PR |
| **80 mg, day 1-12** | 6 | - | N= 5, 2 PR, 3 SD |
| **80 mg, day 1-21** | 5 | 2 (grade 4 platelets, ANC) | N= 1, 1 PR |

**4024 Poster Highlights Session (Board #43), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Prognosis model for overall survival in locally advanced pancreatic cancer (LAPC): An ancillary study of the LAP 07 trial.** *Presenting Author: Dewi Vernerey, Methodological and Quality of Life in Oncology Unit, EA 3181, University Hospital of Besancon, France, BESANCON, France*

**Background:** The management of LAPC patients remains controversial. Better discrimination for Overall Survival (OS) is needed to improve therapeutic decisions. We aimed to address this issue on the largest phase III cohort of LAPC by establishing the first prognosis model for OS with the full spectrum of parameters currently available at diagnosis. **Methods:** We enrolled the 442 LAPC patients recruited in LAP07, an international multicenter randomized phase III trial (NCT00634725). Thirty-five baseline variables among demographic, cancer history, clinical, biological and radiological parameters were evaluated in univariate and multivariate analyses as prognostic factors for OS. The predictive value of the final model was evaluated with Harrell's C-index. This analysis was repeated 1000 times with the use of bootstrap sample to derive 95%CI for the C. A prognostic score was then developed based on the identified prognostic factors in the final model. **Results:** Independent prognostic factors identified in multivariate analysis (n=370) for OS were: age (HR= 1.01; 95%CI 1.00 - 1.03; p=0.0418), pain (HR= 1.36 ; 95%CI 1.08 - 1.71; p=0.0094), albumin (HR= 0.96; 95%CI 0.94 - 0.98; p=0.0001) and tumor size (HR= 1.01; 95%CI 1.00 - 1.02; p=0.0033). Harrell's C-statistic for the final model was 0.60 (95%CI 0.56 - 0.63). A prognostic score between 0 and 4 was then calculated for each patient, based on the previous model. Three risk groups for death could be identified: "lower risk" (score∈[0,1]; n=17; median OS = 18.8 months; HR=1), "intermediate risk" (score∈(1,2]; n=166 ;median OS = 13.4 months; HR=1.7), "higher risk" (score∈(2,4]; n=187 ; median OS = 11.8 months; HR=2.1), p = 0.0101 by the global log rank test. **Conclusions:** Our results highlighted four OS's independent pronostic factors among a broad spectrum of parameters at time of diagnosis.We have identified three groups with clearcut different prognostic profiles. The determination of this simple prognostic score should allow risk stratification that may help guiding clinical management of patients with LAPC and to design for future clinical trials. An external validation with a cohort issued from ARCAD meta-analysis is pending.

**4025 Poster Highlights Session (Board #44), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Phase II study of refametinib (BAY 86-9766), an allosteric dual MEK 1/2 inhibitor, and gemcitabine in patients with unresectable, locally advanced, or metastatic pancreatic cancer.** *Presenting Author: Jean-Luc Van Laethem, Erasme University Hospital, Brussels, Belgium*

**Background:** Refametinib is a potent oral allosteric MEK 1/2 inhibitor with single-agent and synergistic activities in combination with gemcitabine in preclinical pancreatic cancer (PC) models. We report the results of a single-arm, open-label, phase 2a study combining refametinib and gemcitabine in advanced PC. **Methods:** Eligibility criteria included: ECOG PS $\leq 2$; locally advanced, unresectable or metastatic pancreatic adenocarcinoma; and no prior systemic therapy. Refametinib was administered 50 mg bid po in combination with gemcitabine (1000 mg/m2 IV weekly for 7 of 8 weeks in C1; 3 of 4 weeks in subsequent cycles). The primary objective was overall response rate (ORR); secondary objectives were duration of response (DOR), disease control rate (DCR), time to progression (TTP), progression-free survival (PFS), overall survival (OS) and safety. All responses were confirmed by central independent radiological review. Genetic biomarker analysis was conducted on circulating tumor DNA from plasma samples (BEAMing). **Results:** Sixty patients were treated: median age 63 yrs, 53% male, 40% PS 0. KRAS mutations were detected in 39 patients (65%). Best overall response was PR in 35% [median DOR 3.8 mo (117 days; 95% CI: 83-265)]; SD in 38%, PD in 10%, and not evaluable in 17% The DCR was 73%. Median TTP was 7.4 mo (224 days; 95% CI: 188, UL ND); median PFS 6.2 mo (190 days; 95% CI: 112-225); OS 8.9 mo (270 days; 95% CI: 200-355). In the KRAS subgroups (mut/WT respectively) the ORR, mPFS and OS were 28%/48% (p=0.136), 4.6/9.0 mo (HR 0.26) and 6.6/18.2 mo (HR 0.27). Full biomarker analysis is being reported separately (Riess et al, this meeting). The most common grade 3-4 TEAEs were neutropenia (43%), thrombocytopenia (22%) anemia (12%), elevations of AST (12%) or ALT (13%), DVT (10%), hypertension (12%), fatigue (15%) and rash acneiform (10%). **Conclusions:** The combination of refametinib and gemcitabine in advanced PC is active, with an acceptable safety profile. The reported high prevalence of KRAS mutations in PC patients was confirmed by BEAMing. A trend towards improved outcomes (ORR, PFS and OS) in patients with KRAS wild type PC was observed. Clinical trial information: NCT01251640.

**4026 Poster Highlights Session (Board #45), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Feasibility and results of a randomized phase Ib study of fractionated $^{90}$Y-clivatuzumab tetraxetan in patients with metastatic pancreatic cancer having two or more prior therapies.** *Presenting Author: Vincent J. Picozzi, Virginia Mason Medical Center, Seattle, WA*

**Background:** Radioimmunotherapy (RAIT) is an option to avoid side effects of further chemotherapy for advanced metastatic pancreatic ductal cancer (mPC). This multicenter, phase Ib study aimed at determining the contribution of low radiosensitizing doses of gemcitabine (GEM) to fractionated doses of $^{90}$Y-clivatuzumab tetraxetanin pts with mPC after $\geq$ 2prior GEM- or 5FU-containing regimens. **Methods:** Pts were randomized to Arm A (4-week cycles: 200 mg/m$^2$ GEM, weekly, combined with 6.5 mCi/m$^2$ $^{90}$Y-clivatuzumab tetraxetan, once-weekly the last 3 weeks) or Arm B (3-week cycles: 6.5 mCi/m$^2$ $^{90}$Y-clivatuzumab tetraxetan alone, once-weekly), repeating cycles after 4-week delays until unacceptable toxicity or pt deterioration. Safety and efficacy were evaluated. **Results:** Fifty-eight pts (33M/25F; median age 63.5) were treated on arm A (N=29) or B (N=29), 1.6 median years from diagnosis with a median of 3 (2-7) prior treatments. The main toxicity was transient myelosuppression, as expected, with dose reductions for cytopenias (cycle 1, 14%; cycle $\geq$ 2, 70%) limiting the number of Grade 3-4 events per cycle (thrombocytopenia, 13%; neutropenia, anemia, <7%). Serious events (thromboembolism, coagulopathy, infection) in 6 pts were felt to be consistent with known risks in mPC. A total of 53/58 pts (27 Arm A, 26 Arm B, 91% overall) completed $\geq$1 full treatment cycle and thus were evaluable. Pts terminated further treatment due to disease progression, with 23 pts (12 Arm A, 11 Arm B; 40%) receiving multiple cycles, including 7 pts (6 Arm A, 1 Arm B; 12%) with 3-7 cycles. Two pts in Arm A had PRs by RECIST. Kaplan-Meier median overall survival (OS) was 119 days (30-508) in Arm A *v* 84 days (27-287) in Arm B (hazard ratio 0.54, 95% CI: 0.27-0.87; *P*=0.020, log-rank). The median OS for Arm A *v* Arm B increased to 240 *v* 103 days with multiple cycles (*P*= 0.004) and 3 pts in Arm A still being observed (11 – 17 mos). **Conclusions:** This is the first randomized trial completed in mPC pts having $\geq$ 2 prior therapies. Fractionated RAIT with $^{90}$Y-clivatuzumab tetraxetan and low-dose gemcitabineappears promising in this population, supporting Phase 3 studies of this combination now being initiated. Clinical trial information: NCT01510561.

**4027^ Poster Highlights Session (Board #46), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Analyses of updated overall survival (OS) and prognostic effect of neutrophil-to-lymphocyte ratio (NLR) and CA 19-9 from the phase III MPACT study of *nab*-paclitaxel (*nab*-P) plus gemcitabine (Gem) versus Gem for patients (pts) with metastatic pancreatic cancer (PC).** *Presenting Author: David Goldstein, Prince of Wales Hospital, Sydney, Australia*

**Background:** In the phase III MPACT trial, *nab*-P + Gem demonstrated superior OS vs Gem (primary endpoint; median 8.5 vs 6.7 months; HR 0.72; *P*< 0.001) with manageable toxicity in pts with metastatic PC. The primary analyses were based on a cutoff of Sep 17, 2012, at which time 80% of pts had died. Here, we report an updated OS analysis (post hoc) and an assessment of pts with elevated NLR or elevated CA 19-9 at baseline, 2 accepted markers of poor prognosis. **Methods:** 861 pts with metastatic PC and a Karnofsky performance status $\geq$ 70 were randomized at 151 community and academic centers 1:1 to receive *nab*-P 125 mg/m$^2$ + Gem 1,000 mg/m$^2$ on days 1, 8, and 15 of each 28-day cycle or Gem 1,000 mg/m$^2$weekly for 7 wks followed by 1 wk of rest (cycle 1) and then days 1, 8, and 15 of each 28-day cycle (cycle $\geq$ 2). The data for the OS analysis were collected through May 9, 2013. Baseline NLR and CA19-9 were measured in blood samples collected before treatment. **Results:** As of the updated data cutoff, 380 of 431 pts (88%) in the *nab*-P + Gem arm and 394 of 430 pts (92%) in the Gem-alone arm had died. OS was superior for *nab*-P + Gem in the intent-to-treat (ITT) population, and longer follow-up identified > 3-yr survivors in the *nab*-P + Gem arm (Table). In a pooled–treatment-arm analysis, a NLR $\leq$ 5 was associated with longer OS vs a NLR > 5 (median 9.1 vs 5.0 months; HR 1.839; *P* < 0.001). Median OS was longer with *nab*-P + Gem vs Gem for pts with a NLR > 5 and pts with CA 19-9 > 59 × upper limit of normal (ULN; Table). **Conclusions:** Updated data confirmed the treatment effect favoring *nab*-P + Gem for OS. Additional follow-up has identified long-term survivors in the *nab*-P + Gem arm. The improved OS for pts treated with *nab*-P + Gem who have a NLR > 5 or an elevated CA 19-9 supports the relative benefit of the combination, even for pts with markers of poor prognosis. Clinical trial information: NCT00844649.

**Updated OS (May 9, 2013).**

| | *nab*-P+ Gem n = 431 | Gem n = 430 | HR | *P* value |
|---|---|---|---|---|
| **ITT population** | | | | |
| **Median OS, mo** | 8.7 | 6.6 | 0.72 | < 0.001 |
| **OS rates by mo, %** | | | | |
| **6** | 66 | 55 | | |
| **12** | 35 | 22 | | |
| **24** | 10 | 5 | | |
| **36** | 4 | — | | |
| **40** | 3 | — | | |
| **42** | 3 | — | | |
| **Subsets with markers of poor prognosis** | | | | |
| **Median OS, mo** | | | | |
| **NLR > 5 (n = 309)** | 5.6 | 4.3 | 0.81 | 0.079 |
| **CA 19-9 ≥ 59 × ULN (n = 392)** | 8.4 | 5.7 | 0.61 | < 0.001 |

**4028^ Poster Highlights Session (Board #47), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Biomarker analyses and association with clinical outcomes in patients with advanced hepatocellular carcinoma (HCC) treated with sorafenib with or without erlotinib in the phase III SEARCH trial.** *Presenting Author: Andrew X. Zhu, Massachusetts General Hospital Cancer Center, Boston, MA*

**Background:** Sorafenib (S) is the current standard therapy for advanced HCC but validated biomarkers predicting its clinical outcome are lacking. The present study aimed to identify biomarkers predicting prognosis and/or response to S ± erlotinib (E) in HCC patients from the randomized phase III SEARCH trial. **Methods:** A total of 720 patients were randomized to receive oral S 400 mg bid plus either E 150 mg qd or placebo (P). VEGF-A, VEGF-C, PDGF-BB, KIT (extracellular domain), HGF, bFGF, IGF-2, amphiregulin, betacellulin, EGF, epigen, epiregulin, heregulin, hbEGF, and TGF-a were measured in baseline plasma samples. Mutations in 19 oncogenes were analyzed in archival biopsies (Sequenom OncoCarta). **Results:** Baseline plasma biomarker data were available for 494 (69%) patients; n=243 S/E and 251 S/P. Treatment-independent analyses (combining both treatment arms) indicated that elevated HGF was associated with poor overall survival (OS; HR=0.598 [low vs high expression], multiplicity adjusted (adj) p=0.0007). Elevated plasma VEGF-A levels and low levels of KIT showed a similar trend towards poor survival (VEGF-A: HR=0.722 [low vs high expression], p=0.03, adj-p=0.39; KIT: HR=0.713 [high vs low expression], p=0.05, adj-p=0.60). High levels of plasma VEGF-C correlated with longer time to tumor progression (HR=0.626 [high vs low expression], adj-p=0.0042). Finally, in 67% of evaluable patients (339/494), a multi-marker composite signature consisting of HGF, VEGF-A, KIT, epigen, and VEGF-C correlated with improved OS: median OS 349 vs 184 days, HR=0.505, p=0.00002. None of the 15 baseline plasma biomarkers predicted efficacy from E in biomarker-treatment interaction analyses. Oncogenic mutations were detected in only 2 patient samples. **Conclusions:** HGF, VEGF-A, KIT, and VEGF-C baseline plasma levels were associated with clinical outcomes in HCC patients treated with S ± E, and these biomarkers plus epigen constituted a multi-marker composite signature for improved OS. Because S was used in both arms, whether these biomarkers are prognostic or also predictive of benefit from S alone in this population remains to be determined. Clinical trial information: NCT0901901.

**4029 Poster Highlights Session (Board #48), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Final analysis: Randomized, blinded, placebo-controlled phase II trial of sorafenib with and without mapatumumab in patients with advanced hepatocellular carcinoma (HCC).** *Presenting Author: Tudor-Eliade Ciuleanu, Prof. Dr. I. Chiricuta Institute of Oncology, Cluj County, Romania*

**Background:** TRAIL is a member of the tumor necrosis factor ligand super family that induces programmed cell death primarily in tumor cells (including liver tumors) through TRAIL death receptors. Mapatumumab (M) is an agonistic monoclonal antibody that targets one of the TRAIL death receptors, TRAIL-R1, and may promote apoptosis of cancer cells. **Methods:** Patients (Pts) with chemotherapy-naive advanced HCC were randomized 1:1 to sorafenib 400 mg BID continuously + IV Placebo (SP) or sorafenib 400 mg BID continuously + mapatumumab 30 mg/kg (SM) on day 1 every 21 days. Stratification variables were BCLC C vs B, and ECOG PS 0 vs 1, 2. Eligibility: bilirubin < 3 mg/dL, AST and ALT ≥ 5 x ULN, and INR ≥ 1.5. Radiologic progression was determined by blinded independent central review. The primary endpoint was time to progression (TTP). The sample size of 100 was sufficient to estimate median TTP with a precision of -1.9 to +2.6 months (mo). **Results:** 101 pts were in the ITT population: 51 SP and 50 SM. Treatment arms were balanced for the stratification variables. Demographics (SP vs SM): mean AFP 3177.7 vs 1534 mg/L, Male 76.5% vs 52%, Age 60.8 vs 60 years. Median (med) duration of M dosing was 3.3 mo and 84% pts received ≥ 90% of planned dose. Med cumulative sorafenib (S) dose (SP vs SM) was 73600 vs 75200 mg; 52.9% (SP) and 54% (SM) received ≥ 90% of the planned S dose. **Conclusions:** The addition of mapatumumab to sorafenib did not improve TTP (primary endpoint) or other efficacy endpoints. The combination did not substantially change the toxicity profile of sorafenib. Clinical trial information: NCT01258608.

**Efficacy and safety.**

| | Treatment groups | |
|---|---|---|
| | SP | SM |
| N | 51 | 50 |
| Median TTP (mo)[1] | 5.6 | 4.1 |
| Median TTP at | | |
| ECOG 0 (mo) | 6.9 | 4.1 |
| ECOG 1 or 2 (mo) | 5.6 | 4.2 |
| BCLC Stage C(mo) | 5.4 | 4.2 |
| BCLC Stage B (mo) | 11.1 | 4.1 |
| Median OS (mo) | 10.1 | 10.0 |
| Overall Response (pts) | 5 | 7 |
| | % | % |
| AEs of interest to S and M | | |
| Diarrhea | 37.3 | 32.0 |
| Blood bilirubin increased | 17.6 | 14.0 |
| Rash | 7.8 | 12.0 |
| Related AEs to S/M | | |
| Blood bilirubin increased | 5.9/3.9 | 4.0/2.0 |
| Fatal AEs | 25.5 | 24.0 |
| Serious AEs | 51.0 | 40.0 |
| Gastrointestinal disorders | 11.8 | 12.0 |

[1]P-value 0.7382, HR (90% CI) 1.192 (0, 1.737). P-value for comparison of treatment groups from stratified log-rank test – stratified by BCLC and ECOG PS.

**4030 Poster Highlights Session (Board #49), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**SWOG S0809: A phase II trial of adjuvant capecitabine (cap)/gemcitabine (gem) followed by concurrent capecitabine and radiotherapy in extrahepatic cholangiocarcinoma (EHCC) and gallbladder carcinoma (GBCA).** *Presenting Author: Edgar Ben-Josef, University of Pennsylvania, Philadelphia, PA*

**Background:** The role of adjuvant therapy after resection of EHCC or GBCA is unknown. S0809 was designed to estimate the stratum-specific (R0 and R1) and overall 2-year survival (OS), overall disease-free survival (DFS), local relapse (LR), and toxicity in patients (pts) treated with this adjuvant regimen. **Methods:** Eligibility included tissue diagnosis of EHCC or GBCA s/p radical resection, pT2-4, N+ or R1, M0, and PS 0-1. Pts received 4 cycles of gem (1 g/m2 IV, d1, d8) and cap (1500 mg/m2/d, days 1-14) q 21 days followed by concurrent cap (1330 mg/m2/d) and radiation (45 Gy to regional lymphatics and 54-59.4 Gy to the tumor bed). A total of 80 evaluable pts were needed; results would be considered promising if the 95% confidence interval (CI) for 2-year OS excluded a rate <45% and if the stratum specific point estimates were ≥65% for R0 and ≥45% for R1. Central pathology and radiation therapy reviews were performed. **Results:** 79 evaluable pts (54 R0, 25 R1) were registered; median age 62 yrs, 52% women, 62% EHCC and 38% GBCA. 86% of pts completed planned therapy; 3 pts discontinued therapy due to adverse effects (AEs). Grade 3 and 4 AEs were observed in 53% and 11% of pts. Most common grade 3/4 AEs included neutropenia (44%), hand-foot syndrome (13%), diarrhea (8%), lymphopenia (8%), and leukopenia (6%). There was one death from GI hemorrhage. Median OS was 33 months (33/30 for R0/R1). 12 pts developed LR, of whom 9 had a concurrent distant relapse. 24 patients developed distant-only relapse. **Conclusions:** This trial establishes the feasibility of adjuvant treatment in EHCC and GBCA and provides critically needed prospective data acquired in a multi-institutional setting. Both efficacy data and completion rate are promising and warrant further investigation in a phase 3 trial. Clinical trial information: NCT00789958.

| | All pts % (95% CI) | R0 cohort % (95% CI) | R1 cohort % (95% CI) | EHCC % (95% CI) | GBCA % (95% CI) |
|---|---|---|---|---|---|
| 2- year OS | 62 (50-72) | 65 (51-77) | 56 (33-74) | 66 (50-78) | 56 (37-72) |
| 2- year DFS | 50 (38-60) | 52 (38-65) | 44 (23-63) | 51 (36-65) | 47 (28-63) |
| 2-year LR | 12 (5-19) | 10 (2-18) | 18 (2-33) | 11 (2-21) | 13 (1-25) |

**4031 Poster Highlights Session (Board #50), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**A comparison between 5-fluorouracil/mitomycin (FM) and capecitabine/mitomycin (CM) in combination with radiation (RT) for squamous cell carcinoma (SCC) of the anal canal.** *Presenting Author: Dante D.C. Wan, BC Cancer Agency, Vancouver Centre, Vancouver, BC, Canada*

**Background:** There are no randomized phase III trials comparing 5FU versus capecitabine in combination with mitomycin and RT for locally advanced anal cancer. Capecitabine has been increasingly adopted in substitution for infusional 5FU, based on data from other disease sites as well as the easier administration. In this retrospective cohort analysis, we aim to evaluate the outcomes of patients treated with both regimens. **Methods:** Patients with new histologic diagnosis of SCC of the anal canal who initiated curative-intent RT (50-54 Gy) with CM or FM between 1998 and 2013 at one of 6 provincial cancer centers in British Columbia were included. Their characteristics and outcomes were retrospectively analyzed. Differences in proportions were analyzed using the Chi-square test. Disease free survival was estimated using the Kaplan Meier method with log rank test for comparison. **Results:** A total of 300 patients (195 females) were reviewed. Median age was 58.5 (range 18-85). 34% of the patients were T3 or above and 29% were N2 or above. Median tumor size was 4 cm. Only 4.3% were HIV positive. 194 pts (64.6%) were treated with FM and 106 (35.3%) with CM. The groups were balanced for age, gender, histology, HIV status, T and N status. Median follow-up was 61.7 months (75.2 for FM and 15.8 for CM). Median DFS was not reached in both groups (p 0.24, HR 0.774). The remainder of response and outcomes are included in the Table. **Conclusions:** There is no difference between the two cohorts in this retrospective study. Additionally, there is a trend towards lower recurrence rates favoring capecitabine that may be explored in larger phase III studies. Capecitabine can be considered an alternative to 5FU in the chemoradiation treatment of SCC of the anus.

| Total (n=300) | Capecitabine (n=106) | 5-FU (n=194) | p value |
|---|---|---|---|
| Complete response | 97 (91.5%) | 179 (92.2%) | 0.817 |
| Recurrence rates | 15 (15.2%) | 42 (23.3%) | 0.105 |
| Rates of APR | 6 (5.6%) | 14 (7.8%) | 0.267 |
| Rates of colostomy | 7 (6.6%) | 13 (6.7%) | 0.974 |
| DFS (1 year) | 93.9% | 91.1% | 0.511 |

**4032 Poster Highlights Session (Board #51), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Patient and tumor characteristics impacting on lymph node metastases rate (LNMR) in squamous cell carcinoma of the anal canal and margin (SCCA) using data from the NCRI randomized phase III ACT II trial: Implications for radiotherapy target volume.** *Presenting Author: Robert Glynne-Jones, Mount Vernon Centre for Cancer Treatment, Middlesex, United Kingdom*

**Background:** The prognosis of SCCA is linked to lymph node involvement. TNM Staging of SCCA is clinically based using physical examination, proctoscopy, and imaging. We aimed to determine tumour- and patient-related clinical LNMR in SCCA. **Methods:** The ACT II trial results are reported. We investigated the LNMR as determined by clinical examination and CT (cN+) from patient-related (age, sex, baseline WBC, platelets and Hb) and tumour-related factors (site, differentiation, histological type, cT stage and size of tumour (≥/<5cm). Magnetic resonance imaging (MRI) was commonly used from 2005. **Results:** We examined 892 evaluable patients (of 940 recruited). Median age 58 years (IQR 51-65 years); tumour site – canal (750/892 - 84%), margin (125/892 - 14%); stage cT1-T2 (467/892 - 52%), cT3-T4 (406/892 - 46%). Overall cN+ (305/940 - 32%), cN0 (587/940 – 62%, cNX (48/940 - 5%). Estimates of LNMR for anal canal only were 15% (113/750), 14% (102/750) and 8% (60/750) for N1 N2 and N3 respectively. There is evidence of an association between nodal status and cT-stage (p<0.0001)- stage cT1: (19/88 -22%) cT2:(85/379 -22%), cT3:(122/276-44%), cT4:(74/130-57%), cTX:(5/19-26%). In multivariate analysis only tumour site (canal vs margin HR=0.51, p=0.008), WBC (≥11 109/l HR=1.55, p=0.026) and T-stage (T2 vs T1 HR=1.00, T3 vs T1 HR=2.42, T4 vs T1 HR=3.79, p<0.0001) remained significant. 99 of 355 patients (28%) randomised pre-2005 were cN+ compared with 206 of 537 patients (38%) randomised post-2005 (p-value=0.0013). **Conclusions:** In the ACT II trial for stages cT1 and cT2, the baseline risk of clinical nodal involvement is 22% and in stages cT3 or cT4 is 48%.Radiotherapy field sizes should continue to be determined by N stage in second phase. The introduction of MRI after 2005 may have influenced the baseline nodal staging, and its utility in determining clinical target volume within intensity-modulated radiotherapy plans needs evaluation. Clinical trial information: NCT00025090.

**4033 Poster Highlights Session (Board #52), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Nomograms to predict prognosis in pseudomyxoma peritonei: A Peritoneal Surface Oncology Group International (PSOGI) multicenter study.** *Presenting Author: Shigeki Kusamura, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

**Background:** We built nomograms for predicting overall (OS) and progression-free survivals (PFS) in patients with pseudomyxoma peritonei (PMP) treated with cytoreductive surgery (CRS)+/-intraperitoneal chemotherapy (IPCT). **Methods:** Data from 1,715 PMP patients in 31 centers from 1993 to 2012 constituted the developing set. The covariates were previous systemic chemotherapy (sCT), histologic subtype (Ronnett's criteria), peritoneal cancer index (PCI), completeness of cytoreduction (CC), IPCT (Hyperthermic intraperitoneal chemotherapy [HIPEC], early postoperative chemotherapy [EPIC], or both), lymph node status (LN), G3-5 morbidity (NCI CTCAE v3), and surgical proficiency. Centers with >100 procedures for PMP were considered proficient. Continuous variables were transformed using restricted cubic splines. We handled missing data using multiple imputation with chained equations (MICE) approach. We fitted a Cox model in each of the different completed developing datasets generated by MICE. Pooled estimates of regression coefficients, variances, and models' discriminations (bootstrap corrected Harrell C indexes) were obtained using Rubin's rule. The nomograms were externally validated on 733 PMP patients from two high-volume referral centers in USA (validating set). **Results:** In the developing set the median follow-up was 39 months. Five-year OS and PFS rates were 74.1% (95%CI: 71.3-76.8) and 52.3% (95%CI: 49.4-55.2), respectively. The means of adjusted Harrell C indexes for OS and PFS were 0.80 and 0.74 in the developing set and 0.74 and 0.72 in the validating set. In the developing set significant predictors of OS were sCT, PCI, CC, IPCT, histological subtype, LN, and G3-5 morbidity while those of PFS were surgical proficiency, sCT, histological subtype, PCI, CC, and IPCT. **Conclusions:** These nomograms may allow predicting OS and PFS providing individualized outcome prognostication. They would support therapeutic decision-making and stratification of future clinical trials.

**4034 General Poster Session (Board #121), Sat, 8:00 AM-11:45 AM**

**Phase II trial of panitumumab (P) plus mytomicin C (M), 5-fluorouracil (5-FU), and radiation (RT) in patients with squamous cell carcinoma of the anal canal (SCAC): Safety and efficacy profile—VITAL study, GEMCAD 09-02 clinical trial.** *Presenting Author: Jaime Feliu, Medical Oncology Department. La Paz University Hospital, Madrid, Spain*

**Background:** Standard of care for SCAC has remained unchanged over the past 4 decades. More than 80% of these tumors overexpress the EGFR receptor and <5% present KRAS mutations (Van Damme, BMC 2010). We therefore initiated a multicenter phase II study (NCT01285778) to assess the efficacy and tolerability of adding the EGFR inhibitor panitumumab to the standard M/5FU/RT regimen in patients with non-metastatic SCAC. **Methods:** Patients received P (6 mg/kg on day 1, every 2 weeks for 8 weeks), M (10mg/m2 q28 days x2) and 5-FU (1000mg/m2/day IV infusion days 1-4 q 28 days x 2) concurrently with RT 45 Gy (1,8 Gy per fraction) to the primary tumor, mesorectal, iliac and inguinal nodes, followed by a boost of 10-15 Gy to the primary tumor and affected lymph nodes. The trial was designed to include 58 pts with stage >T2N0 to have 80% power to detect an increment of 3y-DFS rate from 50% (Ajani, JAMA 2008) to 70%. **Results:** Between 1/2011 and 11/2013, 58 pts were accrued. To date, results of 36 patients are available (56% female, median age 54 years, VIH positive 6%, ECOG PS: 0 (44%)/1 (53%)/2 (3%), stage I (3%)/II (25%)/IIIA (19%)/IIIB (50%). Thirty-three (92%) patients developed G3/4 adverse events (Table 1). There were no toxic deaths. At 8 weeks, 56% pts experienced CR; 36% persistent but not progressive disease and 8% disease progression. At 24 weeks 55% had CR, 6% persistent but not progressive disease; 19% disease progression, and 20% had not been evaluated. **Conclusions:** The addition of P to M/5-FU/RT is a tolerable regimen with a good compliance and an acceptable safety profile. Full data of toxicity and post-treatment CR rate will be reported at ASCO Meeting. Clinical trial information: NCT01285778.

| | Adverse events grade 1-2 no. patient (%) | Adverse events grade 3 no. patient (%) | Adverse events grade 4 no. patient (%) |
|---|---|---|---|
| **Anemia** | 5 (14%) | 3 (8%) | |
| **Neutropenia** | 4 (11%) | 7 (19%) | 3 (8%) |
| **Febril neutropenia** | | 2 (6%) | 2 (6%) |
| **Trombopenia** | 4 (11%) | 2 (6%) | |
| **Rash** | 28 (78%) | 2 (6%) | |
| **Radiodermatitis** | 11 (26%) | 12 (33%) | 2 (6%) |
| **Diarrhea** | 22 (61%) | 8 (22%) | 2 (6%) |
| **Vomiting** | 8 (22%) | 1 (3%) | |
| **Stomatitis** | 7 (19%) | 1 (4%) | |
| **Fatigue** | 17 (47%) | 2 (6%) | |
| **Pain** | 10 (28%) | 3 (8%) | |
| **Hypomagnesemia** | 8 (22%) | | |

**4035 General Poster Session (Board #122), Sat, 8:00 AM-11:45 AM**

**Tumor HPV status and invasive squamous cell carcinoma of the anus: Outcomes from a single institution.** *Presenting Author: Bhargavi Yalamarti, University of Massachusetts Medical School, Worcester, MA*

**Background:** Squamous cell carcinomas (SCC) of the anus are associated with infection with Human Papilloma Virus (HPV) genotypes 16 and 18 in 80% of cases. Chemoradiotherapy (CRT) confers 70% 3-year relapse-free survival. Clinical outcomes of anal SCC in relation to common tumor HPV genotypes 16 and 18, has not been reported in patients from the USA. **Methods:** 81 patients with anal SCC were treated between January 1998 and December 2013 at our institution. Complete data on clinical outcomes and archived specimens for genotyping were available for 62 patients. Tumor HPV status was determined by HPV DNA testing from paraffin-embedded tumor tissues. **Results:** All 62 patients received radiation therapy > or = 50Gy and 87% received concurrent chemotherapy with 5-FU plus Mitomycin in 90.4% and 5-FU plus Cisplatin in 9.6%. 52 patients (83%) had HPV positive (+) tumors and 46 patients had genotype 16, 3 patients (3/52) had both genotype 16 and 18, 1 had genotype 18. 10 (17%) patients had HPV negative (-) tumors. The mean age at diagnosis for the HPV+ group was 55.06 years, compared to 64.8 years in the HPV- group (p=0.017). The percentage of males in the HPV+ group is 36.5% (19/52) and 60% (6/10) in the HPV- group (p=0.291). In the HPV+ group, 41 patients (78.8%) were T stage 1 to 2, 36 patients (69.2%) had no lymph node (LN) involvement. In the HPV- group, 5 patients (50%) were with T stage 1 to 2 and 5 patients (50%) had no LN involvement. After a median follow up of 7 years, 16/62(25.8%) patients had recurrence of anal cancer and 12 of them were HPV+ with genotype 16. The HPV+ group had longer time to relapse (HR=0.571, [95% CI=0.144 to 2.265], p=0.425) after adjustment for the size of the tumor and nodal status. 4/62(6.4%) patients died, two in the HPV+ and 2 in the HPV- group. 93.5% (58/62) of patients are alive at 5 yrs. In the HPV+ group, 96.1%(50/52) are alive as compared to 80% (8/10) alive in the HPV- group at the end of 5 yrs. The HPV+ group had longer time to death (HR=0.736, [95% CI=0.141 to3.854], p=0.717) after adjustment for tumor size and nodal status **Conclusions:** In our cohort, HPV+ anal SCC is more commonly diagnosed at a younger age and in women. There was a trend towards longer time to loco-regional relapse and death in HPV+ group than in the HPV- group.

**4036 General Poster Session (Board #123), Sat, 8:00 AM-11:45 AM**

**Prognostic significance and therapeutic implications of c-MET in esophageal squamous cell cancer.** *Presenting Author: Ching Tzao, Division of Thoracic Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*

**Background:** c-MET is a receptor tyrosine kinase (RTK) that has been shown to be overexpressed and may serve as a potential therapeutic target in a variety of human cancers. We aimed to study if c-MET expression correlates with patients' outcome with therapeutic implications in esophageal squamous cell cancer (ESCC). **Methods:** Expression of c-MET was analyzed by immunohistochemistry in tumors from 97 resected ESCC with correlative analysis with clinicopathologic variables. Cytotoxicity (MTT), cell migration, and assays for cell cycle and apoptosis were conducted in KYSE-510 and KYSE-170 ESCC cell lines in response to two c-Met inhibitors, SU11274 and PHA665752. Expression of cell cycle regulators, cyclin A and B1, tumor suppressors including Rb, p53 p21 and p27, and intrinsic apoptotic factors were determined by immunoblotting. Mice inoculated with KYSE 170 ESCC cell line were used to test effects of c-MET inhibitors in vivo. **Results:** Expression of c-Met within resected ESCC correlated positively with T status ($P = 0.008$), N status ($P < 0.001$), M status ($P = 0.048$) and stage ($P < 0.001$). Patients with low expression of c-Met showed better survival compared to those with high expression ($P = 0.0001$). SU11274 and PHA665752 significantly inhibited viability and migration of KYSE-170 and 510-ESCC cells with decreased expression of phosphorylated c-MET (p-c-MET). When treated with c-MET inhibitors, p27and p53 was upregulated with a concomitant decrease in cyclin-dependent kinase 6 (Cdk6) in KYSE-170 cells, whereas cyclin A and B1 in was decreased in KYSE-170 cells with an induction of G1 or G2 cell cycle arrest. Apoptosis was induced by c-Met inhibitors with upregulation of pro-apoptic factors, Bcl-2-associated X protein (BAX) and BCL2-interacting killer (BIK) in KYSE-170 cells. Growth was significantly suppressed in murine tumors of KYSE-170 when treated with c-MET inhibitors with decreased expression in p-c-MET. **Conclusions:** c-MET expression may serve as a predictor for poor prognosis in resected ESCC. c-MET inhibitors, SU11274 and PHA665752 had significant anticancer effects in ESCC cell lines in vitro and in vivo, suggesting that c-MET may serve as a potential therapeutic target for ESCC.

**4037 General Poster Session (Board #124), Sat, 8:00 AM-11:45 AM**

**Perioperative versus preoperative chemotherapy with surgery in patients with resectable squamous-cell carcinoma of esophagus: A phase III randomized trial.** *Presenting Author: Yang Zhao, Second Affiliated Hospital to Xi'an Jiaotong University, Xi'an, China*

**Background:** We assessed whether a regimen of perioperative PCF (paclitaxel, cisplatin, and fluorouracil) to surgery improves outcomes among patients with potentially curable squamous-cell carcinoma of esophagus comparing with preoperative chemotherapy and surgery. **Methods:** We randomly assigned patients with resectable squamous-cell carcinoma of esophagus to receive either perioperative chemotherapy (175, Arm A) or preoperative chemotherapy (171, Arm B) with surgery.Chemotherapy consisted of two preoperative with or without two postoperative cycles of intravenous paclitaxel (200 mg per square meter of body-surface area) and cisplatin (60 mg per square meter) on day 1, and a continuous intravenous infusion of fluorouracil (700 mg per square meter per day) for 5 days. Primary end point was progression-free survival (PFS), secondary end point was overall survival (OS). **Results:** PCF-related adverse effects were similar to the previously reported among patients with the squamous-cell carcinoma of esophagus. The postoperative morbidities were similar between the perioperative-chemotherapy-surgery group and the preoperative-chemotherapy-surgery group, as were the numbers of deaths within 30 days after surgery. There were no significant differences in resectability and postoperative pathological stage. With a median follow-up of 50 months of all patients, 104 patients in the perioperative-chemotherapy-surgery group and 114 in the preoperarive-chemotherapy-group had died. As compared with the preoperative-chemotherapy-surgery group, the perioperative-chemotherapy-surgery group had a greater likelihood of progression-free survival (hazard ratio for progression, 0.62; 95 percent confidence interval, 0.49 to 0.73; $P < 0.001$) and of overall survival (hazard ratio for death, 0.79; 95 percent confidence interval, 0.59 to 0.95; $P < 0.001$; five-year survival rate, 38 percent vs. 24 percent). **Conclusions:** In patients with operable esophageal squamous-cell carcinoma, a perioperative regimen of PCF can significantly improved 5-year progression-free and overall survival comparing to preoperative chemotherapy. NCT01225523 Clinical trial information: NCT01225523.

**4038 General Poster Session (Board #125), Sat, 8:00 AM-11:45 AM**

**The revised AJCC staging (7th edition) and prognostic stratification in esophagogastric adenocarcinoma.** *Presenting Author: Haris Zahoor, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA*

**Background:** AJCC esophageal staging assigns prognostic groups based on tumor, node, and metastasis classifications. In 2010, AJCC 7th ed. separated adenocarcinoma from squamous cell histology and added tumor grade and number of involved regional nodes. Our study aim was to compare survival prognostication for esophagogastric adenocarcinoma between AJCC 7 and AJCC 6th ed. stage groupings. **Methods:** We abstracted pathology and survival for surgically resected esophagogastric adenocarcinoma patients (n=836; 1997 to 2011); 256 received induction therapy. AJCC stage was assigned; overall survival in months (esophagectomy to death or most recent alive contact) was analyzed. Discriminatory ability and homogeneity, by stage, was assessed with Kaplan-Meier (KM) curves. Monotonicity comparisons were evaluated with linear trend chi-squared tests. Overall survival was compared using Cox regression and Akaike Information Criterion (AIC) was used to assess model fit. **Results:** Compared to AJCC 6, AJCC 7 restaged 165 patients (Table). KM log-rank statistic indicated stronger differentiation in AJCC 7 curves compared to AJCC 6 (166.128 vs 185.523 overall). Cox likelihood ratio (162.957 vs. 173.951 overall) and AIC (4831.011 vs 4820.016 overall) indicate better model fit to the survival data for AJCC 7 versus AJCC 6, overall and for induction subgroups (data not shown). As stage group increases, stronger linear trends for survival were observed at 24, 36, and 60 months using AJCC7 stage groupings, overall and for induction subgroups, compared to AJCC 6. **Conclusions:** AJCC 7 stage groupings demonstrate superior homogeneity, discriminatory ability, and monotonicity compared to AJCC 6. Incorporating the extent of nodal disease, and tumor grade into the revised AJCC 7 stage classification improves prognostic stratification of surgically resected esophagogastric adenocarcinoma patients, including patients who received induction therapy.

**Patients upstaged or downstaged comparing AJCC 6 to AJCC 7.**

| Upstaged | Number of patients |
|---|---|
| IIa to IIb | 77 |
| IIb to IIIa | 29 |
| IIb to IIIc | 10 |
| **Downstaged** | **Number of patients** |
| IIa to Ib | 32 |
| IVa to IIb | 1 |
| IVa to IIIa | 3 |
| IVa to IIIb | 3 |
| IVa to IIIc | 10 |

**4039 General Poster Session (Board #126), Sat, 8:00 AM-11:45 AM**

**Candidate drug therapies for molecularly defined subgroups of esophageal cancer identified from high-throughput drug screening.** *Presenting Author: Irene Yu-Shing Chong, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, United Kingdom*

**Background:** There is a pressing clinical requirement to identify novel treatment strategies for oesophageal cancers, especially considering the rising incidence and poor patient prognosis. The use of high-throughput small molecule drug screens has the potential to identify therapies not previously acknowledged to be efficacious for individual cancer types. **Methods:** To identify effective drug therapies for molecularly defined subgroups of patients with oesophageal cancer, high-throughput drug screening was undertaken in 17 oesophageal cancer cell line models using a small molecule library incorporating 78 drugs. Genomic profiles regarding gene mutation and copy number variation for each of the oesophageal cell line models used in the drug screen were obtained from publically available data repositories (Cancer Cell Line Encyclopedia and COSMIC cell line project). **Results:** Broad spectrum sensitivity across the oesophageal cell line models was observed for targeted agents including PF03758309 (PAK4 inhibitor) and BI2536 (PLK-1 inhibitor). A differential sensitivity between the oesophageal cancer cell lines was observed for other targeted agents including BEZ235 (PIK3CA/mTOR inhibitor). The oesophageal cell lines most sensitive to BEZ235 harboured COSM760 PIK3CA p.E542K, a missense mutation located in the helicase domain. Sensitivity to small molecule tankyrase inhibitors which inhibit the Wnt pathway was most pronounced in OE19, which harbours biallelic methylation of the APC promotor 1A. Single agent in vivo efficacy of a novel tankyrase inhibitor was also demonstrated, with significant differences in tumour weight and volume between the drug and vehicle groups (P=0.0024 and P=0.0048, respectively). **Conclusions:** High-throughput drug screening of oesophageal cancer cell lines has identified novel sensitivities to drugs including small molecule tankyrase inhibitors. It is possible that promotor hypermethylation of APC contributes towards the activation of Wnt signalIng, and may serve as a candidate predictive biomarker for tankyrase inhibitor sensitivity.

**4040 General Poster Session (Board #127), Sat, 8:00 AM-11:45 AM**

**The effect of FGFR4 Gly388Arg polymorphism on treatment outcomes after chemoradiotherapy in esophageal cancer patients.** *Presenting Author: Sanghee Cho, Department of Hematology-Oncology, Chonnam National Univeristy Hwasun Hospital, Gwangju, South Korea*

**Background:** Fibroblast growth factor receptor 4 (FGFR4) has been associated with increased risk, staging, and metastasis in several type of cancer. The purpose of this study was to evaluate the prognostic role of FGFR4 Gly388Arg polymorphism in esophageal cancer after chemoradiotherapy. **Methods:** Peripheral blood samples from 250 patients who were treated with chemoradiotherapy were used for this study. Patients were diagnosed as a stage of I in 12 (5%), II in 54 (21%), III in 115 (46%) and IV in 69 (28) patients. All of the patients were received chemotherapy using cisplatin and fluorouracil or cisplatin and docetaxel. **Results:** The overall response was 85%, with 21% complete response and 64% partial response. The overall survival (stage II, 34 months; stage III, 23.3 months; stage IV, 19.3 months, p=0.005) and progression survival (stage II, 23.8 months; stage III, 12.8 months; stage IV, 9 months, p=0.001) was significantly improved according to stage. In FGFR4 genotypic analysis, 96 patients (38.6%) were homozygous for Gly388 allele, with 113 heterozygous (45.4%) and 40 (16.0) homozygous for Arg388 allele. There was no significant association between FGFR4 genotype and stage. However, Gly388 allele patients show better overall response rate (90.6%) than Arg388 carriers (82.4%, p=0.050). In early stage (stage I and II, n=66), Gly388 allele patients tended to have a better OS or PFS (not available until this analysis) than Arg388 carriers (PFS: 38 months, 95% CI 7.7-68.1; OS: 49 months, 95% CI 24.8-73.5). However, in advanced stage (III, IV), the survival outcomes was similar between genotypes. **Conclusions:** Present study shows that FGFR4 Gly388 allele has a prognostic role in response after chemoradiotherapy in esophageal cancer. Especially in early stage of esophageal cancer, FGFR4 might have an important role in disease progression and survival outcomes. It suggests that the possibility of new therapeutic target for esophageal cancer treatment.

**4041 General Poster Session (Board #128), Sat, 8:00 AM-11:45 AM**

**A phase II study of MK-2206, an allosteric inhibitor of AKT as second-line therapy for advanced gastric and gastroesophageal junction (GEJ) cancer: A SWOG Cooperative Group trial (S1005).** *Presenting Author: Ramesh K. Ramanathan, TGen-Virginia G. Piper Cancer Center at Scottsdale Healthcare, Scottsdale, AZ*

**Background:** The PI3K/AKT/MTOR pathway is frequently activated in gastric/GEJ cancers. This study evaluated the activity of single agent MK-2206 at the dose of 60 mg every other day in this tumor type. **Methods:** Eligible patients (pts) had gastric /GEJ adenocarcinoma with measurable disease, who had had progression after first-line treatment, or recurrence within six months after adjuvant therapy. Other pertinent eligibility criteria included a Zubrod performance status of 0-1, a fasting serum glucose ≤150 mg/dL, and < Grade 2 malabsorption or chronic diarrhea. Adequate hematologic, renal, hepatic, and cardiac function were required. Prior treatment with a PI3, AKT, or mTOR inhibitor was not allowed. MK-2206 (60 mg every other day) was given until progression or intolerable toxicity. Primary endpoint was overall survival (OS), secondary endpoints were safety, progression free survival (PFS) and response rate (RR). The study required 60 evaluable pts and a median OS of 6.5 months (mo) (power of 89%, significance level 0.07) to be considered encouraging for further investigation. **Results:** Seventy-five pts were enrolled between 1/1/11 to 5/1/13. Eight pts were ineligible and one pt withdrew; 66 pts were included in the analyses. Median age is 60.7 yrs (range 30.4-86.7), Males 70%, White 89% and Asian 6%. There were 2 deaths possibly related to study drug (cardiac arrest and respiratory failure). Gr 4 adverse events (AEs) were hyperglycemia, anemia and lung infection (1 each). Gr 3 AEs were infrequent and < 5% except for fatigue (6%). Other all Gr AEs included anemia 15%, anorexia 27%, diarrhea 24%, fatigue 48%, hyperglycemia 29%, nausea 40%, vomiting 20%, maculopapular rash 30%, and acneiform rash 8%. The RR is 2%, median PFS is 1.8 mo. (95% CI of 1.7- 1.8) and median OS is 5 mo (95% CI 4 - 10 mo). **Conclusions:** MK-2206 as 2nd line therapy in an unselected group of gastric/GEJ cancers was well tolerated with some evidence of activity (RR 2%, OS 5.0 mo) and in the range of other second line agents (irinotecan, docetaxel, ramucirumab). The primary study endpoint of 6.5 mo was not met. (Support: NIH/NCI cooperative group grants CA32102 and CA38926). Clinical trial information: NCT01260701.

**4042 General Poster Session (Board #129), Sat, 8:00 AM-11:45 AM**

**Effect of metastasis associated in colon cancer-1 on lymphangiogenesis in human gastric cancer.** *Presenting Author: Li Sun, Department of Oncology, Nanfang Hospital, Southern Medical University, Guangzhou, China*

**Background:** Metastasis-associated in colon cancer-1 (MACC1), a new oncogene predominantly expressed in several solid tumors including gastric cancer (GC), is associated with cancer lymph node positivity. Nodal dissemination of GC critically determines clinical outcome of affected patients. Therefore, we conducted the study to investigate whether MACC1 influences GC lymphatic metastasis and to explore the potential underlying mechanism. **Methods:** Immunohistochemistry analysis was performed in 190 GC tissues with MACC1, LVYE-1 to find out the relationship between MACC1 and lymph node metastasis as well as lymphangiogenensis. MTT, Transwell migration and 3D-culture assay were conducted to evaluate the effects of MACC1 on the proliferation, migration and capillary-like structure capacity of human lymphatic endothelial cells (HLECs) after co-cultured with MACC1 supernatant. Besides, vascular endothelial growth factor-C (VEGF-C)/VEGF-D expression in GC cells were detected by qRT-PCR, Western blot and ELISA. **Results:** Presence of MACC1 was correlated with lymph node metastasis ($p<0.01$) and lymphangiogenesis ($p<0.001$); meanwhile, absence of MACC1 expression contributed to a better prognosis for GC patients ($p<0.001$). Additionally, in vitro studies demonstrated that MACC1 upregulated HLECs' capacity of tube-like formation through enhancing cell proliferation and migration. MACC1 also promoted both lymphangiogenesis and lymphatic invasion in nude mice transplantation assay. Moreover, MACC1 significantly increased the expression of VEGF-C/VEGF-D in GC cells and transplanted tumors both in protein and gene level, which was subsequently suppressed by inhibitor of hepatocyte growth factor (HGF)/c-Met signaling axis. **Conclusions:** All these data suggested a critical role for MACC1 in lymphatic dissemination of gastric cancer, providing evidence that MACC1 upregulated VEGF-C/VEGF-D expression to promote lymphangiogensis partially via HGF/c-Met pathway.

**4043 General Poster Session (Board #130), Sat, 8:00 AM-11:45 AM**

**The R0 resection rate after neoadjuvant bevacizumab (Bev) plus DOF versus DOF in local advanced gastric carcinoma (LAGC) and its association with circulating tumor cell (CTC).** *Presenting Author: Nan Du, Department of Oncology, First Affiliated Hospital, Chinese PLA General Hospital, Beijing, China*

**Background:** Local advanced gastric carcinoma (LAGC) is suggested to be potentially cured by R0 resection, and neoadjuvant chemotherapy can increase the R0 resection rate but not enough. Bevacizumab (Bev), an anti-tumor angiogenesis monoclonal antibody, combined with chemotherapy has been shown effective in advanced GC. In addition, CTC has been suggested as an indicator of the anti-tumor drugs' efficacy. Therefore, in this study, we plan to evaluate the efficacy and safety of neoadjuvant Bev plus docetaxel/oxaliplatin/5-FU/CF (DOF) versus DOF in mainly gastric antrum LAGC, and to investigate whether CTC is an effectiveness indicator. **Methods:** 80 patients diagnosed as IIIb-IIIc GC have been enrolled and randomly assigned (1:1) to receive neoadjuvant Bev (5 mg/kg, d1) plus DOF (docetaxel, 75 mg/m$^2$, iv, d1; oxaliplatin, 85 mg/m$^2$, iv, d1; 5-FU, iv infusion 600 mg/m$^2$ and iv injection 400mg/m$^2$, d1-2; CF, 200 mg/m$^2$, d1 and d2) or DOF each 3-week, up to 2-4 cycles preoperation, and another 2-4 cycles postoperation up to total 6 cycles. The primary endpoint is R0 resection rate. CTC was detected every 8 weeks. All patients signed the informed consent. **Results:** For ORR and R0 resection rate, there were significant differences between the Bev plus DOF and DOF groups (65.0% vs. 42.5% and 77.5% vs. 52.5%; $P<0.05$). Compared to DOF group, Bev plus DOF group had dramatically more CTC number declined ($P<0.05$), and had 21 of 24 (87.5%) patients achieving R0 resection [10 of 15 (66.7%) patients with DOF]. The medium survival was 17.6 months (95% CI: 14.153-21.047) with Bev plus DOF versus 16.4 months (95% CI: 12.949-19.851) with DOF; OS of the two groups had no significant statistical difference ($p=0.776$). Furthermore, both single-variant and multi-variants Cox regression analysis found that neoadjuvant regimen,R0 resection rate and CTC were independent survival prognostic predictors in LAGC ($P<0.05$). **Conclusions:** Neoadjuvant Bev plus DOF can reduce TN staging and improve ORR and R0 resection rate in LAGC with controllable adverse effects. CTC number declined may act as an effectiveness and survival predictor in LAGC.

**4044 General Poster Session (Board #131), Sat, 8:00 AM-11:45 AM**

**Reduction of heart volume during neoadjuvant chemoradiation in patients with resectable esophageal cancer.** *Presenting Author: Nadia Haj Mohammad, Academisch Medisch Centrum, Amsterdam, Netherlands*

**Background:** Neoadjuvant chemoradiation (nCRT) followed by surgery based on the Dutch CROSS scheme is considered curative intent treatment for patients with resectable esophageal cancer. Ideally the high dose region of the radiotherapy treatment would only include the esophagus as target organ. However, inevitably the heart will receive a part of the chemoradiation dose. Recently, decreases in heart volume have been reported during nCRT. This change in heart volume can be of great importance because it could result in inaccurate dose delivery to the tumor and organs at risk. The aim of the study was to establish hemodynamic aspects and predictors of changes in heart volume during nCRT. **Methods:** A prospective pilot study was conducted in patients who were treated with 5 weeks nCRT consisting of carboplatin AUC 2 and paclitaxel 50 mg/m2 concomitant with radiotherapy (41.4 Gy/1.8 Gy per fraction) followed by resection. Physical parameters, cardiac volume on CT, cardiac blood markers (troponin, NT-proBNP, CK, CK-MB) and cardiac ultrasound including 2D strain analysis were obtained at baseline and at the end of treatment. **Results:** 23 patients were included. A significant mean decrease of 55.3 ml (6.1%) in heart volume was detected (95% CI 36.7-73.8 ml p=0.000). Blood pressure (BP) significantly decreased (systolic BP mean decrease of 18 mmHg (95% CI 11-26 mmHg p=0.000) and diastolic BP mean decrease of 8 mmHg (95% CI 2-14 mmHg p=0.008) and heart rate during cardiac ultrasound significantly increased with 6 beats/min (95% CI 1-11 beats/min p=0.021). An evident trend of an increased vena cava inferior collaps index of 5.1 % (95 % CI -0.8-11 % p=0.086) was observed, all suggesting dehydration in the course of treatment. Left ventricle ejection fraction, 2D strain and cardiac blood markers showed no significant changes. Independent predictors for reduced heart volume were low baseline creatinin (p=0.001) and low left ventricle endsystolic volume (p= 0.012). **Conclusions:** The heart volume is significantly reduced after 5 weeks of nCRT and is not accompanied by overt cardiac dysfunction. Patients with low baseline creatinin and low left ventricle endsystolic volume are more at risk for heart volume reduction. Clinical trial information: NL42999.018.12.

**4045 General Poster Session (Board #132), Sat, 8:00 AM-11:45 AM**

**Prognostic factors for patients with advanced thoracic esophageal squamous cell carcinoma receiving preoperative cisplatin plus 5-fluorouracil (JCOG9907).** *Presenting Author: Tomoya Yokota, Divison of Gastrointestinal Oncology, Shizuoka Cancer Center, Sunto-gun, Japan*

**Background:** Preoperative chemotherapy with cisplatin plus 5-fluorouracil followed by esophagectomy with 2-3 field lymph node dissection is one of the standard treatments for patients with clinical stage II/III squamous cell carcinoma (SCC) of the esophagus. This study investigated the prognostic factors for patients who received preoperative chemotherapy. **Methods:** Of 164 patients assigned to receive preoperative chemotherapy in JCOG9907 study, multivariate analyses were performed in 159 patients for evaluating preoperative prognostic factors and in 154 patients for postoperative prognostic factors. **Results:** Multivariate analyses using preoperative factors showed that clinical T3 (vs.cT1-2) (HR 3.602, p=0.0007) and serum albumin (Alb)<4.0g/dl (vs.>=4.0g/dl) (HR 2.293, p=0.0005) were associated with a poor prognosis. A prognostic index using these preoperative factors was constructed dividing patients into good (cT1-2 and Alb>=4.0: 3yOS 92.3%), moderate (cT1-2 and Alb<4.0 or cT3 and Alb>=4.0: 66.3%), and poor (cT3 and Alb<4.0: 37.2%) risk groups. Three independent prognostic factors were identified by multivariate analysis using postoperative factors: pathological curability pB [either R1, R0 with stage IV, or the nodal dissection area smaller than the extent of nodal metastasis] or pC [R2] (vs. pA [R0]) (HR 2.199, p=0.0027), pathological N1-4 (vs. pN0) (HR 3.397, p=0.0012) and histological therapeutic effect (Grade>=2) (HR 0.301, p=0.0104). A prognostic index using postoperative factors was constructed dividing patients into good (no or one risk factor), moderate (two risk factors) or poor (three risk factors) risk groups. 3yOS for good, moderate and poor risk groups were 87.7%, 56.0%, and 31.6%, respectively. **Conclusions:** cT, Alb and postoperative pathological findings are independent prognostic factors for advanced thoracic esophageal SCC patients who received preoperative chemotherapy. Information from this analysis can be used to aid clinical decision-making and help individual patient risk stratification.

**4046 General Poster Session (Board #133), Sat, 8:00 AM-11:45 AM**

**Molecular profiling of resected esophageal cancer and its correlation with clinical outcome.** *Presenting Author: Tomoya Yokota, Divison of Gastrointestinal Oncology, Shizuoka Cancer Center, Sunto-gun, Japan*

**Background:** The tumor related gene profiling in esophageal cancer remains unknown and requires further investigation in order to promote efficient and rapid development of molecular-target agents. The aim of this study was to evaluate the expression level and mutations of tumor related genes in resected esophageal cancer and to assess correlation of the profiling with clinical outcome. **Methods:** 135 consecutive patients with esophageal cancer who underwent esophagectomy at Shizuoka Cancer Center and Toyama University between October 2002 and November 2011 were analyzed. Protein expression of MET, EGFR, ALK and HGF was determined by Automated QUantification Analysis. Copy number of EGFR, PIK3CA, MET and FGFR1/2 was analyzed by real time PCR. The translocation of ALK gene and mutations of tumor related genes were evaluated by fluorescence in situ hybridisation and TruSeq Amplicon Cancer Panel, respectively. Prognostic factors associated with survival were identified by multivariate analyses using the Cox proportional hazards model. **Results:** Overall, heavy smoking was significantly associated with high HGF expression (p=0.03938), but was not an independent prognostic factor. After adjustment for clinical features by multivariate Cox regression analysis, high expression of ALK was associated with poor OS in patients without neoadjuvant therapy (HR 4.589, p=0.0102). The translocation of ALK gene was present only in 1 patient. High expression of MET was associated with poor OS in patients with neoadjuvant therapy (HR 5.68, p=0.043). Mutations in p53 and PIK3CA were present in 73% and 13%, respectively. The frequency of mutations in APC, BRAF, ERBB4, VHL, KRAS and EGFR was less than 10%. PIK3CA amplification was observed in 2%. **Conclusions:** High expression of ALK and MET may be prognostic factors for resected esophageal cancer. Esophageal cancers with high expression level of ALK and MET might be possible candidates for ALK and MET targeting therapies.

**4047 General Poster Session (Board #134), Sat, 8:00 AM-11:45 AM**

**Phase I study of epigenetic priming using azacitidine prior to neoadjuvant chemotherapy in patients with resectable esophageal and gastric adenocarcinoma.** *Presenting Author: Bryan J. Schneider, Weill Cornell Medical College, New York, NY*

**Background:** Epigenetic silencing of tumor suppressor genes (TSGs) is an acquired abnormality observed in cancer and is prototypically linked to DNA methylation. 5-Azacitidine (V) is a cytosine analog and a DNA hypomethylating agent (DHA). Reactivated expression of TSGs is commonly implicated in the clinical activity of DHAs since TSGs often regulate apoptosis, DNA repair, and checkpoint control. We postulated that pretreatment (priming) with V would increase the efficacy of neoadjuvant chemotherapy by reactivating TSGs during administration of cytotoxics. The study was conducted to identify a tolerable dose of V prior to epirubicin (E), oxaliplatin (O), capecitabine (X), (EOX) neoadjuvant chemotherapy. **Methods:** Eligible patients (pts) had locally-advanced, resectable esophageal/gastric adenocarcinoma, no prior therapy, ECOG 0-2 and adequate organ function. V (75mg/m$^2$) was given subcutaneously for 3 (Dose Level, DL 1) or 5 (DL 2) days with EOX (E 50 mg/m$^2$, O 130 mg/m$^2$, X 625 mg/m$^2$ bid x 21 d) beginning on the last day of V. Cycles were repeated every 21 days. Residual tumor was resected after cycle 3. Standard 3+3 methodology guided V dose escalation. DNA methylation at control and biomarker regions was measured by digital droplet, bisulfite qPCR in tumor samples prior to therapy and at resection. **Results:** 10 pts were mostly male (9M:1F), median age 54 yrs (40-84) and esophageal (3), gastric (5), or GEJ (2) tumors. 9 pts completed the planned 3 cycles; 3 on DL1, 7 on DL2. A MTD was not identified. One DLT was identified (DL2) during cycle 2: Grade 4 dehydration and hypokalemia. Other toxicities included grade 4 neutropenia (n = 4), pulmonary embolus (n = 1) and grade 3 nausea (n = 3). Overall response rate was 60% (CR/PR: 2/4) by PERCIST and included 2 pathologic CR and a third with only a microscopic tumor focus found at resection. Responding pts with informative DNA methylation abnormalities at baseline demonstrated significant DNA hypomethylation at CDKN2A, HPP1, ESR1 and TIMP3 in the resected specimen. **Conclusions:** Neoadjuvant V-EOX was well tolerated with significant clinical and epigenetic responses. Research was partially, supported by a grant from Celgene, Inc. Clinical trial information: NCT01386346.

**4048 General Poster Session (Board #135), Sat, 8:00 AM-11:45 AM**

**Prevalence of MET and HER2 biomarkers in stage IV gastric cancer.** *Presenting Author: Robert D. Loberg, Molecular Sciences & Computational Biology, Amgen, Inc., Thousand Oaks, CA*

**Background:** Estimates of the frequency of genomic alterations in *MET* and *HER2* in gastric cancer vary widely, but alterations in *MET* are generally less common than alterations in *HER2*. We examined a large set of stage IV gastric cancer samples for variation in *MET* and *HER2*gene copy number. We also assessed HER2 protein expression in these samples. **Methods:** Formalin-fixed, paraffin-embedded (FFPE) stage IV gastric cancer tumor samples (N = 309) were collected in Russia (n = 195), China (n = 99), and other countries (n = 15). Samples were analyzed by fluorescence in situ hybridization (FISH) for *MET* gene amplification (Dako *MET* IQFISH pharmDx) and *HER2* gene amplification (Dako *HER2* IQFISH pharmDx) and by immunohistochemistry (IHC) for HER2 protein expression (Dako HercepTest). All assays were performed according to the manufacturer's instructions. This is the first published use of the Dako *MET* IQFISH pharmDx assay. Cohen's kappa coefficient, a statistical measure that takes into account agreement that occurs by chance, was used to assess agreement between measurements. **Results:** We found *MET* gene copy number variation ($\geq$ 5 copies) in 17 of 305 samples (6%), and *MET* gene amplification (*MET/CEN-7* $\geq$ 2.0) in 12 of 305 samples (4%). The proportion of samples that were *MET* gene amplified was similar in the Chinese and Russian samples. We found *HER2* gene copy number variation ($\geq$ 5 copies) in 54 of 280 samples (19%), and *HER2* gene amplification (*HER2/CEN-17* $\geq$ 2.0) in 43 of 280 samples (15%). Of the 201 evaluable HER2 IHC samples, 22 (11%) were positive for HER2 protein expression. *HER2* FISH and HER2 IHC results showed that *HER2* gene amplification and protein expression commonly occur in the same tumors (kappa = 0.71 to 0.76). *HER2* and *MET* FISH results showed that *MET* and *HER2*gene amplification rarely occur in the same tumors (kappa $<$ 0.05); only one sample was amplified for both genes. **Conclusions:** *MET* gene amplification was observed in 4% of this large set of stage IV gastric cancer samples. Prevalence of *HER2* gene amplification and expression was in the same range as found in previously published studies. Our results indicate that *MET* gene amplification and *HER2* gene amplification may occur in different subpopulations of stage IV gastric cancers.

**4049 General Poster Session (Board #136), Sat, 8:00 AM-11:45 AM**

**Survival benefit of metastasectomy plus chemotherapy versus chemotherapy alone for Krukenberg tumors from advanced stomach cancer.** *Presenting Author: Jang Ho Cho, Department of Medical Oncology, Gangnam Severance Hospital, Seoul, South Korea*

**Background:** Although systemic chemotherapy is the optimal treatment strategy for metastatic stomach cancer, several local treatments have been investigated to improve overall survival (OS) in patients with oligometastasis or limited metastasis. Because the survival benefit of metastasectomy has not been clearly validated for krukenberg tumors, we evaluated the survival benefit of ovarian metastasectomy in krukenberg tumor from stomach cancer and identified prognostic factors for survival. **Methods:** Of 27,103 patients who were diagnosed with stomach cancer between March 2004 and February 2013 at Yonsei University Medical Center, 244 female patients with krukenberg tumor detected by abdominal-pelvis computed tomography or gynecologic ultrasonography were included in the study and reviewed retrospectively Patients were divided into two arms according to treatment modality: arm A, metastasectomy plus chemotherapy and arm B, chemotherapy alone. **Results:** OS was increased by 9 and 11 months in arm A compared with arm B for patients initially diagnosed with stage IV stomach cancer (21.0 vs. 12.0 months; $p < 0.001$) and those with recurrent krukenberg tumors (19.0 vs. 8 months; $p = 0.002$), respectively. Metastasectomy (hazard ratio [HR] = 0.517 [95% confidence interval {CI}, 0.330–0.809]; $p = 0.004$), signet-ring cell pathology (HR = 1.753 [95% CI, 1.187–2.588]; $p = 0.005$), peritoneal carcinomatosis (HR = 1.564 [95% CI, 1.041–2.350]; $p = 0.031$), and an elevated serum CA125 level (>35 U/mL) (HR = 1.786 [95% CI, 1.148–2.780]; $p = 0.010$) were significant prognostic factors for survival. **Conclusions:** OS was prolonged with chemotherapy plus metastasectomy than with chemotherapy alone in patients with krukenberg tumors from stomach cancer. This survival benefit was observed both in patients initially diagnosed with stage IV stomach cancer and in those diagnosed with recurrent krukenberg tumor. Metastasectomy, signet-ring cell pathology, peritoneal carcinomatosis, and an elevated serum CA125 level were prognostic factors for survival. Future prospective randomized trials are needed to confirm the optimal treatment strategy for krukenberg tumors from stomach cancer.

**4050 General Poster Session (Board #137), Sat, 8:00 AM-11:45 AM**

**Clinical impact of induction chemotherapy followed by surgery for gastric cancer with positive peritoneal cytology.** *Presenting Author: Masaki Aizawa, Niigata Cancer Center Hospital, Niigata, Niigata, Japan*

**Background:** The gastric cancer patients with peritoneal metastasis have poor survival. Nevertheless, the survival rate in patients who accompany with positive peritoneal cytology as only the evidence of distant metastasis has been superior to that in patients with overt peritoneal dissemination. In such patients, the combination of preoperative chemotherapy and surgery may enable to perform potentially R0 resection. The aim of this study was to verify the clinical significance of R0 resection following the clearance of free cancer in the peritoneal cavity. **Methods:** The retrospective study was conducted using a prospectively maintained database. A total of 53 gastric cancer patients with free cancer cells in the peritoneal cavity, as evaluated by staging laparoscopy between January 2001 and December 2010, but no other evidence of distant metastasis, which underwent induction chemotherapy (mostly S-1+cisplatin regimen) followed by surgery were identified. Then, the correlation between clinicopathological features and the prognosis was assessed by COX proportional hazards analysis. **Results:** The MST and 5-year OS rate of the 53 study participants were 19.7 months and 25.6%, respectively. In 28 patients, the peritoneal cytology converted from positive to negative after the induction chemotherapy, and microscopically margin negative gastrectomy was performed subsequently. The MST of 31.4 months and 5-year OS rate of 36.1% of these patients were significantly more favorable than the corresponding values of 12.7 months and 15.0% in the patients who failed to diminish the free cancer cell in the peritoneal cavity ($P< 0.001$). Multivariate survival analysis identified the residual tumor (HR: 3.419, 95%CI: 1.695-6.895, $p=0.001$) as well as macroscopic Type 4 tumor (HR: 2.636, 95%CI: 1.022-6.798, $p=0.04$) as an independent prognostic factor. **Conclusions:** The conversion of positive peritoneal cytology by induction chemotherapy might improve the prognosis. The results suggested an adequate impact to accept the induction chemotherapy followed by surgery with curative intent for gastric cancer patients with positive peritoneal cytology as only the evidence of metastasis.

**4051 General Poster Session (Board #138), Sat, 8:00 AM-11:45 AM**

**Safety, tolerability, and pharmacokinetics (PK) of rilotumumab (R) combined with cisplatin (C) and capecitabine (X) in Japanese patients (pts) with MET-positive metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma.** *Presenting Author: Toshihiko Doi, National Cancer Center Hospital East, Kashiwa, Japan*

**Background:** R is an investigational, fully human monoclonal antibody to hepatocyte growth factor, the MET receptor ligand. This study assessed the safety, PK, and tumor response of R + CX in Japanese pts with MET-positive G/GEJ cancer. **Methods:** An initial cohort evaluating dose-limiting toxicities (DLTs) is described; an expansion cohort has fully enrolled and will be reported. Eligible pts were Japanese, age ≥20 years, ECOG ≤1, and had pathologically confirmed MET-positive unresectable, locally advanced/metastatic G/GEJ adenocarcinoma. In each 21-day cycle, pts received R 15 mg/kg IV (day 1), C 80 mg/m$^2$ IV (day 1; up to 6 cycles), and X 1000 mg/m$^2$ BID orally (days 1−14). Endpoints included DLTs, adverse events (AEs), PK of R and CX, and objective response. **Results:** The initial cohort enrolled 6 pts; there was 1 DLT (grade 3 decreased appetite). All pts had treatment-emergent AEs (TEAEs). TEAEs occurring in >3 pts were decreased appetite (n=5), nausea (n=5), fatigue (n=4), and palmar-plantar erythrodysesthesia (n=4). Three pts had grade ≥3 TEAEs (diarrhea and neutropenia [n=2 each]; decreased appetite, hypoalbuminemia, hypocalcemia, hyponatremia, hypophosphatemia, leukopenia, and stomatitis [n=1 each]). Grade ≥3 treatment-related AEs (TRAEs) were diarrhea (n=2), neutropenia (n=2), decreased appetite, leukopenia, and stomatitis (n=1 each). There was 1 grade 4 TRAE (neutropenia). One pt discontinued R due to nonserious arterial thrombosis. There were no life-threatening or fatal R-related AEs. The mean end-of-infusion concentrations of R were 212, 275 and 272 μg/mL in cycles 1, 2 and 3, respectively. Exposures to CX were similar across cycles. The mean $C_{max}$ of X and its metabolite 5-FU was 6.1 and 0.3 μg/mL. The mean $C_{max}$ of total and unbound C was 3.8 and 1.4 μg/mL. The mean $t_{1/2}$was 0.5, 0.7, and 12.3 h for X, 5-FU, and unbound C. Two pts had a partial response. **Conclusions:** The toxicity profile of R + CX in Japanese pts with MET-positive G/GEJ cancer was consistent with that of Western pts. Safety and PK results support further evaluation of R + chemotherapy in MET-positive G/GEJ cancer. Clinical trial information: NCT01791374.

**4052 General Poster Session (Board #139), Sat, 8:00 AM-11:45 AM**

**Association of polymorphisms in the CCL2/CCR2 axis with clinical outcome in localized advanced gastric cancer (AGC) patients (pts) from the United States and Japan.** *Presenting Author: Yu Sunakawa, USC Norris Comprehensive Cancer Center, Los Angeles, CA*

**Background:** CCL2/CCR2 chemokine axis controls the recruitment of leukocytes to tissues during inflammation and has a number of tumor-promoting activities including the polarization of tumor associated macrophages which play immunosuppressive roles. Overexpression of CCL2 was associated with a higher risk of gastric cancer. We hypothesized that single nucleotide polymorphisms (SNPs) in genes encoding for CCL2/CCR2 axis may be associated with clinical outcome in pts with localized AGC. **Methods:** This study included 160 Japanese pts for evaluation set and 104 U.S. pts for validation set, with localized AGC treated with surgery alone or plus adjuvant therapy (stage Ib-IV; AJCC-6$^{th}$). The median age were 68 (31-88) and 59 (26-85) years-old, median follow-up were 4 and 3.3 years, respectively. Genomic DNA was extracted from pts' blood or tissues. Seven functional SNPs in genes encoding for CCL2/CCR2 axis, *CCL2* (rs4586 and rs1024611) and *CCR2* (rs743660, rs1799864, rs3138042, rs3918358, and rs3092964), were analyzed by PCR-based direct sequencing for association with disease-free survival (DFS) / time to recurrence (TTR) and overall survival (OS). **Results:** In the evaluation set, the univariate analysis showed pts with any T allele of *CCL2* rs4586 had significantly longer DFS and OS compared to those with the C/C genotype (HR: 0.61; 95% CI: 0.39-0.96; P=0.03, HR: 0.58; 95% CI: 0.36-0.93; P=0.02, log-rank test, respectively) although median DFS and OS both had not been reached yet. This remained no significant upon multivariate analysis. In the validation set, pts with any T allele of *CCL2* rs4586 had a trend toward shorter TTR (HR: 1.73; P=0.07) and significantly shorter OS compared to those with the C/C genotype (3.8 vs. 7.3 yrs; HR: 2.43; 95% CI: 1.14-5.18; P=0.01, log-rank test) in univariate analysis. Interestingly, the impact of the T allele on OS in the U.S. cohort was the opposite to that in the JPN cohort and reached statistical significance (P=0.001). **Conclusions:** Our results suggest that the CCL2 polymorphism, rs4586, may serve as a prognostic marker in pts with localized AGC and that there may be ethnic differences in immunoesurveillance impacting clinical outcome.

**4053 General Poster Session (Board #140), Sat, 8:00 AM-11:45 AM**

**A phase II study of preoperative chemotherapy and chemoradiation for localized gastric and gastroesophageal junction adenocarcinoma (LGCA).** *Presenting Author: Elena Elimova, MD Anderson Cancer Center, Houston, TX*

**Background:** For patients with LGCA, adjunctive therapies improve the 5-year survival rates by ≈10% over surgery alone. We studied preoperative oxaliplatin/5-FU-based chemotherapy followed by chemoradiation. **Methods:** Patients with LGCA with baseline eusT2-T3 any N, M0 (M stage by laparoscopy and imaging) were eligible. Patients received ≤4 doses of oxaliplatin and infusional 5-FU q 2 weeks then oxaliplatin and infusional 5-FU with 45 Gy of conformal radiation in 25 fractions. 5-6 weeks after chemoradiation, patients underwent an attempted D2 dissection and were followed. **Results:** Between Feb. 2004 and Nov. 2010 a total of 58 patients were enrolled. Most patients were men (66%) and had clinical stage IIIA cancer (52%). 14% (95%CI: 6%, 25%) of patients achieved a pathCR. With a median follow-up of 37.4 months, the median survival was 39.4 (95%CI: 27.6, NR) months. The 5-yr OS was 44% and the 5-yr PFS was 42%. 72% of patients proceeded to surgery and 86% of these had an R0 resection. The 5-yr OS for patients who had surgery was 56%. 44.8% of patients experienced grade 3 and/or 4 toxicities (commonly, fatigue, anorexia and insomnia) due to induction chemotherapy. 58.6% experienced grade 3 and/or 4 toxicities due to chemoradiation (commonly, fatigue, myelosuppression, vomiting, and dysphagia). No treatment-related death occurred. **Conclusions:** The 5-yr OS for all patients treated on this study was 44%. Our data show that if LGCA patients can complete the described therapeutic strategy (i.e., including surgery), their outcome may be excellent. Therefore, we must refine patient selection for future trials based on clinical variables and biomarkers. This will help in identifying patients who are likely to respond to pre-operative treatment versus those who are not. Biomarker studies (with mTOR, Gli-1, Sox9, ALDH-1, and Shh, etc.) are underway and will be presented. Clinical trial information: 2003-0769.

**4054 General Poster Session (Board #141), Sat, 8:00 AM-11:45 AM**

**Visceral fat content, clinical features, and prognosis in a database of 507 upper gastrointestinal cancers.** *Presenting Author: Kazuto Harada, Department of Gastroenterological Surgery, Graduate School of Medical Science, Kumamoto University, Japan, Kumamoto, Japan*

**Background:** Excess visceral adipose tissue may promote cancer development and progression through obesity-related metabolic disturbances, such as adipocytokine-related Inflammation, insulin resistance, and hypoxia. Although the relationship between visceral fat content and patient prognosis has been reported in some cancer types, the clinical, pathological and prognostic value of visceral fat volume in upper gastrointestinal cancers has yet to be investigated. We therefore examined the relationship between visceral fat status and clinical outcome in patients with the upper gastrointestinal cancers (esophageal cancer and gastric cancer) treated by surgical resection. **Methods:** Preoperative visceral fat content in 507 upper gastrointestinal cancer patients was retrospectively quantified by radiologic measures using standard computed tomography scans. The Cox proportional hazards model was used to compute mortality hazard ratio, adjusting for clinical and tumoral features. Throughout this study, the term "prognostic marker" is used in the context of the REMARK Guidelines. **Results:** Higher visceral fat content was correlated with male sex ($p = 0.0012$), presence of preoperative comorbidity ($p = 0.0009$), absence of preoperative therapy ($p < 0.0001$), low tumor stage ($p = 0.029$), low tumor depth ($p = 0.0032$) and gastric cancer ($p = 0.0053$). Subjects with low visceral fat experienced a higher overall mortality rate than their high visceral fat counterparts [log-rank p=0.0050; univariate HR= 1.73, 95% confidence interval (CI) 1.16–2.54; p=0.0075; multivariate HR 1.57; 95% CI, 1.02–2.37; p=0.031]. Interestingly, the influence of low visceral fat on patient outcome was modified by age at surgery (p for interaction = 0.036); low visceral fat was associated with a poor prognosis, especially in elderly patients (log rank p<0.0001). **Conclusions:** We identified a correlation between low visceral fat in upper gastrointestinal cancer patients and poor prognosis, suggesting that low visceral fat may provide a biomarker for identifying patients likely to experience an inferior outcome

**4055 General Poster Session (Board #142), Sat, 8:00 AM-11:45 AM**

**The survival difference between gastric cancer patients from the United Kingdom and Japan after using weighted propensity score for adjustment of differing background factors.** *Presenting Author: Takaki Yoshikawa, Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan*

**Background:** Previous studies comparing survival between gastric cancer (GC) patients (pts) from the East and the West either used calibrated survival based on a Western nomogram, only considered a highly selected set of background factors in multivariate analyses or did not consider differences in background factors and prognostic factors at all . The present study aimed to first compare all available characteristics from GC pts from the UK and Japan and then compare the survival of the two cohorts after adjusting for all significantly different background factors using weighted propensity score. **Methods:** Data from 654 pts from the Kanagawa Cancer Center, Yokohama, Japan (KCCH) and 680 pts from the Leeds Teaching Hospital NHS Trust, Leeds, UK (LTHT) who had surgery for GC were analyzed. Patient characteristics, surgery, pathology, and outcome were compared. Prognostic factors for overall survival (OS) and cancer specific survival (CSS) were identified by univariate and multivariate analyses. After initial comparison of 'unadjusted' survival, survival was compared after adjusting for all significantly different background factors. **Results:** Significant differences between KCCH and LTHT pts were observed for age, gender, tumor location, type of gastrectomy, splenectomy, pancreatectomy, residual tumor (R), number of examined lymph nodes, and histological tumor type. Unadjusted stage-specific OS and CSS were significantly better in KCCH. Independent prognostic factors for unadjusted OS and CSS were age, tumor location, depth of invasion (T), nodal metastasis (N), and distant metastasis (M) in KCCH; and age, tumor location, splenectomy, T, N, M, R status and number of examined lymph nodes in LTHT. Even after adjusting for all background characteristics, survival remained better in KCCH in TNM stages I, II, and III for OS and TNM stages II and III for CSS. **Conclusions:** These results suggest that the differences in background factors between GC pts from UK and Japan cannot fully explain differences in survival. Further studies are needed to investigate whether survival differences are due to GC tumor biology and/or host specific factors.

**4056 General Poster Session (Board #143), Sat, 8:00 AM-11:45 AM**

**Pretreatment neutrophil to lymphocyte ratio as an independent predictor of disease-specific survival in resectable GE junction and gastric adenocarcinoma.** *Presenting Author: Sam C Wang, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Preoperative methods to estimate disease specific survival (DSS) for resectable gastroesophageal junction and gastric adenocarcinoma (GEJ/GA) are inadequate. The patient's inflammatory state may impact cancer outcome, as suggested by the consistent association of decreased DSS with postoperative complications or transfusions. The aim of this study was to evaluate the relationship between DSS and pretreatment neutrophil to lymphocyte ratio (NLR), which may reflect the systemic inflammatory state, following complete resection of GEJ/GA. **Methods:** Review of a prospective database identified all patients diagnosed with primary GEJ/GA who underwent complete resection from 1998-2013. Patient, tumor, treatment characteristics and pretreatment neutrophil and lymphocyte counts were recorded. Patients were stratified into quartiles based on NLR values. Five year DSS was estimated by the Kaplan-Meier method. A Cox proportional hazards model was used to evaluate the independent associations between clinicopathologic variables and DSS. **Results:** We identified 1,498 patients, with median follow-up of four years. On univariate analysis, elevated NLR was associated with increased age, male gender, Caucasian race, increased T and N stage, and neoadjuvant therapy. On multivariate analysis, decreased DSS was associated with Caucasian race (p=0.02), increased T stage (p<0.01), increased N stage (p<0.01) and neoadjuvant therapy (p<0.01). Elevated pre-treatment NLR was also independently associated with worse DSS (HR=1.09 [95%CI: 1.05-1.13], p<0.01, Table). **Conclusions:** In patients with resectable GEJ/GA, pretreatment NLR is significantly and independently associated with DSS. NLR is a simple and effective value available during treatment planning to help risk stratify patients with GEJ/GA for cancer specific outcome.

**Five-year DSS and multivariate DSS using NLR as quartiles.**

| | NLR | N | Five-year DSS | Adjusted HR* | 95% CI |
|---|---|---|---|---|---|
| **Quartile 1** | 0.23-2.00 | 389 | 70% | Ref | |
| **Quartile 2** | 2.00-2.76 | 362 | 66% | 1.1 | 0.8-1.4 |
| **Quartile 3** | 2.76-3.85 | 374 | 56% | 1.2 | 0.9-1.5 |
| **Quartile 4** | >3.85 | 372 | 50% | 1.5 | 1.1-1.9 |

*Adjusted for age, gender, race, T stage, N stage, and neoadjuvant therapy.

**4057 General Poster Session (Board #144), Sat, 8:00 AM-11:45 AM**

**REGARD: A phase 3, randomized, double-blind trial of ramucirumab (RAM) and best supportive care (BSC) versus placebo (PL) and BSC in the treatment of metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma following disease progression (PD) on first-line platinum- and/or fluoropyrimidine-containing combination therapy: Age subgroup analysis.** *Presenting Author: Charles S. Fuchs, Dana-Farber Cancer Institute, Boston, MA*

**Background:** The REGARD trial demonstrated significant improvements in overall survival (OS), progression free survival (PFS), and disease control rates in pts receiving RAM, a human IgG1 receptor targeted antibody. We examined outcomes by age (<65 and ≥65 years [yrs]). **Methods:** Pts were randomized 2:1 to receive RAM (8 mg/kg IV) plus BSC or PL plus BSC every 2 wks until PD, unacceptable toxicity, or death. Eligible patients had PD within 4 months (m) after 1st-line therapy for metastatic disease or within 6 m after adjuvant therapy. The primary endpoint was OS. Secondary endpoints included PFS, 12-wk PFS rate, overall response rate (ORR) and safety. **Results:** 355 pts. were randomized; 227 were age <65 yrs (RAM 156; PL 71) and 128 were ≥ 65 yrs (RAM 82; PL 46).Baseline characteristics were well balanced between the treatment arms and subgroups. RAM efficacy was similar in younger and older patients. Median OS was 5.3 vs 4.1 m in the RAM:PL arms for pts <65 yrs and 5.2 vs 3.8 m in the RAM:PL arms for pts ≥65 yrs. The OS HR was 0.846 (95% CI, 0.611-1.171) in pts <65 years and 0.722 (95% CI 0.471-1.106) in pts ≥65 yrs (treatment-by-age group interaction p = 0.5569). Median PFS was 1.9 vs 1.3m in the RAM:PL arm for pts <65 yrs and 2.8 vs 1.4 m for Ram:PL for pts ≥65 yrs. The PFS HR was 0.450 (95% CI, 0.327-0.620) <65 yrs and 0.490 (95% CI, 0.319-0.752) (interaction p=0.9445). The incidence of Grade ≥3 adverse events was comparable between treatment arms for both age groups (55% vs 57% pts <65 yrs; 60% pts ≥65 yrs in both arms). The most frequent grade ≥ 3 AEs in ≥ 5% of pts RAM arm were: hypertension (7.8% RAM; 1.4% PL [<65 yrs] and 7.3% RAM; 4.4% PL [≥65 yrs]), abdominal pain (7.1% RAM; 4.3% PL [<65 yrs]), fatigue (7.3% RAM; 2.2% PL ≥ 65 yrs) and anemia (9.1% RAM; 7.1% PL [<65 yrs]. No specific AE was observed at grade ≥ 3 in > 10% of patients.**Conclusions:** When compared to placebo, RAM conferred similar improvements for OS and PFS between pts age < 65 yrs and those age ≥ 65; AE profiles were also similar for pts ≥ 65 and <65 yrs. Clinical trial information: NCT00917384.

**4058 General Poster Session (Board #145), Sat, 8:00 AM-11:45 AM**

**RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel patients with previously treated gastric or gastroesophageal junction (GEJ) adenocarcinoma: Quality-of-life (QoL) results.** *Presenting Author: Salah-Eddin Al-Batran, Krankenhaus Nordwest, Frankfurt, Germany*

**Background:** Ramucirumab (RAM) added to paclitaxel (PTX) resulted in statistically significantly improved overall survival, progression-free survival and response rate for previously treated patients (pts) with advanced gastric or GEJ cancer (Wilke et al, GI Cancer Symposium 2014). Here we present the secondary endpoint of QoL. **Methods:** Pts who had previously received fluoropyrimidine- and platinum-based therapy were randomized to receive RAM 8 mg/kg IV or placebo (PL) on Days 1 and 15 every 4 weeks (wks); both arms received PTX 80 mg/m$^2$on Days 1, 8 and 15. Pts completed the EORTC QLQ-C30 (v3) at baseline, every 6 wks from start of therapy and at discontinuation. Time to deterioration (TtD) in each QoL parameter was defined as randomization to first worsening of ≥10 points (on 100-point scale). Hazard ratios (HRs) for treatment effect were estimated using stratified Cox proportional hazards models. In addition, scores were classified as improved or worsened if changed by ≥10 points relative to baseline, otherwise classified as stable. **Results:** Of 665 pts randomized, 322/330 (98%) of RAM+PTX and 328/335 (98%) of PL+PTX pts provided baseline (BL) QoL data and 87% and 81%, respectively, provided both BL and post-BL data. BL scores were similar between arms. Of the 15 QoL parameters, 14 had HRs <1, indicating similar or longer TtD in QoL for RAM+PTX. HRs <0.75 were observed for emotional functioning and nausea/vomiting and >1 for diarrhea. For all QoL parameters and at all on-therapy assessment times, the proportion of pts reporting improved or stable scores was numerically greater for RAM+PTX; in general, more pts were classified as stable than improved. **Conclusions:** For pts with advanced gastric cancer, addition of RAM to PTX did not impair QoL. Compared with PL+PTX, QoL was maintained for a longer time and more pts reported stable or improved scores. Clinical trial information: NCT01170663.

**Rates of improvement/stability for select QoL parameters.**

| | RAM+PTX (N=330) | | PL+PTX (N=335) | |
|---|---|---|---|---|
| | Wk 6 | Wk 12 | Wk 6 | Wk 12 |
| **Global QoL** | 53% | 36% | 50% | 27% |
| **Physical functioning** | 56% | 41% | 47% | 28% |
| **Fatigue** | 45% | 35% | 42% | 25% |
| **Pain** | 56% | 41% | 49% | 27% |
| **Appetite loss** | 60% | 43% | 54% | 30% |

**4059 General Poster Session (Board #146), Sat, 8:00 AM-11:45 AM**

**Patient-derived xenografts as models for the identification of predictive biomarkers in esophagogastric cancer.** *Presenting Author: Yelena Yuriy Janjigian, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Individual EG cancer subtypes have heterogeneous tumor characteristics and clinical outcome, making EG adenocarcinoma a complex disease to treat. Cytotoxic agents are applied to all disease subtypes with only modest success. Emergence of HER2 and MET as therapeutic targets underscores the importance of tumor profiling to allow optimal treatment planning. Preclinical models that recapitulate tumor biology may aid in discovery of new biomarkers and therapeutic targets. The purpose of this study is to establish PDXs accompanied by annotated molecular and clinical data for identification of predictive biomarkers and testing of targeted therapies. **Methods**: Fresh specimens obtained under aseptic conditions, mixed with matrigel and inoculated into 8 wks old NOD scid gamma mice subcutaneously (SQ) into flanks or orthotopically (OT) into the gastric wall. PDXs are kept in an *in vivo* microenvironment to retain a degree of the polyclonality of the tumors from which they were derived. Once established, tumor material is collected for molecular analysis, histology, and primary cultures. **Results**: To date 90 tumor samples have been implanted SQ, 20 of which were also implanted OT. To date, 22 PDXs have been established and 12 additional tumors (5 SQ, 7 OT) are being monitored for engraftment. Tumor engraftment rate was 46% for OT and 26% for SQ implants. The table below summarizes the results including molecular tumor characteristics. The established PDXs include HER2+ trastuzumab refractory models, MET+ models, and a signet ring gastric cancer model with germ line CDH1mutation. **Conclusions:** The established EG PDXs provide a platform to further validate differences in tumor biology and guide rational design of clinical trials. Comprehensive molecular profiling and therapeutic experiments with PDXs are underway.

| Tumor characteristic | Established PDX n=22 N (%) |
|---|---|
| **Esophagus/GE junction** | 8 (36) |
| **Diffuse/signet ring** | 2 (9) |
| **Distal stomach/intestinal** | 12 (54) |
| **Primary tumor** | 13 (59) |
| **Metastasis** | 9 (41) |
| **HER2-positive** | 3 (19) |
| **MET-positive** | 13 (81) |
| **CDH1 germ-line mutation** | 1 (4) |

**4060 General Poster Session (Board #147), Sat, 8:00 AM-11:45 AM**

**Neoadjuvant versus adjuvant treatment: Which one is better for resectable locally advanced esophageal squamous cell carcinoma?** *Presenting Author: Qixun Chen, Zhejiang Cancer Hospital, Hangzhou, China*

**Background:** In China, the main treatment of esophageal squamous cell carcinoma (ESCC) is surgery combined with postoperative adjuvant chemoradiotherapy.The role of preoperative neoadjuvant chemoradiotherapy is not well established. We compared neoadjuvant chemoradiotherapy followed by surgery with surgery followed by adjuvant chemoradiotherapy in a Chinese ESCC population. **Methods:** We randomly assigned patients with resectable locally advanced tumors (T3-4N0-1M0, T1-2N1M0) to receive surgery and weekly administration of carboplatin (AUC=2) and paclitaxel (50 mg/m$^2$) for 6 weeks and concurrent radiotherapy (50.4 Gy/28f, 5 days per week) at preoperative (the neoadjuvant group) or postoperative (the adjuvant group). **Results:** From April 2011 through December 2013, we enrolled 42 patients: 23 were randomly assigned to chemoradiotherapy followed by surgery, and 19 to surgery followed by adjuvant chemoradiotherapy. Among these 42 patients, the most common major hematologic toxic effects were leukopenia (9.5%), neutropenia (11.9%), thrombocytopenia (14.3%), and anaemia (16.6%); the most common major nonhematologic toxic effects were anorexia (14.3%), fatigue (11.9%), and cervical anastomotic fistula (19.1%). Complete resection with no tumor of the resection margins (R0) was achieved in 100% of patients in the neoadjuvant group versus 90.4% in the adjuvant group. A pathological complete response was achieved in 8 of 23 patients (34.8%) who underwent resection after chemoradiotherapy. Postoperative complications and treatment-related mortality were similar in the two groups. The disease free survival rate at 18 months was 78.7% in the neoadjuvant group as compared with 63.6% in the adjuvant group, which exceeded the goal of this study design. **Conclusions:** Our preliminary result suggests that, in patients with resectable locally advanced ESCC, there is a benefit tendency for the preoperative neoadjuvant chemoradiotherapy compared with postoperative adjuvant chemoradiotherapy. The regimen was associated with acceptable adverse-event rates. These trends warrant further study. Clinical trial information: ChiCTR-TRC-12002665.

**4061 General Poster Session (Board #148), Sat, 8:00 AM-11:45 AM**

**Metabolic landscape and prognostic value of HER2 in advanced gastric cancer.** *Presenting Author: Chan-Young Ock, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea*

**Background:** In advanced gastric cancer (AGC), HER2 is a validated therapeutic target. However, the metabolic landscape of AGC based on the HER2 status has not been reported. Furthermore, the prognostic value of HER2 in AGC is under debate. Purpose of this study is to elaborate the metabolic landscape and prognosis based on HER2 status in AGC. **Methods:** We consecutively enrolled the 615 AGC patients treated with chemotherapy and whose HER2 status was evaluated from 2004 to 2013 (225 HER2+, 390 HER2-). Among them, 248 patients were evaluated with 18F FDG-PET before chemotherapy. Among 225 HER2+ patients, 67 patients were not exposed to any HER2-targeting agents. We analyzed overall survival (OS) according to HER2 IHC, FISH (HER2/CEP17 ratio, HER2 copy number) and maxSUV (mSUV). **Results:** The mSUV of HER2+ GC was significantly higher than those of HER2- GC (11.2 vs 7.5, p=0.001). Increased HER2 IHC positivity was correlated with higher mSUV (IHC-: 7.4, IHC 1+: 6.5, 2+: 9.4, 3+: 11.2, p=0.001), and high HER2/CEP17 ratio showed the trend for higher mSUV (<2: 8.9, 2-4: 9.2, ≥4: 10.5, p=0.925). Excluding HER2+ patients who received HER2-targeting agents, OS of AGC patients treated with cytotoxic chemotherapy was not different based on HER2 status (HER2+: 12.6 vs HER2-: 12.5 months, p=0.663). In parallel, neither increased HER2 IHC positivity (IHC-: 12.4, IHC 1+: 13.4, 2+: 11.8, 3+: 12.9 months, p=0.891) nor HER2/CEP17 ratio (<2: 12.1, 2-4: 17.8, ≥4: 13.4 months, p=0.448) nor HER2 copy number (copy<4: 11.2, 4-6: 13.0, ≥6: 11.3 months, p=0.273) influenced on OS. However, based on tumor metabolism, patients with higher mSUV showed higher response rate, but worse OS regardless of HER2 positivity (HER2-: mSUV<12.5: 13.4 vs mSUV≥12.5: 8.9 months, p=0.01, HER2+: mSUV<14.3: 18.5 vs mSUV≥14.3: 6.4 months, p=0.001). **Conclusions:** Tumor metabolism is higher in HER2+ AGC and this metabolic activity influenced on the OS. However, HER2 is not prognostic factor in AGC patients who receive cytotoxic chemotherapy.

**4062 General Poster Session (Board #149), Sat, 8:00 AM-11:45 AM**

**Biomarkers to predict sensitivity to HER2-targeting treatment in HER2-positive advanced gastric cancer.** *Presenting Author: Tae Yong Kim, Department of Internal Medicine and Cancer Research Institute, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea*

**Background:** Trastuzumab-based chemotherapy is considered as standard treatment for patients with HER2-positive advanced gastric cancer (AGC). However, the biomarkers to predict the sensitivity to this HER2-targeting treatment have not been clarified. We evaluated the association of sensitivity to HER2-targeting treatment with HER2 status and tumor metabolic activity in HER2-positive AGC. **Methods:** We consecutively enrolled 133 patients with HER2-positive AGC treated with trastuzumab-based chemotherapy. HER2 IHC status, HER2/CEP17 ratio, HER2 copy number and maximum standardized uptake value (maxSUV) from 18F FDG-PET were analyzed for the clinical outcomes. **Results:** Overall survival (OS) of patients with HER2 IHC 3+ was significantly longer than that of IHC 2+/FISH+ (26.9 vs 15.2 months, p=0.012). A median number of HER2/CEP17 ratio and HER2 gene copy number were 5.4 (95% CI, 1.1-14.6) and 10.2 (95% CI, 2.1-30.3), respectively. A higher HER2/CEP17 ratio more than 5.4 was identified as a good predictor to treatment sensitivity (<5.4: OS 11.9 vs ≥5.4: OS 25.7 months, p=0.040). For HER2 copy number, patients with higher HER2 copy number showed the tendency for better OS (HER2 copy number <10.2: 14.7 vs ≥10.2: 25.7 months, p=0.20). Patients with HER2/CEP17 ratio>5.4 and HER2 copy>6 showed best OS than the others (26.9 vs 11.9 months, p=0.044). Contrary to this, patients with IHC same or less than 2+ and HER2/CEP17 ratio<5.4 showed worst prognosis than the others (7.7 vs 26.9 months, p<0.001). However, there was no significant impact of maxSUV on predicting treatment sensitivity so far, even though tendency of higher response rate in high maxSUV patients. **Conclusions:** The higher HER2/CEP17 ratio and higher HER2 copy number could be biomarkers for sensitivity to HER2 targeting treatment in HER2-positive AGC. Further study on the role of tumor metabolism in this area is needed.

**4063 General Poster Session (Board #150), Sat, 8:00 AM-11:45 AM**

**Impact of age on the feasibility and efficacy of neoadjuvant chemotherapy in patients with locally advanced gastroesophageal cancer: A retrospective pooled analysis of individual patient data.** *Presenting Author: Silvia Spörl, 3rd Department of Internal Medicine (Hematology/Medical Oncology), Klinikum rechts der Isar, Technische Universität München, Munich, Germany*

**Background:** Neoadjuvant chemotherapy (neoCTx) improves the prognosis of patients (pts) with locally advanced esophagogastric adenocarcinoma (EGC), but its value is unknown in elderly patients (pts). **Methods:** Pts from 4 institutions who received neoCTx followed by surgery for EGC between 2000 and 2012 were analyzed. We compared the feasibility and outcome of neoCTx in pts aged ≥70 (cohort I) and their younger counterparts (cohort II). **Results:** Data were available for 460 pts among which 173 (37.6%) were ≥70 years. The median age in cohort 1 and 2 was 59 and 73 years, respectively. Older age was associated with an increased rate of comorbidities (66.0% vs. 42.1%, p<0,001). As compared to the younger, elderly pts were more likely to receive doublet instead of triplet neoCTx (64% vs 38%, p<0.001) and oxaliplatin- instead of cisplatin-based regimens (60% vs 32%, p<0.001). Of the 460 pts who started neoCTx, 83% and 90% in cohort I and II completed neoCTx without major alterations. Dose reductions to < 80% were necessary in 27% and 20% in cohort I and II (p=0.129). No significant difference was observed in the rate of ≥ grade 3 toxicities for cohort I and II (47% vs. 41%) and postoperative morbidity was also not different (24% vs. 28%). 60 day mortality for cohort I and II was 1.8% and 3.5%. After a median follow up of 30.4 months, median DFS in cohort I and II was 30 and 31 months, with a 3-years DFS of 48% and 46%, respectively. Median OS was 78 and 81 months, with a 3-year OS of 69% and 65%, respectively. On multivariate analysis, age was not significantly correlated with overall survival after adjustment for the rate of co-morbidities, gender and the number of neoCTx drugs applied (HR for age: 0.947; p=0.80). **Conclusions:** Despite slightly more adverse events and dose reductions, neoCTx is feasible in elderly pts with EGC. Elderly pts achieve comparable survival outcomes compared with their younger counterparts.

**4064 General Poster Session (Board #151), Sat, 8:00 AM-11:45 AM**

**Randomized phase II study of CPT-11 versus PTX versus each combination chemotherapy with S-1 in patients with advanced gastric cancer refractory to S-1 or S-1 plus CDDP.** *Presenting Author: Tomono Kawase, Department of Surgery, Sakai City Hospital, Sakai, Japan*

**Background:** S-1 plus cisplatin (SP) is recognized as standard first-line chemotherapy for advanced gastric cancer (AGC) and S-1 monotherapy is recognized as standard adjuvant chemotherapy for locally AGC in Japan. Taxane and CPT-11 are two main options and a retrospective analysis has reported that S-1 combination chemotherapy extended overall survival (OS) as second-line chemotherapy for AGC refractory to S1-based chemotherapy. Thus, this prospective multicenter phase II study was carried out to examine efficacy and safety comparing CPT-11, PTX, and each combination chemotherapy with S-1 refractory to S-1 or SP. **Methods:** Patients with AGC after first-line chemotherapy with S-1 or SP, or during adjuvant chemotherapy or within 26 weeks after adjuvant chemotherapy completion with S-1 who confirmed disease progression by imaging were eligible. Patients were randomly divided into four groups by treatment as follows; Group A: CPT-11 150 mg/m$^2$, day1, q14days, Group B: PTX 80 mg/m$^2$, day1, 8, 15, q28days, Group C1: CPT-11 80 mg/m$^2$, day1, 15, S-1 80 mg/m$^2$, day1-21, q35days, Group C2: PTX 50 mg/m$^2$, day1, 8, S-1 80 mg/m$^2$, day1-14, q21days. Primary endpoint was OS, and secondary endpoints were progression free survival (PFS), response rate and safety. **Results:** From July 2008 to March 2012, 127 patients were enrolled. Median OS was 11.3/11.3/14.6/10.5 months(M) (Group A/B/C1/C2), 11.8 M in Group A+C1 and 11.1 M in Group B+C2 (p=0.922, HR: 0.981 [0.679-1.419]), and 11.3 M in Group A+B and 11.1 M in Group C1+C2 (p=0.808, HR: 0.952 [0.643-1.412]), respectively. Median PFS was 3.0/4.4/3.8/3.5 M (Group A/B/C1/C2), 3.6 M in Group A+C1 and 4.1 M in Group B+C2 (p=0.035, HR:0.674 [0.468-0.972]), and 3.7 M in Group A+B and 3.7 M in Group C1+C2 (p=0.931, HR: 1.017 [0.643-1.412]) , respectively. Grade 3 or 4 adverse events (Group A/B/C1/C2, %) were leukopenia (12/7/5/0), neutropenia (29/16/24/24), anemia (7/9/14/14), anorexia (10/2/14/10), nausea (7/2/10/5), diarrhea (5/0/10/0), and fatigue (5/2/10/5). **Conclusions:** The difference in OS between CPT-11 and PTX, and the efficacy of S-1 sequential therapy were not observed in second-line chemotherapy for AGC refractory to S-1 or SP. Clinical trial information: 000000677.

**4065 General Poster Session (Board #152), Sat, 8:00 AM-11:45 AM**

**The relationship between HER2 expression and Lauren classification in Chinese gastric cancer patients.** *Presenting Author: Rui-hua Xu, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China*

**Background:** Intestinal type of gastric cancer has a better prognosis than diffuse type and intestinal type tends to have a higher incidence rate of HER2 positive. However the prognosis value of HER2 is still controversial. There might be some factors affecting the HER2's survival value. What is the relationship between HER2 expression and Lauren classification? We would also analyze the survival differences among the gastric cancer patients with different HER2 and Lauren classification status. **Methods:** All the patients received the detection of human epidermal growth factor receptor 2 (HER2) by immunohistochemistry (IHC). HER2 amplification levels were detected when the result of IHC was 2+. Fluorescence in situ hybridization (FISH) analysis was carried out according to the manufacturer's protocol using the PathVysion HER2 DNA Probe kit (LSI HER2/neu Spectrum OrangeTM/ chromosome 7 centromere probe (CEP) 17 Spectrum GreenTM). FISH positive was defined as HER2:CEP17 ratio ≥2. Any case with IHC 3+ or IHC2+/FISH+ was considered to be HER2-positive, while the cases with IHC 0 and IHC 1+ as well as IHC 2+/FISH− were considered to be HER2-negative according to the European Medicines Agency. Two pathologists were responsible for the Lauren classification. There were totally 840 patients for analysis. Survival was defined as the time from metastasis to the time of death. **Results:** The positive rate of HER2 is 11.2% (94/840). As for the Lauren classifications, there are 51.8% (435/840) diffuse type, 33.0% (277/840) intestinal type and 15.2% (128/840) mixed type. The HER2 positive rate was 25.6%, 2.8% and 8.6% in intestinal type, diffuse type and mixed type, respectively (P<0.001). We ignored the mixed type and divided the rest patients into four groups: A, HER2 positive and diffuse type; B, HER2 positive and intestinal type; C, HER2 negative and diffuse type; D, HER2 negative and intestinal type. The median overall survival was 7.9months, 10.2 months, 10.8 months and 13.7 months, P=0.001. **Conclusions:** Intestinal cancer has a higher incidence rate of HER2 positive. Patients with HER2 negative and intestinal type have a best survival, while patients with HER2 positive and diffuse type have a worst survival.

**4066 General Poster Session (Board #153), Sat, 8:00 AM-11:45 AM**

**Simvastatin plus capecitabine-cisplatin (XP) versus placebo plus capecitabine-cisplatin (XP) in patients with previously untreated advanced gastric cancer: A double-blind randomized phase 3 study.** *Presenting Author: Seung Kim, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea*

**Background:** Patients with advanced gastric cancer (AGC) have a poor prognosis and few efficacious systemic treatment options. We aimed to the addition of synthetic 3-hydroxy-3-methyglutaryl coenzyme A (HMG-CoA) reductase inhibitor, simvastin to capecitabine-cisplatin (XP) in patients with previously untreated advanced gastric cancer. **Methods:** In this double-blind, placebo-controlled, phase III study, we enrolled patients aged 18 years or older with histological or cytological confirmed metastatic (M1) adenocarcinoma of stomach or gastroesophageal junction at 9 centres in the KOREA. Patients, stratified by disease measurability and participating site, were randomly assigned (1:1) to receive capecitabine 1,000mg/m2 twice daily for 14 days and cisplatin 80 mg/m2 on day 1 every 3 weeks plus either simvastatin 40 mg or placebo, once daily. Cisplatin was given for 8 cycles; capecitabine and simvastatin were administered until disease progression or unacceptable toxicities. The primary end point was progression free survival (PFS). We assessed safety in all patients who received at least one dose of study drugs. This study is registered with ClinicalTrials-.gov, number NCT01099085. **Results:** Between February 2009 and November 2012, 244 patients were enrolled and assigned to treatment groups (120 simvastatin, 124 placebo). Median PFS for 120 patients allocated XP plus simvastatin was 5.2 months (95% CI 4.3-6.1) compared with 4.63 months (95% CI 3.5 -5.7) for 124 patients who were to allocated to XP plus placebo (hazard ratio 0.930, 95% CI 0.684-1.264; p=0.642). 63 (52.5%) of 120 patients in simvastatin group and 70 (56.4%) of 124 had grade 3 or higher adverse events. Most common grade 3 or higher adverse events were neutropenia (40.5%, simvastatin plus XP; 51% placebo plus XP), anemia (13.3% v 10.5%) and anorexia (7.5% v 10.5%). **Conclusions:** Addition of 40 mg simvastatin to XP does not increase PFS in our trial, although it does not increase toxicity. Low dose of simvastatin (40mg) to chemotherapy is not recommended in untargeted population with advance gastric cancer. Clinical trial information: NCT01099085.

**4067 General Poster Session (Board #154), Sat, 8:00 AM-11:45 AM**

**Quality of life (QoL) analysis from the randomized phase III REAL3 trial of epirubicin, oxaliplatin, and capecitabine (EOC) with or without panitumumab (P) in advanced esophagogastric adenocarcinoma.** *Presenting Author: Tom Samuel Waddell, The Royal Marsden NHS Foundation Trust, London and Surrey, United Kingdom*

**Background:** REAL3 evaluated EOC + P in advanced oesophago-gastric adenocarcinoma. We previously reported that addition of P was associated with increased diarrhoea, skin rash and mucositis without improvement in survival endpoints. This analysis reports QoL outcomes for participants in both arms of the trial. **Methods:** QoL was assessed via EORTC QLQ-C30 questionnaires requested at baseline (BA), post-cycles 4 (C4) and 8 (C8), and at 3 months follow-up (3M). Functional and symptomatic scores were calculated using recommended EORTC methods. Comparison of differences between study arms was performed using one sample t-test with 2-sided p-values and repeated measures analysis investigated scores over time. A threshold of 0.05 indicated statistical significance. Data in both arms was censored at time of early trial closure (Oct 2011) when all patients crossed to EOC. **Results:** 553 patients were recruited between June 2008 and October 2011. Excluding duplicates and those censored, the questionnaire response rate at each timepoint was: BA 470/553 (85%); C4 163/418 (39%); C8 72/196 (37%); 3M 35/64 (55%) with similar response rate in both arms. Irrespective of treatment allocation there was a non-significant decrease in global health score during chemotherapy which recovered by 3M. A similar trend was observed for physical, role and social function scales with no difference between arms. Cognitive function scores showed more marked deterioration in patients receiving EOC+P with mean decrease of 15 points between BA and 3M, compared to no change in patients receiving EOC (p=0.026). Chemotherapy was associated with a trend towards improved nausea and vomiting, appetite, and pain scores in both arms. Conversely it worsened scores related to fatigue, dyspnoea and diarrhoea. Diarrhoea was increased by addition of P (p=0.007) with no other significant differences in symptom scores between arms. **Conclusions:** Chemotherapy did not have a detrimental effect on global QoL and seemed to improve some disease-related symptoms. Increased scores related to diarrhoea with addition of P are in keeping with the known toxicity profile. Clinical trial information: 2007-005976-15.

**4068 General Poster Session (Board #155), Sat, 8:00 AM-11:45 AM**

**MAGIC germline polymorphism analysis.** *Presenting Author: Elizabeth Catherine Smyth, The Royal Marsden NHS Foundation Trust, London & Surrey, United Kingdom*

**Background:** Germline polymorphisms may affect chemotherapy efficacy and survival. We examined the effect of polymorphisms in drug metabolism and DNA repair genes on survival for patients (pts) randomised to surgery alone or perioperative ECF chemotherapy in the MRC MAGIC trial. **Methods:** DNA was extracted from nontumor resection FFPE blocks. ERCC1, ERCC2, XRCC1, DYPD, and OPRT SNPs were evaluated using Sequenom, GSTP1, GSTT1 deletion and TS 5' 2R/3R using multiplex PCR. Post PCR amplification TS 2R/3R and GSTT1 samples underwent gel electrophoresis. **Results:** Results are available on 289/456 resected pts. Duplicate pair concordance with Sequenom was excellent (98%). Discrepancy was significant for duplicate pairs analysed for 5' TS 2R/3R and GSTT1 length based polymorphisms; these were not analysed further. For genotype frequency and survival see Table. There was no evidence of an interaction between any genotype and treatment. **Conclusions:** No polymorphism examined was predictive of survival in MAGIC. SNP analyses from FFPE are reproducible but due to DNA fragmentation length based polymorphisms may not be; results from such studies should be interpreted with caution.

| | | Genotype and Frequency | | | Effect of genotype on OS: Median OS (y) from surgery | |
|---|---|---|---|---|---|---|
| Gene | SNP | XX | XY | YY | Surgery | Chemo + Surgery |
| OPRT | G638C (Gly213Ala) | GG 64% | GC 33% | CC *3% | GG 2.09 (ref)<br>GC 1.68; HR 1.01, p=0.963 | GG 1.83 (ref)<br>GC 2.86; HR 0.74, p=0.263 |
| ERCC1 | C118T | CC 17% | CT 48% | TT 35% | CC 2.83 (ref)<br>CT 1.71; HR 1.08, p=0.764<br>TT 1.59; HR 1.17, p=0.577 | CC 1.36 (ref)<br>CT 1.71; HR 0.99,p=0.973<br>TT 3.54; HR 0.68, p=0.286 |
| ERCC1 | C8092A | TT *6% | GT 43% | GG 51% | GG 1.69 (ref)<br>GT 1.76; HR 0.97, p=0.879 | GG 2.36 (ref)<br>GT 2.13; HR 1.05, p=0.832 |
| ERCC2 | Lys751Gln | GG 15% | GT 44% | TT 41% | GG 1.51 (ref)<br>GT 3.27; HR 0.80, p=0.5<br>TT 1.57; HR 1.21, p=0.548 | GG 1.28 (ref)<br>GT 2.86; HR 0.57, p=0.066<br>TT 1.71; HR 0.69, p=0.223 |
| XRCC1 | A399G | AA 13% | AG 43% | GG 44% | AA 0.8 (ref)<br>AG 1.85; HR 0.68, p=0.24<br>GG 2.6; HR 0.63, p=0.156 | AA 0.98 (ref)<br>AG 1.94; HR 0.72,p=0.323<br>GG 2.46; HR 0.7, p=0.288 |
| GSTP1 | I105V | AA 51% | AG 41% | GG 8% | AA 2.11 (ref)<br>AG 1.59; HR 1.19, p=0.416 | AA 1.89 (ref)<br>AG 2.82; HR 0.84, p=0.478 |
| DPYD | A1627G | AA 69% | AG 26% | GG *6% | AA 2.31 (ref)<br>AG 1.28; HR 1.75 p=0.008 | AA 2.82 (ref)<br>AG 1.60; HR 1.23, p=0.371 |
| DPYD | IVS14+1G>A | GG >99% | GA *<1% | AA *0% | No analysis due to low % GA/AA genotypes | |

* Genotypes ≤ 8% frequency not analysed for OS.

**4069 General Poster Session (Board #156), Sat, 8:00 AM-11:45 AM**

**Randomized, multicenter, phase III trial to compare S-1 plus docetaxel (DS) with S-1 plus cisplatin (SP) in gastric cancer patients with stage III (POST trial).** *Presenting Author: Choong-kun Lee, Division of Medical Oncology, Yonsei University College of Medicine, Seoul, South Korea*

**Background**: Even among completely resected gastric cancer patients treated with adjuvant chemotherapy, stage III patients show bad prognosis and somewhat better treatment option is needed. Docetaxel or cisplatin each added to S1 monotherapy showed survival benefits in advanced gastric cancer. **Methods**: We conducted randomized, multicenter, phase III trial to compare S-1 plus docetaxel (DS) with S1 plus cisplatin (SP) in stage III gastric cancer patients. Gastric cancer patients (AJCC 7$^{th}$ stage III) who had had curative D2 gastrectomy were randomized 1:1 to receive adjuvant chemotherapy of eight 3 week cycles of DS (S-1 70mg/m$^2$/day on day 1-14 plus docetaxel 35mg/m$^2$ on day 1, and day 8) or SP (S-1 70mg/m$^2$/day on day 1-14 plus cisplatin 60mg/m$^2$on day 1). The primary endpoint was 3-year disease-free survival (3Y-DFS). Secondary endpoints include overall survival (OS) and safety. (NCT01283217) **Results**: As a result of early closure due to slow accrual, 153 patients of planned 290 patients were randomly assigned (75 patients to DS and 78 patients to SP) from 8 institutions for 31 months. The median follow up duration was 15.8 months (range, 0.8 to 36.2 months). There was no difference in DFS (HR, 1.088; 95% CI, 0.589 to 2.01; p=0.787) or OS (HR, 1.621; 95% CI, 0.707 to 3.720; p=0.254) between DS and SP. Most common grade 3 or 4 adverse event was neutropenia (42.7% among DS group and 38.5% among SP group, p=0.351). SP group suffered more grade 3 or 4 anemia (1.3% vs. 11.5%, p=0.037), where grade 3 or 4 hand-foot syndrome (4.1% vs. 0%, p=0.025) and mucositis (10.7% vs. 2.6%, p=0.001) were more common among DS group. **Conclusions**: Although the trial closed prematurely and had short follow up duration, S-1 plus cisplatin or docetaxel is an effective and tolerable option for patients with stage III advanced gastric cancer patients. Clinical trial information: NCT01283217.

**4070 General Poster Session (Board #157), Sat, 8:00 AM-11:45 AM**

**Nimotuzumab plus paclitaxel and cisplatin as first-line treatment for esophageal squamous cell cancer: Final results of a single-center prospective clinical trial.** *Presenting Author: Ming Lu, Peking University School of Oncology, Beijing Cancer Hospital & Institute, Beijing, China*

**Background:** Nimotuzumab (N) was a humanized anti-EGFR monoclonal antibody. We conducted a prospective, single-armed, open label phase II study to evaluate the efficacy and safety of paclitaxel (T)/cisplatin (C)/ Nimotuzumab (N) as first-line treatment in advanced ESCC. **Methods:** Patients with pathologic confirmed unresectable local-regional advanced or metastatic ESCC were treated with the TPN regimen: Nimotuzumab 200mg weekly, Paclitaxel 175mg/m2 on d1, and Cisplatin 30mg/m2 on day1 and 2, repeat cycle every 3 weeks for six cycles. Local-regional advanced disease was defined as tumor lesion limited in 1 radiation field without organ metastasis. Metastatic disease was defined as organ (liver, lung et al) metastasis or lymph nodes metastasis exceeding 1 radiation field. Radiotherapy was allowed to be admitted after 4 cycle of TPN treatment.The primary endpoint is the objective response rate (ORR) and the safety. The secondary endpoint is the progression free survival (PFS) and the overall survival (OS). **Results:** 59 pts were enrolled from 2011 to 2013 and 56 were eligible. 29 pts were local-regional advanced disease and 27 pts were metastatic disease. Overall RR was 51.8%(29/56) and DCR was 92.9%(52/56). As a median follow-up of 24 months, 33 pts had progressed, of which 22 pts were metastatic disease. The median PFS for patients with metastatic disease and local-regional advanced disease were 8.2 months (95% CI 5.3 to 11.2 months) and more than 23 months (95% CI: 9.0 to 37.1).The overall survival for patients with metastatic disease was 13.9 months (95% CI: 6.8 to 21.2). The most common G3/4 toxicities were Neutropenia (58.9%), Leukopenia(32.1%), Nausea/Vomiting (7.1%), Anorexia (5%). Febrile neutropenia was reported in 3.6% of patients. No chemotherapy related death occurred. **Conclusions:** The TPN regimen, as first-line chemotherapy, was a more active treatment option in patients with advanced ESCC compared to other regimens published in previous studies. The addition of anti-EGFR treatment of nimotuzumab to standard chemotherapy was well tolerated with no serious AEs. Clinical trial information: NCT01336049.

**4071 General Poster Session (Board #158), Sat, 8:00 AM-11:45 AM**

**Preoperative chemoradiation versus preoperative chemotherapy alone for esophageal cancer: Higher response rates but equivalent survival.** *Presenting Author: Brendon Matthew Stiles, Weill Cornell Medical College, New York, NY*

**Background:** Controversy exists over the optimal neoadjuvant therapy in patients with locally advanced esophageal cancer (EC). While most groups favor neoadjuvant chemoradiation (nCRT), some advocate preoperative chemotherapy (nCT) without radiation. The objective of this study was to compare outcomes in EC patients undergoing either regimen, followed by surgery. **Methods:** We reviewed a prospectively collected database of EC patients undergoing esophagectomy following nCT or nCRT (1989-2013). Choice of therapy was at the discretion of the multidisciplinary team. Demographic data, clinical and pathologic staging, and survival (KM) were compared. **Results:** From 600 patients, 261 patients were identified with EC treated with nCRT (n=63) or nCT (n=199) followed by surgery. Patients were well matched for age, gender, PS, histology, and clinical stage. Following therapy, more nCRT patients had a complete clinical response (36% vs. 14%, p<0.001) by post-induction endoscopy and CT/PET. At surgery, 88% and 92% of CRT and CT patients underwent transthoracic esophagectomy. nCRT, in comparison to nCT, was associated with similar rates of cardiovascular (23% vs. 28%, p=0.43), pulmonary (24% vs. 25%, p=0.95), and infectious (13% vs. 9%, p=0.38) postoperative complications, and higher anastomotic leaks (23% vs. 14%, p=0.09). Perioperative (6% vs. 2%, p=0.06) and 90-day (11% vs. 4%, p=0.03) mortality was higher in nCRT than nCT patients. Following nCRT, 30% of patients had complete pathologic response vs. 6% of nCT patients (p<0.01). nCRT patients were more often node negative on final pathology (62% vs. 33%, p<0.001). Despite improved pathologic downstaging, nCRT patients had no improvement in 3-year disease-free (33% vs. 39%, p=0.84) or overall (54% vs. 52%, p=0.36) survival. No benefit of nCRT vs. nCT was apparent in 3-year overall survival in either adenocarcinoma (52% vs. 47%, p=0.25) or squamous cell carcinoma (44% vs. 61%, p=0.51). **Conclusions:** For patients undergoing surgery for EC, nCRT leads to increased local tumor response compared to nCT alone. However, nCRT is associated with increased early mortality and did not translate to improved long-term survival.

**4072^ General Poster Session (Board #159), Sat, 8:00 AM-11:45 AM**

**Concordance study of *HER2* fluorescence in situ hybridization (FISH) assays in upper gastrointestinal (UGI) adenocarcinomas.** *Presenting Author: Michael F. Press, USC Norris Comprehensive Cancer Center, Los Angeles, CA*

**Background:** Patient inclusion to the primary efficacy population of TRIO-013/LOGiC trial of lapatinib in combination with chemotherapy in advanced HER2-positive UGI adenocarcinomas required evidence of *HER2* gene amplification confirmed by central lab. As no HER2 tests were approved for use in UGI cancers at trial start, the HER2 FISH assay used in the 2 trial central labs was PathVysion. A study was conducted in a cohort of UGI adenocarcinomas to determine concordance of PathVysion HER2 FISH assay between the 2 central labs and concordance between PathVysion HER2 FISH and HER2 IQFISH pharmDx, an assay recently approved in UGI adenocarcinomas. **Methods:** 488 UGI adenocarcinoma cases, procured as formalin-fixed, paraffin-embedded blocks, were screened by HercepTest to ensure representation of 4 immunochemistry (IHC) staining intensities. All IHC3+ and 2+cases were included; IHC1+ and 0 cases were binned by primary tumor (gastric, gastro-esophageal junction [GEJ] and esophageal) then randomly selected. Selected cases were sent to 2 trial central labs for HER2 FISH testing, blinded to the IHC results. Overall acceptance criteria were predefined as positive percent agreement (PPA) and N (negative) PA of at least 90%. **Results:** 159 cases were selected: 31 IHC3+; 20 IHC2+; 55 IHC1+; 53 IHC0. Of the 159 cases, 105 were gastric, 35 GEJ and 19 esophageal adenocarcinomas. All 159 cases were tested by 1 central lab using both assays; the PPA (95% Confidence Interval [CI]) and NPA (95% CI) were 97.9% (89.1, 99.6) and 99.1% (94.8, 99.8), respectively. Preliminary analysis in 126 cases tested by both central labs resulted in PPA of 95.6% (85.2, 98.8) and NPA of 94.5% (86.7, 97.8). Majority of IHC1+/0 cases were *HER2* non-amplified by both assays (89%) and in both central labs (89% versus 93%). Of the 31 IHC3+ cases, 2 were considered *HER2* non-amplified; both exhibited heterogeneity in HER2 IHC staining: 1 case was *HER2* non-amplified by 1 central lab for both assays, yet amplified by the other central lab; other case was *HER2* non-amplified by PharmDx assay only. **Conclusions:** There was reasonably high level of concordance within laboratory for different *HER2* FISH assays as well as between labs for the same *HER2* FISH assay. Clinical trial information: NCT00680901.

**4073^ General Poster Session (Board #160), Sat, 8:00 AM-11:45 AM**

**HER-FLOT: Trastuzumab in combination with FLOT as perioperative treatment for patients with HER2-positive locally advanced esophagogastric adenocarcinoma: A phase II trial of the AIO Gastric Cancer Study Group.** *Presenting Author: Ralf Hofheinz, University Hospital Mannheim, Mannheim, Germany*

**Background:** Perioperative chemotherapy is a mainstay in the treatment of locally advanced esophagogastric adenocarcinomas (EGA). Trastuzumab improved survival when added to chemotherapy in pts with HER-2-positive metastatic EGA. We investigated the combination of trastuzumab and FLOT as perioperative treatment in pts with locally advanced EGA. **Methods:** A multicenter phase II study evaluated the efficacy & toxicity of perioperative HER-FLOT (24-h 5-FU 2,600 mg/m$^2$, leucovorin 200mg/m$^2$, oxaliplatin 85mg/mg$^2$, docetaxel 50 mg/m$^2$, trastuzumab 6mg/kg then 4 mg/kg d1, repeated d15 for four cycles pre- and postoperatively followed by 9 cycles of trastuzumab monotherapy 6mg/kg 3-weekly) in pts with HER-2 positive EGA (IHC 3+ or IHC 2+/ ISH+). Pts had to have ≥cT2, any N, M0 EGA. The primary endpoint was the rate of centrally tested pathological complete remissions (pCR). Secondary endpoints comprised disease-free and overall survival, R0 resection rate, toxicity and surgical morbidity. Here we report data of an interim safety analysis conducted in the first n=25 pts as well as surgical and pathological results of the first n=45 pts. **Results:** n=58 pts with a median age of 62 years were included. n=40 pts had tumors originating from the esophagogastric junction. T stage was: (cT2/3/4/unk) 4/44/9/1. n= 52 pts had cN+ disease. The interim safety analysis of four cycles of preoperative HER-FLOT revealed no unexpected safety findings (adverse events grade 3-4: neutropenia 28%, diarrhea 8%, nausea 8%). Thus far, data on surgery and central pathology of 45 patients are evaluable. R0 resection rate was 93.3%. In five pts anastomotic leakage was diagnosed, and five pts came in need of operative revision. One postoperative death occurred. Regarding the primary endpoint, pCR was found in 10 /45 pts (22.2%) and a further n=11 pts (24.4%) had near complete regression (<10 % residual tumor cells). **Conclusions:** HER-FLOT was found to be safe and no new or unexpected safety issues were noticed. Preliminary data on centrally assessed pCR rate is very promising with >20% achieving a pCR. Final analysis will be presented at the meeting. Clinical trial information: NCT01472029.

**4074 General Poster Session (Board #161), Sat, 8:00 AM-11:45 AM**

**A Bayesian multiple-treatments meta-analysis of neoadjuvant treatments for locally advanced, resectable esophageal cancer.** *Presenting Author: Kelvin K. Chan, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*

**Background:** While many studies have compared the different neoadjuvant treatments in patients with locally advanced, resectable esophageal cancer, the relative benefit and risk across these treatments remain unclear. **Methods:** A systematic review was conducted using MEDLINE, EMBASE and Cochrane Central of Registered Trials to identify randomized controlled trials (RCTs) up to June 2013 investigating the following regimens in esophageal cancer patients: resection alone, neoadjuvant chemotherapy (N-CT), neoadjuvant radiotherapy (N-RT) and neoadjuvant chemoradiotherapy (N-CRT). Two reviewers independently reviewed the studies and discrepancies were resolved either by discussion or by a third reviewer. Data including characteristics of studies and outcomes such as overall survival (OS), postoperative mortality, site of recurrence and quality of the studies were extracted. Parmar method was used to extract survival outcomes. A Bayesian multiple treatments meta-analysis (MTM) with random effect was constructed using WinBUGS to compare the relative efficacy and postoperative mortality of all neoadjuvant treatments simultaneously. **Results:** Thirty-three RCTs involving 6710 patients were identified. For the comparison between N-CRT vs. N-CT, 2 RCTs involving 194 patients were identified. Direct pairwise meta-analysis showed that there is a trend that N-CRT might result in better OS when compared to N-CT but not reaching statistical significance (HR: 0.83 95% CI (0.59-1.18)). When combining both direct and indirect evidence in MTM to improve precision, N-CRT was found to be statistically superior to N-CT for OS (HR: 0.84 95% credible regions (CR) (0.71-0.97)). In addition, there was no direct RCT comparing N-CRT to N-RT identified. The results of MTM showed that N-CRT was better than N-RT for OS (HR: 0.80 95% CR (0.67 – 0.97)). Probabilistically, N-CRT has a 98% chance of being the best treatment. There were no significant differences in the risk for postoperative mortality. **Conclusions:** This study provides additional evidence that N-CRT is the optimal neoadjuvant therapy with respect to OS without increasing postoperative mortality when compared with N-CT or N-RT.

**4075 General Poster Session (Board #162), Sat, 8:00 AM-11:45 AM**

**Outcomes of asymptomatic metastatic gastric cancer (MGC) patients when the initiation of systemic therapy is delayed.** *Presenting Author: Roopma Wadhwa, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Despite many investigations, the median survival of MGC patients remains well below 12 months. The purpose of this analysis was to assess if the onset (instant or delayed) of systemic chemotherapy affected patient survival. **Methods:** We retrospectively compared the outcome of MGC patients who received first line systemic treatment based on symptoms (symptomatic versus asymptomatic) and treatment timing (instant or delayed). The OS was calculated from time of initiation of chemotherapy. **Results:** 125 patients with MGC were analyzed. Patients were mostly men (65%) with good PS (0-1) but most (70%) were symptomatic. In all asymptomatic patients, the median time to start of chemotherapy was 7 weeks (95% CI: 5, 10). More treated asymptomatic patients were alive at 1 year (71%) post-therapy compared to symptomatic patients (45%; p=0.03). Patients were also grouped based on treatment delay of >4 weeks or no delay. Patients with >4-week delay were more likely to be alive 1 year after treatment (61%) compared to those treated within ≤4 weeks (34%; p =0.01). Asymptomatic patients in whom chemotherapy was delayed >4 weeks had 78% 1-year survival after treatment versus 53% in patients who started treatment ≤4 weeks but this was not significant (p=0.06). **Conclusions:** Acknowledging that asymptomatic MGC patients are likely to have a lower tumor burden than those with symptoms, our data suggest that we need not rush to initiate systemic treatment in asymptomatic MGC patients, thus allowing them time without chemotherapy toxicities. Frequent patient evaluations (q 8-10 weeks) are routine.

**4076 General Poster Session (Board #163), Sat, 8:00 AM-11:45 AM**

**RAINBOW: A global, phase 3, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy: Results of a multiple Cox regression analysis adjusting for prognostic factors.** *Presenting Author: Hansjochen Wilke, Kliniken Essen Mitte Center of Pallative Care, Essen, Germany*

**Background:** RAINBOW, a global, randomized, double-blind, phase 3 trial demonstrated significant improvements in overall survival (OS), progression-free survival (PFS), and response rate in metastatic gastric adenocarcinoma patients receiving ramucirumab (RAM), a human IgG1 VEGF2-receptor targeted antibody, plus paclitaxel (PTX) after prior chemotherapy. **Methods:** 665 pts were randomized 1:1 to receive RAM (8 mg/kg IV q2w) or placebo (PL) plus PTX (80 mg/m$^2$d1, 8, 15 of a 4 week cycle) until disease progression, unacceptable toxicity, or death. Primary analysis was a log-rank test stratified by geographic region, time to progression on first-line therapy and disease measurability. A prespecified stepwise Cox multiple regression analysis selected baseline covariates that were significantly associated with OS and PFS using the pooled (RAM+PTX;PL+PTX) data, and then adjusted for these potential prognostic factors in a Cox proportional hazards model that included a term for treatment arm. **Results:** The primary stratified analysis showed a statistically significant benefit in OS (stratified HR=0.807, 95% CI 0.678, 0.962; p=0.0169) and PFS (stratified HR=0.635, 95% CI 0.536, 0.752; p<0.0001) for the RAM+PTX arm. Factors significantly associated with OS were geographical region, ECOG PS, weight loss, number of metastatic sites, presence of ascites, tumor differentiation, and prior gastrectomy; for PFS liver metastasis, number of metastatic sites, sex, and weight loss. The HR for both OS and PFS improved after adjusting for these factors (OS HR= 0.745, 95% CI: 0.626, 0.888; p=0.0010; PFS HR=0.599, 95% CI 0.506, 0.708; p <0.0001). **Conclusions:** The study showed statistically significant and clinically meaningful benefit in OS and PFS for RAM+PTX as compared to PL+PTX. After adjusting for prognostic factors in the Cox regression analyses, the benefits seen in both OS and PFS improved, confirming the robustness of the primary analysis results. Clinical trial information: NCT01170663.

**4077 General Poster Session (Board #164), Sat, 8:00 AM-11:45 AM**

**Association of adjuvant chemotherapy with improved survival after esophagectomy without induction therapy for node-positive adenocarinoma.** *Presenting Author: Paul J Speicher, Duke University Medical Center, Durham, NC*

**Background**: Adjuvant therapy is recommended when patients undergo esophagectomy without induction therapy for node-positive (pN+) adenocarcinoma, but some patients may not receive adjuvant treatment due to complications related to surgery (CRS). This study investigated adjuvant chemotherapy (AC) use in this clinical setting using the National Cancer Database (NCDB). **Methods**: In the NCDB, 2,442 patients from 2003-2011 who underwent R0 esophagectomy without induction therapy for pN+ adenocarcinoma of the middle or lower esophagus and survived at least 30 days were reviewed. Predictors of AC were identified with multivariable logistic regression. The impact of AC on survival was estimated using Kaplan-Meier and Cox proportional hazards methods. **Results**: AC was given to 874 of 2,442 (35.8%) patients; 618 (70.7%) AC patients received radiation. Older age (AOR 0.58/decade, p<.001), longer travel distance (AOR 0.78/100 miles, p=.03) and CRS (AOR 0.45, p<.001) predicted that AC was not used. Patients given AC had better 5-year survival than patients not given AC (24.2% vs 14.3%, p<.001), and AC use predicted improved survival in multivariate analysis (HR 0.67, p=0.008, Table). Receiving radiation in addition to AC did not improve survival (p=0.3). Although CRS was associated with worse survival, patients who had CRS but received AC had superior survival compared to patients who did not have CRS or get AC (p=.016). **Conclusions**: AC is associated with significantly improved survival but used in a minority of patients treated with esophagectomy without induction therapy for pN+ esophageal adenocarinoma. CRS lower the chance of getting AC and predict worse long-term survival, but even patients with CRS had improved survival when given AC.

**Predictors of long-term mortality.**

| Predictor | HR | Upper 95% CI | Lower 95% CI | P |
|---|---|---|---|---|
| **Adjuvant chemotherapy** | 0.67 | 0.49 | 0.9 | 0.008 |
| **Age (per decade)** | 1.1 | 0.97 | 1.2 | 0.13 |
| **Female sex** | 0.9 | 0.5 | 1.5 | 0.7 |
| **Race (ref = White)** | | | | |
| **Black** | 2.2 | 0.8 | 5.9 | 0.14 |
| **Other** | 8.1 | 1.1 | 60.1 | 0.04 |
| **Charlson score** | 1.2 | 0.9 | 1.4 | 0.2 |
| **Pathologic T stage** | 1.6 | 1.3 | 1.9 | < 0.001 |
| **Facility volume** | 0.6 | 0.3 | 1.1 | 0.077 |
| **CRS** | 1.5 | 1.1 | 2.1 | 0.012 |

**4078 General Poster Session (Board #165), Sat, 8:00 AM-11:45 AM**

**Chemoradiation with or without nimotuzumab in locally advanced esophageal cancer (LAEC): A randomized phase II study (NICE trial).** *Presenting Author: Gilberto Castro, Instituto do Cancer do Estado de Sao Paulo, São Paulo, Brazil*

**Background:** Chemoradiation is the standard therapy for patients (pts) with inoperable LAEC. We sought to assess the safety and activity of chemoradiation combined with nimotuzumab, a humanized antibody against the epidermal growth factor receptor, in LAEC. **Methods:** We randomized pts with inoperable LAEC, previously untreated, and with no distant metastases 1:1 to chemoradiation (cisplatin 75 mg/m$^2$ D1, and 5-FU 1 g/m$^2$/d CI D1-4, both for four 28-day cycles, combined with external-beam radiation 50.4 Gy) or the same chemoradiation plus nimotuzumab 200 mg IV, once weekly for 26 wks. The primary endpoint was endoscopic complete response (eCR, defined as absence of elevated, vegetative or exophytic lesions), whereas combined eCR/pathologic CR (pCR), overall survival (OS), quality of life and safety were secondary endpoints. **Results:** We enrolled 107 pts, 82% male, mean age 59 y. 100 pts (93%) had squamous cell carcinoma (SCC); performance status (ECOG-PS) was 0/1 in 34%/60% of cases. The relative dose intensity of chemotherapy and radiotherapy was nearly identical in both arms, and the median number of nimotuzumab doses was 24. We performed post-treatment endoscopy in 67 pts, in 60 of whom with biopsy. In the ITT population, eCR rates with vs. without nimotuzumab were 47.2% vs. 33.3% (p=0.17), whereas combined eCR/pCR rates were 62.3% vs. 37.0% (p=0.02). In a median follow-up of 14.7 mo., the hazard ratio (HR) for OS was 0.68 (95%CI 0.44-1.07; p=0.09), with a median OS of 15.9 vs. 11.5 months, respectively. In an unplanned subgroup analyses, the HR for OS in pts with ECOG-PS 0 was 0.32 (95%CI 0.12-0.85; p=0.02). We found no significant differences in quality of life between arms. Toxicity was manageable in both arms, with no significant differences in adverse events or serious adverse events. **Conclusions:** Combined chemoradiation and nimotuzumab is safe in pts with LAEC, and appears to increase the combined eCR/pCR rate and to impact favorably on OS. This is a promising regimen in pts with locally advanced esophageal SCC, and a phase III trial is under consideration. Clinical trial information: NCT01249352.

**4079 General Poster Session (Board #166), Sat, 8:00 AM-11:45 AM**

**Survivin expression in peripheral blood as a prognostic marker in patients with gastric cancer.** *Presenting Author: Masanori Terashima, Shizuoka Cancer Center, Nagaizumi, Japan*

**Background:** Detection of circulating tumor cells (CTC) in peripheral blood is thought to be a promising method to evaluate the extent of minimal residual disease. However, unlike breast or lung cancer, little information is available in gastric cancer. Among them, evaluation of survivin, a member of the inhibitor of apoptosis (IAP) family, mRNA expression in peripheral blood appears to be a promising procedure with relative good performance for predicting recurrence after curative resection. In order to evaluate the clinical significance of surviving expression in peripheral blood, we performed real-time RT-PCR analysis using whole blood obtained from healthy volunteers and patients with gastric cancer. **Methods:** A total of 22 healthy volunteers and 96 patients with gastric cancer were enrolled in this study. Peripheral blood samples were collected using PAXgene and RNA was isolated using Boom method. After cDNA synthesis, quantitative real-time PCR targeting survivin gene was performed. The relative expression level of survivin mRNA was calculated with actin beta as an internal standard. Correlation between survivin expression and clinicopathologic factors and survival was investigated. **Results:** Survivin mRNA expression level in peripheral blood was significantly higher in gastric cancer (median: 370, range: 35-1890) than in healthy volunteers (median:117, range: 46 to 538) in healthy volunteers. Tere was no significant correlation between survivin mRNA expression level and clinicopathologic factors. If the cut-off level of survivin was determined at 540 from ROC analysis, survivin was positive in 28 of 96 patients (29%). Disease-free survival was significantly worse in survivin positive patients than in negative patients (p=0.0216). In multivariate analysis, survivin was selected as independent prognostic factor as well as lymph node involvement. **Conclusions:** Survivin expression in peripheral blood was significantly higher in gastric cancer patients than in healthy volunteers. In addition, survivin was selected as an independent prognostic factor in patients with gastric cancer.

**4080 General Poster Session (Board #167), Sat, 8:00 AM-11:45 AM**

**Increased circulating levels of VEGF-C to predict outcome in resectable gastric cancer patients.** *Presenting Author: Fernando De Vita, Medical Oncology Division, Second University of Naples, Naples, Italy*

**Background:** Vascular Endothelial Growth Factor C (VEGF-C), is a VEGF growth factor family member playing a key-role in lymphangiogenesis. It is overexpressed in 30-60% of gastric cancer patients, showing a strong correlation with an advanced stage and a poor survival. Based on this background we investigated the meaning of serum levels of VEGF-C in gastric cancer patients suitable for surgery. **Methods:** Preoperative VEGF-C serum levels were determined by enzyme-linked immunoadsorbent assay (ELISA) in 183 patients with gastric carcinoma and 51 healthy subjects (control group) observed at our department from January 2008 until December 2012. **Results:** Patients characteristics were the following: median age was 64 years (range 22 - 91), the male/female ratio was 115/68. The stage at diagnosis was 1A: 2.2%, 1B: 10.9%, 2A: 13.1%, 2B: 11.5%, 3A: 25.1%, 3B: 15.3%, 4: 21.9%. 29% of patients showed a proximal primary site of tumor, 32.2% a middle and 38.8% a distal primary site localization. Preoperative VEGF-C serum levels were significantly higher in gastric cancer patients (mean, 295 pg/mL; range, 55–865 pg/mL) if compared with the control group (mean, 30 pg/mL; range, 11.8–60,2 pg/mL; *P*< 0.001). High VEGF-C serum levels correlated with nodal diffusion: in fact, node positive patients showed significantly higher levels (mean, 339 pg/mL – 95% C.I, 307.4 – 370.6; *P< 0.001*) when compared to node negative ones (mean 93 pg/mL – 95%C.I, 72 – 114; *P<0.001*). Moreover, preoperative VEGF-C serum levels were significantly lower in patients who underwent curative surgery (248.7 pg/mL, range: 54.9 – 865.2 pg/mL) compared with patients who underwent palliative surgery (mean 461.1 pg/mL, range: 120.5 - 805.8; *P* < 0.001). Pearson correlation analysis demonstrated a significant negative correlation between preoperative VEGF-C serum levels and OS (Pearson correlation -0.281; *Sig.2 tails 0,001*). Finally at multivariate analysis elevated serum VEGF-C levels were an independent prognostic factor in our population. **Conclusions:** Our data obtained in this setting suggest that increased serum VEGF-levels appear as a poor prognostic factor correlating with a wide nodal involvement, a palliative surgery, and a worse overall survival.

**4081 General Poster Session (Board #168), Sat, 8:00 AM-11:45 AM**

**LEOPARD-II: A randomized phase II study of radiochemotherapy (RCT) with 5FU and cisplatin plus/minus cetuximab (Cet) in unresectable locally advanced esophageal cancer (LAEC).** *Presenting Author: Dirk Rades, Department of Radiation Oncology, University of Lübeck, Lübeck, Germany*

**Background**: Patients (pts) with LAEC have a poor prognosis; new therapies are required. A study showed the addition of Cet to RCT to be safe and effective for resectable EC [Ruhstaller et al, *J Clin Oncol* 29;2011:626-31]. A phase II/III trial showed increased grade ≥3 acute toxicity and worse OS if Cet was added for localized EC [Crosby et al, *J Clin Oncol* 30;2012(suppl 34;abstr LBA3)]. However, increased toxicity in the Cet-arm was due to skin and metabolic toxicity, which usually can be easily managed. Furtermore, capecitabine (Cap) was used; Cap+Cet is less effective than 5-FU+Cet. More trials are required investigating RCT+Cet for LAEC, particularly unresectable EC. **Methods**: This is an open-label, randomized (1:1) multicenter phase II study. Pts with unresectable non-metastatic EC, age 18-75 yrs, + KPS ≥70 are eligible. Pts receive RCT+Cet (Arm A) or RCT alone (Arm B). RCT included 5-FU (1000 mg/m²/d iv, d 1-4 + 29-32, and 750 mg/m²/d, d 64-67 + 92-95), cisplatin (20 mg/m²/d iv, same days as 5-FU) and RT (59.4 Gy/6.5 wks). If resectability is achieved at 45 Gy, surgery is performed. In Arm A, Cet starts 1 wk pre RCT (400 mg/m² iv), followed by 250 mg/m² weekly for a total of 14 wks. Endpoints of this planned interim analysis (20/134 pts) are toxicity, response (RECIST 1.1), and PFS. **Results:** GI toxicity occurred in all pts of both arms (9 arm A, 11 arm B). Skin toxicity was more frequent in arm A (100% vs. 36%). All skin toxicities were gr. 1-2. Regarding all toxicities, in arm A, 19 gr. 3 + 4 gr. 4 events occurred; in arm B, 20 gr. 3 + 2 gr. 4 events. 1 Cet-related SAE (nail toxicity) occurred. 2 fatal SAEs occurred in arm B. Response rates were 67% (95%CI [30-90]) in Arm A and 27% in arm B (95%CI [8-61]) (p=0.051). 5 (56%) pts in arm A and 1 (9%) pt in arm B had CR (p=0.01), 1 (11%) pt and 2 (18%) pts PR, and 0 pt (0%) and 3 (27%) pts PD. Median PFS was 15.5 mos (95%CI [3.6-19.3]) in arm A and 4.1 mos (95%CI [1,0]) in arm B. 6-mos PFS was 78% in arm A and 48% in arm B. **Conclusions:** Treatment was similarly tolerated in both groups. Most adverse events were mild to moderate. This interim analysis showed a trend towards higher response for RCT+Cet than for RCT. CR was significantly higher in the RCT+Cet group. Clinical trial information: NCT01787006.

**4082 General Poster Session (Board #169), Sat, 8:00 AM-11:45 AM**

**Difference in outcomes among patients undergoing open versus laparoscopy-assisted approach for gastric cancer: A multi-institutional analysis.** *Presenting Author: Gaya Spolverato, The Johns Hopkins University School of Medicine, Baltimore, MD*

**Background:** In the United States, gastric cancer is a relatively uncommon tumor. Overall surgical experience with minimally invasive surgery (MIS) has increased, however published reports on laparoscopic resection of gastric cancer are mostly limited to small, single institution experiences. **Methods:** Between 2000 and 2012, 880 patients who underwent surgical resection of a gastric cancer were identified from a multi-center database. Clinicopathological characteristics, receipt of peri-operative therapy, operative details, and oncologic outcomes were analyzed and defined. **Results:** Median patient age was 65.8 years and 42.6% (375/880) were female. Median tumor size at diagnosis was 4.0 cm (2.5-6.8 cm). A minority of patients received neoadjuvant therapy (207, 32.7%). Overall, 70 (8%) patients had a minimally invasive (MIS) approach: laparoscopic (60, 85.7%) and laparoscopic hand assist (10, 14.3%). Patients who underwent MIS resections were more likely to a smaller tumor (MIS: 3.0 cm vs. open: 4.5 cm) (p<0.001). MIS resections were associated with similar estimated blood loss (MIS: 150 cc vs. open: 250 cc, p=0.14) and similar operative time (MIS: 271 min vs. open: 232 min, p=0.07) compare to open surgery. An R0 resection was achieved in the overwhelming majority of patients (MIS: 98.6% vs. open: 90.9%; p=0.03). Post-operatively, MIS patients had a similar incidence of complications (MIS: 20% vs. open: 33.1%, p=0.07) and a similar length of stay (MIS: 7 d vs. open: 9 d, p=0.13) compare to open surgery patients. For the entire cohort, median recurrence-free survival was 27.34 months and median overall survival was 33.42 months. In analyzing the entire cohort, the overall 5-year survival of patients treated with MIS was 42.6% vs. 35.8% for patients treated with an open approach (p=0.05). In the propensity score-matched multivariate model, laparoscopy remained associated with an improved long-term overall (HR 0.34) survival (P<0.001). **Conclusions:** An MIS approach to select patients with gastric cancer is associated with a high R0 resection rate. The long-term oncological outcome following MIS is excellent and therefore the MIS approach should be considered.

**4083 General Poster Session (Board #170), Sat, 8:00 AM-11:45 AM**

**A phase II and biomarker study of an irreversible pan-human EGF receptor (HER) tyrosine kinase inhibitor dacomitinib in patients with recurrent and/or metastatic squamous cell carcinoma of esophagus.** *Presenting Author: Hyo Song Kim, Department of Internal Medicine, Division of Medical Oncology, Yonsei University College of Medicine, Seoul, South Korea*

**Background:** Dacomitinib is an oral irreversible tyrosine kinase inhibitor of EGFR, HER2 and HER4 signaling. The goals of this study were to investigate the clinical activity, safety and predictive biomarkers of dacomitinib in patients with advanced esophageal squamous cell carcinoma (ESCC). **Methods:** Forty-nine patients with advanced ESCC, who had failed one line of prior platinum-based chemotherapy, were administered dacomitinib 45mg/day. The primary endpoint was objective response rate and predictive biomarkers were evaluated using tumor material obtained before dacomitinib treatment. We characterized somatic mutations using the Ion AmpliSeq platform (2,800 mutations from 50 genes), gene copy number (86 genes) and gene expression (230 genes) using NanoString nCounter. **Results:** The median age was 64 years (range 47-83) and the majority of patients were male (93.3%), had 0-1 ECOG performance status (91.8%). In terms of previous chemotherapy, 40 (81.3%) and 9 (18.4%) patients received 1 and 2 prior chemotherapy, respectively. Of the 48 evaluable patients, 10 (20.8%) achieved partial responses (PR), of these, 6 (12.2%) showed confirmed PRs. Twenty-nine patients (61.2%) had stable disease. The median treatment duration is 82 days (range 16-335 days), and main reason of treatment discontinuation was progression (n=34, 69.4%) and toxicity (n=4, 8.2%). Seven (14.3%) patients are on treatment and they are all progression free more than 120 days. Among the 34 patients with progression, the median time to progression was 80 days (95% CI, 59-102 days). With a median 169 days of follow up, the median overall survival was 4.5 months (95% CI, 3.1-6 months). Nineteen patients (38.8%) had treatment interruption due to toxicity, and 14 (28.5%) of them had dose reduction. The most common dacomitinib-related adverse effects were diarrhea (69.4%) followed by rash (57.1%). **Conclusions:** Dacomitinib demonstrated promising efficacy with manageable toxicity in platinum-failed ESCC patients. We attempted to identify predictive biomarker for dacomitinib treatment. Updated clinical outcome and final biomarker data will be presented at ASCO 2014. Clinical trial information: NCT01608022.

**4084 General Poster Session (Board #171), Sat, 8:00 AM-11:45 AM**

**Effect of the distribution of lymph node metastases on outcomes for trimodality-eligible patients with esophageal and esophagogastric junction adenocarcinoma (EAC).** *Presenting Author: Hironori Shiozaki, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** In patients with trimodality-eligible EAC, the presence of malignant nodes at baseline portends a poor prognosis. It is difficult to quantify the number of positive lymph nodes using imaging modalities. For clinical staging, distribution of lymph node metastasis on imaging may be a potential surrogate for number and a useful tool to consider prognosis. We hypothesized that the distribution of baseline nodes (above and/or below the diaphragm) will have a correlation with overall and relapse-free survival. **Methods:** We identified 209 EAC patients with baseline malignant nodes. All patients underwent trimodality therapy. Patients were grouped based on the presence of (A) nodes above the diaphragm, (B) nodes below the diaphragm, and (C) nodes above and below the diaphragm. Survival estimates were calculated using the Kaplan-Meier method. The differences in OS and RFS among patient subgroups were assessed using log-rank tests. Differences were considered significant if the 2-sided p-value was less than 0.05. **Results:** The patients were primarily Caucasians (91%), males (93%), and had stage III EAC (89%).The median follow-up was 2.2 years (range, 0.4 to 10.8 years). Of the 209 patients, 35% (73) were in group A, 20% (41) were in group B, and 45% (95) in group C. Patients in group C had the worst 5-year overall survival (33%) compared to those patients in groups A (55%) or B (60%; P=0.02). Patients with high histology grade were also at higher risk of relapse and poor survival outcome (P<0.01 for each). **Conclusions:** The presence of suspicious or confirmed malignant lymph nodes above and below the diaphragm leads to the worst prognosis for EAC patients undergoing trimodality therapy. Therefore, novel therapeutic strategies are needed for these patients.

**4085 General Poster Session (Board #172), Sat, 8:00 AM-11:45 AM**

**A proprietary multi-analyte test to predict neoadjuvant treatment response for esophageal and rectal adenocarcinoma patients.** *Presenting Author: Sunil S. Badve, Indiana University School of Medicine, Indianapolis, IN*

**Background:** Standard of care for locoregional esophageal (EC) and rectal (RC) adenocarcinoma is chemotherapy/radiotherapy (CTRT) followed by surgery. 25-30% of EC and RC patients exhibit extreme resistance to pre-operative CTRT (exCTRT) and receive no therapeutic benefit. A similar number have a pathologic complete response (pathCR) and may benefit from avoiding surgery. We previously reported an IHC-based multi-center study that accurately identified EC patients as exCTRT or non-exCTRT (CTRT responders). The present multi-center study applies the assay for prediction of EC patient pathCR, and extends the test to predict RC patient exCTRT and pathCR. **Methods:** Formalin-fixed, paraffin-embedded (FFPE) tissue sections from diagnostic biopsies were processed by IHC to detect three predictive biomarkers: NF-kB, SHh, and Gli1. Sections were reviewed by a pathologist to determine a labeling index (LI) score for each biomarker correlating with the number of positively stained EC or RC cells within a tissue section. LI scores from each case were compared to a training set of 167 adenocarcinoma tumor samples using logistic regression analysis to predict pathCR in a cohort of 65 EC cases, or pathCR and exCTRT in a cohort of 10 RC cases (5 pathCR and 5 exCTRT). Predicted outcomes were compared to Tumor Regression Grade (TRG), determined by blinded, independent pathology. **Results:** Prediction of EC pathCR achieved an uncorrected area under the curve (AUC) of 0.83 with a specificity of 87%. Initial application of the pathCR assay to RC cases resulted in 100% specificity (5/5 non-pathCR cases called non-pathCR) and 60% sensitivity (3/5 pathCR cases called pathCR). Conversely, application of the exCTRT assay to RC cases resulted in 100% specificity (5/5 non-exCTRT cases called non-exCTRT) and 60% sensitivity (3/5 exCTRT cases called exCTRT). **Conclusions:** The current study demonstrates the potential of this assay to predict pathCR in EC and pathCR and exCTRT in RC. Predicting response to CTRT in both EC and RC will enable design of treatment regimens specific to a patient's response, thereby improving the risk to benefit ratio for both CTRT and surgery.

**4086 General Poster Session (Board #173), Sat, 8:00 AM-11:45 AM**

**Gastric cancer (GC) among California Asians: Analysis of California Cancer Registry (CCR).** *Presenting Author: Afsaneh Barzi, USC Norris Comprehensive Cancer Center, Los Angeles, CA*

**Background:** GC is the 4th cause of cancer death worldwide and is associated with significant morbidity in the affected individuals. In the US, California has the highest number of GC cases per year. We designed a study to explore the disparities in the presentation and outcome of GC in the Asians. **Methods:** Using data from CCR, we investigated the GC incidence, presentation, and survival among Asians from 2000-2010. We explored the significance of race in the anatomic presentation and survival of GC in the Asians compared to non-Hispanic Whites (NHW). We identified 18,377 GC cases in this time period, 70% were NHW, 8% Chinese, 7% Korean and 5% Japanese, the rest included Filipino, Vietnamese and other Asian sub-groups. **Results:** The frequency of GC by anatomical sites were statistically significantly different between Asians and NWH for both males and females ($p<0.001$). Compared to NHW, Asians had significantly lower frequency of cardia and fundus cancers (44% in NHW and 14% in Asians). Asians presented at a younger age ($p<0.001$) and had lower rates of de-novo metastatic disease compared to NHW ($p<0.001$). Survival rates were higher in Asians compared to NHW when adjusted for age, gender, socio-economic status, nativity, stage, anatomical site, and type of treatment received. Prognostic factors for death from gastric cancer included age $>$ 65 and immigration status, with immigrants doing better than US born. There was significant amount of disparity among Asians form different countries, Koreans had the highest age adjusted incidence rate of GC compared to all other Asians. **Conclusions:** The differences in the demographics, anatomical distribution of GC, and outcome in the Asians may be due to differences in etiologic factors that deserve further exploration. In Japan and Korea, early detection had resulted in a dramatic decline in mortality and morbidity. Although overall low incidence of the disease in US is prohibitive for a generalized screening program, there are subpopulations that may benefit from screening. Given that early detection has proven to be effective and cost saving in Asian countries with high incidence of gastric cancer consideration of screening for this population is intriguing and should be explored.

**4087 General Poster Session (Board #174), Sat, 8:00 AM-11:45 AM**

**A comparative study of ultrasonography and non-contrast computerized tomography of upper abdomen as a screening tool for biliary tract cancer detection in endemic community.** *Presenting Author: Teerapat Ungtrakul, Chulabhorn Hospital, Bangkok, Thailand*

**Background:** Biliary tract cancer is the leading cause of cancer-related death among men and women in the north and northeastern region of Thailand. Over 21 million people in this region are at risk for this type of cancer. However, no reliable test is currently available for its detection at the earliest stage. Despite the suggested use of ultrasonography in some reports, it is still not feasible for implementation as a screening tool across the country due to its high operational dependency and difficult quality control. This study aimed to compare the effectiveness between abdominal ultrasonography (AUS) and computerized tomography of upper abdomen (CT) without contrast for better outcome of detecting biliary tract cancer in the endemic area. **Methods:** Both male and female participants, aged 50-60 years old, from Phanomphrai district, Roi Et province, Thailand were enrolled. All of them were sent for AUS screening by a mobile imaging unit while CT without contrast was done using a standard protocol at a nearby imaging center. Confirmation of diagnostic studies or tissue biopsy was subsequently performed in the cases with liver nodules or bile duct dilatation. Experienced radiologists proceeded with CT scan and imaging data interpretation through tele-imaging system. **Results:** Of 839 participants, either liver nodule or bile duct dilatation was found in 54 cases (6%) by US and 44 cases (5%) by CT, respectively. Biliary tract cancer was diagnosed in 7 cases (5 cases of intrahepatic cholangiocarcinoma and 2 cases of extrahepatic cholangiocarcinoma). Five out of 7 cases were successfully treated with a curative intent. In addition, all cases were detected by AUS and CT without contrast, with the sensitivity and specificity of 100% and 94% for AUS and 100% and 95% for CT, respectively. **Conclusions:** Both CT without contrast and ultrasonography were effective screening tools for the detection of biliary tract cancer at an early stage in the endemic area. Nevertheless, the feasibility, cumulative radiation exposure, false positive rates, and operational costs need to be considered before implementation in the screening.

**4088 General Poster Session (Board #175), Sat, 8:00 AM-11:45 AM**

**Final analysis of European patients from the Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of its Treatment with Sorafenib (GIDEON) study: Baseline characteristics and staging systems.** *Presenting Author: Bruno Daniele, G. Rummo Hospital, Benevento, Italy*

**Background:** The global, prospective, non-interventional GIDEON study recruiting >3,000 patients with unresectable hepatocellular carcinoma treated with sorafenib is complete. We report the final analysis of the prognostic value of baseline characteristics and staging systems in European patients. **Methods:** Baseline characteristics were recorded at study entry; safety/outcomes were collected at follow-up. **Results:** Median overall survival (OS) and time to progression (TTP) for baseline characteristics and staging systems in the intent-to-treat population (n=1115) are shown (Table). The safety profile of sorafenib in European patients was consistent with that reported for the interim analyses and in phase III studies. **Conclusions:** Data from European patients indicates that baseline characteristics and staging systems, including Child-Pugh status, BCLC stage, and CLIP and MELD scores, appear to be useful prognostic factors for OS and TTP, while TNM and ECOG PS appear to be predictive of OS only. Clinical trial information: NCT00812175.

**Overall survival and time to progression by baseline characteristics/staging system.**

| | n | Median OS (months) | Median TTP (months) |
|---|---|---|---|
| Baseline characteristics[a] | | | |
| ECOG PS | | | |
| 0 | 504 | 19.3 | 7.6 |
| 1 | 438 | 9.7 | 6.2 |
| 2 | 114 | 3.9 | 3.1 |
| 3 | 17 | 2.3 | 4.6 |
| Bilirubin, μmol/L[b] | | | |
| <34 | 926 | 13.5 | 6.7 |
| 34-50 | 90 | 4.6 | 3.4 |
| >50 | 66 | 3.3 | 4.5 |
| Albumin, g/L[b] | | | |
| >35 | 637 | 16.4 | 6.8 |
| 28-35 | 318 | 6.9 | 5.5 |
| <28 | 57 | 3.3 | 4.5 |
| AFP, ng/mL | | | |
| <400 | 681 | 15.0 | 7.2 |
| ≥400 | 332 | 6.1 | 4.3 |
| Staging system[a] | | | |
| Child-Pugh[b] | | | |
| A | 726 | 15.0 | 6.7 |
| B | 219 | 4.9 | 2.4 |
| C | 12 | 1.5 | 1.2 |
| BCLC[b] | | | |
| A | 94 | NR | 11.6 |
| B | 270 | 14.9 | 7.6 |
| C | 591 | 9.4 | 5.2 |
| D | 45 | 4.0 | 3.4 |
| MELD | | | |
| <10 | 481 | 15.1 | 6.7 |
| 10-<20 | 300 | 8.4 | 5.4 |
| 20-<30 | 16 | NR | 8.1 |
| 30,<40 | 5 | 8.5 | 7.6 |
| CLIP[b] | | | |
| 0 | 94 | 22.9 | 10.1 |
| 1 | 280 | 20.2 | 8.1 |
| 2 | 254 | 9.2 | 5.4 |
| 3 | 147 | 6.2 | 4.8 |
| 4-6 | 91 | 3.0 | 3.1 |
| TNM[b] | | | |
| I | 196 | 19.0 | 7.8 |
| II | 176 | 15.2 | 6.9 |
| IIIa | 286 | 10.4 | 6.9 |
| IIIb | 24 | 9.3 | 8.5 |
| IIIc | 83 | 8.4 | 5.7 |
| IV | 163 | 7.7 | 4.1 |

[a]At study entry; [b]Unknown/Not evaluable patients not shown. AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; ECOG PS, Eastern Cooperative Oncology Group performance status; MELD, model for end-stage liver disease; NR, not reached; TNM, tumor node metastasis.

**4089 General Poster Session (Board #176), Sat, 8:00 AM-11:45 AM**

**Radiogenomics of hepatocellular carcinoma: Computed tomography biomarker to predict microvascular invasion and clinical outcome.** *Presenting Author: Sudeep Banerjee, University of California, Los Angeles, Los Angeles, CA*

**Background:** Microvascular invasion (MVI) is an independent predictor of poor outcome following surgical resection or liver transplantation (LT) in hepatocellular carcinoma (HCC); however, MVI currently cannot be adequately determined until after surgery. **Methods:** We conducted a multicenter evaluation of a computed tomography (CT) biomarker for MVI, termed radiogenomic venous invasion (RVI), in surgical candidates with HCC. RVI is a prospectively-defined imaging surrogate for a 91-gene HCC "venous invasion" gene expression signature. Preoperative contrast enhanced CTs of 203 patients with HCC who underwent surgical resection (n=91) or LT (n=112) between 2000 and 2009 were scored for the presence or absence of RVI. **Results:** Interobserver agreement for scoring RVI was good among 3 radiologists (k=0.62, P<0.001). Diagnostic accuracy, sensitivity and specificity in the overall cohort were 87%, 72% and 93%, respectively. Positive RVI score was associated with lower overall survival than negative RVI score in the overall cohort (P<0.001; 49 vs >147 months), in Barcelona Clinic Liver Cancer (BCLC) A (P = 0.01; 22 vs 105 months), BCLC B (P = 0.044; 66 vs >147 months) and in LT patients within the Milan criteria (P<0.001; 22 vs >147 months). Positive RVI score had lower recurrence-free survival at 3-years than negative RVI score (P<0.001; 62% vs 85.4%). **Conclusions:** RVI is a noninvasive radiogenomic biomarker that accurately predicts histologic MVI in HCC surgical candidates. Its presence is associated with early disease recurrence and poor overall survival and may be useful for stratifying patients less likely to derive a durable benefit from surgical treatment.

**4090 General Poster Session (Board #177), Sat, 8:00 AM-11:45 AM**

**ABC-04: A phase 1b trial of cisplatin, gemcitabine, and selumetinib in patients with advanced biliary tract cancer.** *Presenting Author: John A. Bridgewater, Department of Medical Oncology, University College London Cancer Institute, London, United Kingdom*

**Background.** Cisplatin + gemcitabine (CisGem) is a standard of care for advanced biliary tract cancer (ABC; Valle et al. 2010). Selumetinib (S; AZD6244, ARRY-142886) potently and selectively inhibits MEK1/2, an intracellular kinase (Adjei et al., 2008; Yeh et al., 2007), and has shown activity in ABC (Bekaii-Saab et al., 2009). The objective of the ABC-04 trial was to establish the recommended dose (RD) of S to give in combination with CisGem. **Methods.** Eligible patients (pts) were ≥ 18 years, had histology/cytology confirmed unresectable recurrent or metastatic biliary tract, gallbladder or ampullary carcinoma, WHO performance status 0-2, adequate major organ function. Pts may have had prior surgery, radiotherapy or adjuvant chemotherapy (CT), but no prior CisGem or CT for locally advanced or metastatic disease. Pts received cisplatin 25 mg/m$^2$ plus gemcitabine 1000 mg/m$^2$ intravenously on days 1 and 8 of a 21-day cycle. S capsules were taken daily. A dose de-escalation scheme was used to determine the RD of S. The first dose level was 75 mg bd. Pts were recruited in cohorts of 3 and assessed for dose limiting toxicity (DLT) during the first cycle of treatment. Pts received up to 8 cycles of CisGem and could receive S until disease progression. **Results.** Thirteen pts were recruited of whom 12 were evaluable for DLT (1 did not start treatment). All evaluable pts received the starting dose of 75 mg bd and only one patient experienced a DLT (ischaemic heart disease). Median number of days S taken (adjusted for the number of days of dose interruptions) was 167 (IQR: 75.5 to 311.5). Two pts remained on treatment at 14 and 19 months post registration. There were 3 temporary and 1 permanent interruptions of S in cycle 1. Eight pts had measurable disease (RECIST v1.1) and were evaluable for objective response: 3 had partial response and 5 stable disease. Toxicities related to S included oedema and rash; most were modest and manageable. Pharmacokinetic analysis did not show a significant interaction between gemcitabine and S. **Conclusion.** The RD of S when combined with CisGem is 75 mg bd. Translational studies are underway to determine any potential molecularly favoured subgroup. Clinical trial information: NCT01242605.

**4091 General Poster Session (Board #178), Sat, 8:00 AM-11:45 AM**

**Screening and 6-month surveillance interval ultrasonography in early detection of cholangiocarcinoma in an endemic area.** *Presenting Author: Prakongboon Sungkasubun, Chulabhorn Hospital, Bangkok, Thailand*

**Background:** Very high incidence rates of cholangiocarcinoma have been reported in Southeast Asia, especially in the north and northeastern parts of Thailand where the prevalence of this cancer is the highest in the world. Ban Luang district of Nan province in the northern Thailand is known to have a very high mortality rate from cholangiocarcinoma. Objectives: To ascertain the prevalence of cholangiocarcinoma in Ban Luang districtof Nan province and to implement a screening and surveillance program to identify early-stage cases for better treatment outcome. **Methods:** A 5-year prospective cohort study was conducted in Thai individuals, aged 30-60 years, in Ban Luang district. The initial cholangiocarcinoma screening program included blood testing, stool examination and ultrasonography every 6 months. **Results:** During the first 2 years, from 6,327 targeted participants, screening with abdominal ultrasonography could be completed in 4,337 subjects (68.5%). Cholangiocarcinoma was diagnosed in 22 cases from 4 repeated ultrasonography, 16 of which were in the curative and resectable stages. The prevalence of cholangiocarcinoma was 8 cases (184.5:100,000) and the average 6-month incidence was 4.7 cases (108.4:100,000).The 2-year survival was observed in 19 of 22 cases(86.4%) and the 2-year progression- or recurrence-free survival was found in 13 of 22 cases(59.1%). **Conclusions:** The high prevalence of cholangiocarcinoma in Ban Luang district was confirmed through this population-based study, with satisfactory results from ultrasonography-based screening and surveillance program. Early-stage cholangiocarcinoma cases were uncovered leading to better prognosis.

**4092 General Poster Session (Board #179), Sat, 8:00 AM-11:45 AM**

**A phase II trial of second-line axitinib following prior antiangiogenic therapy in advanced hepatocellular carcinoma (HCC).** *Presenting Author: Mairead Geraldine McNamara, Princess Margaret Cancer Centre, Toronto, ON, Canada*

**Background:** Second line treatment options in advanced HCC are limited. Axitinib, a selective tyrosine kinase inhibitor (TKI) of VEGFRs 1, 2, 3, merits exploration in HCC. **Methods:** This was a single arm, phase II trial of axitinib in advanced HCC. Eligible patients (pts) were Child-Pugh (CP) A/B7, with measurable progressive disease (PD) after TKIs/antiangiogenic drugs. Axitinib started at 5 mg bid orally, titrated from 2-10 mg bid as tolerated; 28 days=1 cycle. Treatment continued to PD or intolerable toxicity. Primary endpoint was tumor control; PR, CR or SD at 16 wks by RECIST 1.1 ($P_0$=5%, $P_1$=20%), secondary endpoints; compare response by RECIST 1.1 to Choi and modified RECIST, explore dynamic contrast enhanced imaging models, safety, PFS and OS. **Results:** Thirty pts were enrolled from 01/11-10/13. Median age; 64y (range 18-78), 21 males (70%) with ECOG PS 0/1 (9/21 pts), CP A (73%), BCLC staging C (100%), etiology hepatitis B/C (30%/30%), alcohol (17%) with prior therapy; Temsirolimus/Bevacizumab (2pts), sorafenib/doxorubicin (2pts) and sorafenib alone (26pts). Med duration of treatment; 4 cycles (range 1-17). Out of 26pts evaluable for response, there were 2 confirmed PRs per RECIST 1.1; 10 PR by Choi, 8 PR and 1 CR by modified RECIST. Tumor control rate at 16 wks; 42% (95%CI 22.3-63.1), 7 pts had SD >28 wks. 2 week perfusion changes were noted on functional imaging. Of 22 pts with evaluable AFP response, 8 (36%) had >50% decrease from baseline. Most common axitinib related grade 3 (G3) AEs were hypertension (HTN) (17%) and diarrhea (10%), 2 had G4 thrombocytopenia. Only 20% of pts tolerated dose escalation above 5 mg bid. Of 11 pts with any grade HTN, 7 had disease control >28 wks. Dose interruptions due to AEs were common (40%); included anorexia (13%), fatigue (10%), HTN (7%). 4 pts discontinued treatment due to related AEs. PFS + OS data are maturing. Current 3 mo PFS rate; 59%. 80% have progressed at this time, 4 pts remain on treatment. **Conclusions:** With 42% tumor control at 16 wks, primary endpoint was met.Axitinib has shown encouraging tolerable clinical activity in this VEGF pretreated HCC pt population and warrants further study incorporating potential biomarkers of response. Clinical trial information: NCT 01334112.

**4093 General Poster Session (Board #180), Sat, 8:00 AM-11:45 AM**

**Second-line chemotherapy for advanced biliary tract cancer after failure of gemcitabine plus platinum: Results of an AGEO multicenter retrospective study.** *Presenting Author: Bertrand Brieau, Hôpital Cochin, Paris, France*

**Background:** First-line chemotherapy (CT1) with the combination of gemcitabine (gem) + platinum has become a new standard in advanced biliary tract cancer (ABTC) but data on second-line CT (CT2) are lacking. The aim of this study was to evaluate the efficacy and tolerability of CT2 in patients (pts) with ABTC who received gem-platinum in CT1. **Methods:** We retrospectively reviewed data of consecutive patients who received CT2 for ABTC after failure to gem-platinum in 17 French institutions from November 2002 to December 2013. Progression-free survival (PFS) and overall survival (OS) were estimated from the start of L2 CT using Kaplan Meier method. Cox models were applied for multivariate analyses. **Results:** Among 603 pts who were treated by gem-platinum in CT1, 196 pts (median age, 63 years, range: 28-82; male, 51.5 %) received a CT2. CT1 included gem + cisplatin (7%) or oxaliplatin (ox) (93%), with a median PFS of 9.7 months (mo) and an ORR of 31%. Characteristics at the beginning of CT2 were: metastatic disease, 94% ; 1-2 metastatic sites, 68%; ECOG PS 0-1, 68%. CT2 CT was 5FU-irinotecan (iri) (n=62), 5FU-ox (n=17), 5FU-cisplatin (n=37), 5FU/capecitabine (CAP) (n=39) or other various regimens (n=41). Among the 186 evaluable pts, there were 22 PR (12%) and 70 SD (38%). After a median follow-up of 26.4 months, median PFS and OS were 3.2 and 6.7 mo respectively. There was no significant difference between CT regimens in terms of PFS (5FU-iri, 2.6 mo; 5FU-ox/5FU-cisplatine, 4.0 mo; 5FU/CAP, 3.2 mo and others, 3.7 mo; p=0,27) and OS (6.0 mo, 6.3 mo, 5.6 mo and 9.7 mo respectively; p=0.27) In multivariate analysis, PS 2-3, bilirubine $>$ 17 $\mu$mol/L and CA19.9 $>$ 400 UI/mL were significantly associated with a shorter PFS while PS 2-3, CA19.9 $>$ 400 UI/mL and non-response to CT1 with a shorter OS. A grade 3-4 toxicity was observed in 32% of pts (neutropenia, 33%; diarrhea, 17%) and a toxic death occurred in 1.4% of pts. **Conclusions:** CT2 is associated with a disease control in a half of pts with ABTC who received gem-platinum in CT1. Nevertheless, the short median PFS observed in this study should encourage the evaluation of new treatments in pts with good clinical conditions and an adequate biliary drainage.

**4094 General Poster Session (Board #181), Sat, 8:00 AM-11:45 AM**

**Assessment of liver dysfunction in hepatocellular carcinoma (HCC): An international collaborative study.** *Presenting Author: Philip James Johnson, Department of Molecular and Clinical Cancer Medicine, Institute of Translational Medicine, University of Liverpool, Liverpool, United Kingdom*

**Background:** Survival in HCC depends on tumour-related features and liver dysfunction, the latter currently characterised by Child-Pugh score (C-P.S). Since some constituents of C-P.S are interrelated and subjective and the tumour may contribute to liver dysfunction, C-P may not be ideal for HCC assessment. Aim:To assess how much discrimination in liver dysfunction is afforded by the C-P.S and develop a simpler evidence-based approach. **Methods:** 5,269 patients were recruited from 4 specialist HCC centres: Japan (n=2,599, predominantly HCV), Hong Kong (1 112, predominantly HBV), Spain (n=834, predominantly HCV and alcohol) and the UK (n=724, multiple aetiologies). Patients undergoing liver transplantation were excluded. A model explaining variation in survival according to liver function was developed in 1,313 Japanese subjects and then validated in the remaining 3,716 cases. **Results:** Overall the classification in C-P.S was A, 69%, B, 25% and C 6%; figures were similar in all ethnic groups. After allowing for tumour size the variation in survival could be accounted for by just serum bilirubin and albumin; these were incorporated into a simple Cox regression model (the 'ALBIS' score) which allows classification into 3 risk groups. Statistical analysis showed that the degree of discrimination was as good as, or better than, C-P.S. Irrespective of country, or tumour stage the ALBIS score showed clear survival differences among C-P. S 'A' patients (Table). **Conclusions:** The "ALBIS score" is simple, objective, and evidence-based and permits classification of patients to a risk group based on liver dysfunction.

**Survival among 777 European patients with Child-Pugh stage A HCC.**

| ALBIS risk group | N | Median survival (months) | Std. err. | [95% CI] | |
|---|---|---|---|---|---|
| **1** | 409 | 26.4 | 1.5 | 24.0 | 29.9 |
| **2** | 367 | 16.3 | 1.1 | 14.2 | 18.9 |
| **3** | 1 | . | . | . | . |

Median survival = 22.6 months.

**4095 General Poster Session (Board #182), Sat, 8:00 AM-11:45 AM**

**Phase 1 study of PF-03446962 (anti-ALK-1 mAb) in hepatocellular carcinoma (HCC): Correlation of tumor and serum biomarker data with disease control.** *Presenting Author: Matteo Simonelli, Humanitas Cancer Center, Rozzano, Italy*

**Background:** PF-03446962 ,a fully human IgG2 mAb against ALK-1 (Activin-Receptor Like Kinase-1, a specific TGF-$\beta$ receptor selectively expressed on vasculature), demonstrated a favorable safety profile in a Phase 1 expansion cohort of HCC patients (pts) whose disease progressed after sorafenib $\pm$ other systemic anti-angiogenic therapies. Tumor immunohistochemistry (IHC), multiplex serum soluble protein, and pharmacokinetic (PK) results are reported here along with disease control data. **Methods:** Child-Pugh A HCC pts progressive on/intolerant to VEGFR TKI were included. Pts were treated with PF-03446962 at 7 mg/kg IV on Day 1, Day 29 and then q 2 weeks. PF-03446962 PK was also monitored. Archival (pre-sorafenib) and *de novo* (pre-PF-03446962) tumor specimens were assessed by IHC for TGF-$\beta$ (low affinity ALK-1 ligand), ALK-1, c-MET and CD31. A multiplex approach was used for assessment of 15 serum soluble proteins involved in angiogenesis and TGF-$\beta$ pathways, including BMP-9 (a high affinity ALK-1 ligand) at baseline, Cycle2 Day1, Cycle3 Day1 and end of treatment. Biomarker data were correlated with Disease Control at 12 weeks (DC) and Objective Tumor Response (OR) by RECIST. **Results:** Higher mean tumor tissue archival (ratio = 15) and *de novo* (1.7) c-MET expression, higher (1.5) mean baseline serum levels of BMP-9, and lower mean baseline serum levels of TGF-$\beta$ (0.44) and VEGFR3 (0.66) were found in the patients with disease control at 12 weeks vs. those patients with progressive disease. No ORs were reported, DCR was 29.2% and mTTP was 3.0 months. In 7 pts, PF-03446962 achieved stable disease $\geq$ 12 weeks, suggesting a role of ALK-1 in sustaining tumor growth. PF-03446962 serum trough concentrations in these pts well exceeded the therapeutic level suggested by non-clinical data. **Conclusions:** Higher tumor c-MET and serum BMP-9, and low serum TGF-$\beta$ and VEGFR3 were found in patients with disease control at 12 weeks vs. those patients with progressive disease. Expanded molecular approaches to identify biomarkers for PF-03446962 are being assessed in an ongoing phase 2 study. The selection of 7 mg/kg every 2 weeks as the RP2D dose is supported by PK results in this population. Clinical trial information: NCT00557856.

**4096 General Poster Session (Board #183), Sat, 8:00 AM-11:45 AM**

**Next-generation sequencing of serum microRNA (miRNA) in hepatocellular carcinoma (HCC) patients on targeted therapy.** *Presenting Author: Robin Kate Kelley, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

**Background:** Circulating biomarkers are urgently needed in HCC. miRNA are noncoding RNA that regulate mRNA expression and are detectable in tumor tissue and extracellular compartments. This pilot study explored the feasibility of using next-generation RNA sequencing to characterize miRNA abundance in serum from HCC patients at baseline and on targeted therapy. **Methods:** Banked serum samples (400$\mu$L) were obtained from HCC patients enrolled on a phase I clinical trial of sorafenib plus the mTOR inhibitor, temsirolimus. Control sera were obtained from patients with non-malignant liver diseases (NMLD). Total RNA was purified using Trizol-LS and miRNeasy kit. Mature miRNA were size-selected by gel electrophoresis. Samples were sequenced by Illumina HiSeq 2500, 5M reads per sample. Raw reads were mapped using Novoalign, quantified, and normalized to total reads and exogenous spike-in miRNA recovery. Comparisons between HCC vs. NMLD and baseline vs. on treatment cohorts were performed using one-way ANOVA and false discovery rate (FDR) correction. Candidate signature miRNA were derived by fold change, p-value, and abundance cutoffs and cross-referenced to literature. **Results:** Cohorts: HCC baseline (n=23) and paired on treatment (n=20 cases, 30 samples), NMLD (n=12). HCC cohort: HBV+/dual 40%, HCV+ 32%. NMLD cohort: HCV+ 83%. 38 of 65 (58%) total samples qualified. Candidate miRNA were identified which showed up-regulation in HCC vs. NMLD (non-significant) and in elevated vs. normal alpha-fetoprotein (AFP) (FDR p$<$0.05). Multiple miRNA families showed a trend toward down-regulation on treatment with temsirolimus plus sorafenib including Let-7 and miR-17/92 family members. Serum signatures for HCC vs. NMLD and elevated AFP overlapped with miRNA expression in a published dataset of HCC tumors. **Conclusions:** Serum miRNA in HCC patients can be characterized by next-generation sequencing. Differences in miRNA abundance were observed between HCC cases and NMLD controls, and within HCC cases according to clinical covariates including treatment status and AFP. Serum miRNA warrant further study as novel biomarkers in HCC.

**4097 General Poster Session (Board #184), Sat, 8:00 AM-11:45 AM**

**Molecular profiling of bile duct and gallbladder cancer to identify different therapeutic options.** *Presenting Author: Randall F. Holcombe, Icahn School of Medicine at Mount Sinai, New York, NY*

**Background:** Biliary tree carcinomas arising in different anatomic locations (intrahepatic IHBC; extrahepatic, EHBC) and gallbladder (GBC) are rare tumors with a poor prognosis. An unmet medical need exists in identifying biomarkers of drug response. We interrogated biomarkers from a large cohort of patient samples with a multiplatform approach and considered associated therapeutic options. **Methods:** 643 cases (291 IHBC, 115 EHBC, 237 GBC) were evaluated using a commercial multiplatform profiling service (Caris Life Sciences, Phoenix, AZ). Specific testing performed included a combination of gene sequencing (Sanger, NGS), protein expression (IHC) and gene amplification (CISH or FISH). **Results:** OverallIHC showed high TOP2A (51%), TOPO1 (43%), SPARC (39%) and low RRM1 (76%), ERCC1 (72%) and TS (70%), indicating potential benefit from anthracycline, irinotecan, nab-paclitaxel, gemcitabine, platinum and fluoropyrimidine, respectively. 16 of 45 genes had mutations, with the highest rates seen in TP53 (29%), KRAS (19%), SMAD4 (9%) and IDH1 (9%). When comparing IHBC, EHBC and GBC, a number of statistically significant differences were observed (p values ranged from <0.0001 to 0.03). IHBC was characterized by the presence of IDH1 mutation (18% vs. 0% vs. 0%), low TP53 mutation (15% vs. 40% vs. 46%), and low HER2 amplification (2% vs.17% vs. 16%); IDH1 and TP53 mutations were mutually exclusive, and IDH1 was associated with high Pgp IHC (89% vs. 47%). EHBC had the highest KRAS mutation rate (EHBC 32% vs. IHBC 18% vs. GBC 13%). GBC had higher TOP2A IHC than IHBC and EHBC (71% vs. 36% vs. 46%) and higher RRM1 IHC (34% vs. 17% vs. 15%). Further, SMAD4 mutation was found in 20% (6/30) of metastatic tumors and 2.3% (1/44) of primary tumors (p=0.02). **Conclusions:** Multiplatform cancer profiling revealsdifferentbiomarker characteristics of biliary tree carcinomas arising in different locations, suggesting a different biology and the need for different therapeutic approaches. Biomarker differences detected by IHC and ISH prompt considerations of HER2-targeted therapies in EHBC and GBC, and anthracylines in GBC, highlighting the need for individualizing patient treatment based on tumor profiling in biliary tree carcinomas.

**4098 General Poster Session (Board #185), Sat, 8:00 AM-11:45 AM**

**A phase II study of temsirolimus in previously treated advanced hepatocellular carcinoma (HCC).** *Presenting Author: Jasgit C. Sachdev, TGen - Virginia G. Piper Cancer Center at Scottsdale Healthcare, Scottsdale, AZ*

**Background**: After Sorafenib failure,there is no effective systemic therapy for advanced HCC. Preclinical data show upregulated mTOR signaling in HCC. We tested the IV mTOR inhibitor (i), Temsirolimus (T), as salvage therapy for HCC. **Methods**: Patients (Pts) had locally advanced or metastatic HCC, progressed on or intolerant of sorafenib, Child Pugh A/B liver cirrhosis, ECOG 0-2. Primary end point of this Simon 2-stage, single-arm phase II study was 3 month PFS. ≥ 1/15 Pts in stage 1 and ≥ 4/25 Pts overall had to achieve this endpoint to reject the $H_0$ (Type I and II errors 0.05 and 0.1). We gave 25 mg T weekly until progression or intolerance, with CT/MRI scans Q 6 wks. Modified (m) RECIST for HCC was used. **Results**: See the Table for Pt characteristics. 17 Pts progressed or died (4 still on study, 4 off study without progression). 13/23 (57%; 95% CI: 34-77%) evaluable Pts were alive without progression at 3 months. Median PFS, 17 wks (95% CI 12-35 wks); PFS at 24 wks, 37%; median OS, 30 wks (95% CI: 27-44 wks). Of 21 Pts evaluable by mRECIST, best responses were 8 PR (38%), 10 SD (48%) and 3 PD (14%) for a disease control rate at ≥ 12 weeks of 43% (9/21). Mean and median decreases in target lesions from baseline were 33% and 23% respectively. Exploratory textural analysis of baseline scans correlated with response (p = 0.008) suggesting a predictive CT marker for anti-tumor activity. Grade 3/4 treatment related AE in ≥10% Pts: thrombocytopenia, neutropenia, AST elevation and hyperglycemia. 2 on-treatment deaths occurred, both unrelated to drug. **Conclusions:** T showed higher responses than previously reported with systemic Rx for HCC. The primary end point was met with >1/2 of the Pts progression free at 3 months, and >1/3 at 6 months. We speculate that IV administration may have overcome compliance issues in drug administration, favorably impacting efficacy, as reflected by the response rates in this study, in contrast with those reported with the oral mTORi. Confirmatory studies with novel correlative biomarkers should clarify the role of this mTORi in HCC. Clinical trial information: NCT01567930.

| | |
|---|---|
| Enrolled | 26 |
| Evaluable | 25 |
| Median age (range) | 62 (52-89) |
| Male | 23 |
| Female | 2 |
| AA | 13 |
| Caucasian | 12 |
| Child Pugh | |
| A | 17 |
| B | 8 |
| BCLC stage | |
| A | 1 |
| B | 2 |
| C | 22 |
| D | 0 |
| Hepatitis B | |
| Y | 1 |
| N | 24 |
| Hepatitis C | |
| Y | 16 |
| N | 9 |
| Prior Rx | |
| Resection | 4 |
| RFA | 4 |
| TACE | 16 |
| Sorafenib | 25 |
| Chemotherapy | 2 |

**4099 General Poster Session (Board #186), Sat, 8:00 AM-11:45 AM**

**Sorafenib with or without everolimus in patients with unresectable hepatocellular carcinoma (HCC): A randomized multicenter phase II trial (SAKK 77/08 and SASL 29).** *Presenting Author: Dieter Koeberle, Claraspital, Basel, Switzerland*

**Background:** Sorafenib (S), a multitargeted tyrosine kinase inhibitor, has become standard of care for first-line systemic treatment of advanced HCC. Everolimus (E) is a potent inhibitor of the mTOR, a pathway frequently up-regulated in HCC. In preclinical HCC-models, S+E has additive effects compared to S. The objective of this trial was to investigate the antitumor activity of combined treatment with S+E. **Methods:** Patients (pts) with unresectable or metastatic HCC and Child-Pugh ≤7 liver dysfunction were randomly assigned to receive daily S 800 mg alone or S 800 mg + E 5 mg until progression or unacceptable toxicity. The primary endpoint was progression free survival at 12 weeks (PFS12). In the S+E arm a PFS12 of ≤ 55% was considered uninteresting and promising if ≥ 75% using a Fleming's single-stage design with 90% power and 5% significance level. The S arm was used for calibration. Secondary endpoints included response rate, PFS, TTP, OS, duration of disease stabilization (DS), safety and quality of life (QoL) assessments. **Results:** 106 pts were randomized;46 pts received S and 60 pts S+E. 93 pts are evaluable for the primary endpoint, 105 pts for the safety analysis. Main reasons for stopping therapy were: progressive disease (S: 64%; S+E: 51%), toxicity (S: 21%; S+E: 28%), or death 5% (both arms). PFS12 rate was 70% in S (95% CI: 54-83) and 68% in S+E (95% CI: 53-81). Response rate was 0% in S arm and 10% in S+E arm. Median PFS was 6.6 vs. 5.7, median TTP was 7.6 vs. 6.3, median DS 6.7 vs. 6.7, and median OS 10 vs. 12 months in the S vs. S+E arm. Activation of Hepatitis C virus was observed in 3 pts in each arm. No re-activation of Hepatitis B virus infection occurred. Grade 3 and 4 adverse events occurred in 72% (S) and in 86% (S+E). Pts receiving S+E had worse QoL scores over time compared to pts receiving S with significant differences for physical well-being and mood. **Conclusions:** Addition of a reduced dose of E to full doses of S is feasible, equally effective, but more toxic than S alone. Phase III testing of S 800 mg + E 5 mg daily appears not warranted in patients with unselected advanced HCC. Clinical trial information: NCT01005199.

**4100 General Poster Session (Board #187), Sat, 8:00 AM-11:45 AM**

**Phase Ib study of RO5137382/GC33 in combination with sorafenib in patients with advanced hepatocellular carcinoma (HCC) (NCT00976170).** *Presenting Author: Ghassan K. Abou-Alfa, Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

**Background:** GC33 is a recombinant humanized monoclonal antibody against Glypican-3 (GPC3) which is highly expressed in HCC. GC33 elicits antibody-dependent cellular cytotoxicity against human HCC cell lines in vitro. GC33 and sorafenib showed an additive anti-tumor effect in xenograft mouse model. This is a phase I dose escalation study to evaluate safety/tolerability and pharmacokinetics (PK) of combination therapy in HCC. **Methods:** In a 3+3 design dose escalation design GC33 given intravenously 2.5, 5 and 10 mg/kg weekly, then 1,600 mg every 2 weeks, and then 1,600mg weekly, all in combination with sorafenib 400mg twice daily. Patients with advanced HCC patients, age ≥18, ECOG 0-1, Child-Pugh A, adequate organ functions (platelets ≥ 100 x$10^9$/L, ANC ≥ 1500, AST/ALT ≤ 5 x ULN, Bilirubin ≤ 1.5 mg/dL, and creatinine ≤ 2 x ULN), and no prior therapy with sorafenib were eligible. Primary endpoints were safety and tolerability and secondary endpoints PK of GC33 and sorafenib and efficacy. Tumor assessment was based on investigators using RECIST 1.0. Safety was evaluated by CTCAE 3.0. **Results:** 40 patients were enrolled between September 2009 and July 2013 as follows (n): 2.5 mg/kg weekly (qw) (12), 5 mg/kg qw(12), 10 mg/kg qw(3), 1,600mg q2w (6) and 1,600mg qw (7). There were 35 men/5 women, median age 60, Asian 21/Non-Asian 19, HBV /HCV/neither 19/9/13, ECOG 0/1 17/23. There were 3 DLT: Grade 3 hyponatremia at 5 mg/kg GC33 cohort, grade 3 hyponatremia and hypoglycemia at 1600mg q2w, and grade 3 ALT increase at 1600 mg qw. Thirty-six patients developed AE's ≥ Grade 3, including 10 (25%) with increased Lipase, 10 (25%) with increased AST, and 3 (7.5%) with increased ALT. Dose delays occurred in 6/7 patients receiving GC33 1600mg qw due to known sorafenib-related toxicities. There were no complete responses, one partial response (unconfirmed), and 6 patients (15%) have experienced stable disease for ≥ 5 months. PK parameters $C_{max}$ and $AUC_t$ of GC33 and sorafenib following combination therapy were comparable to previously reported data of either single agent. **Conclusions:** No maximum tolerated dose of GC33 could be defined when given in combination with sorafenib at the dose of 400mg bid in this study population. Clinical trial information: NCT00976170.

**4101 General Poster Session (Board #188), Sat, 8:00 AM-11:45 AM**

**Phase II study of everolimus monotherapy as first-line treatment in advanced biliary tract cancer: RADichol.** *Presenting Author: Yvonne H. Yeung, Ludwig Institute for Cancer Research, Heidelberg, Australia*

**Background:** Advanced biliary tract cancers (BTC) have a poor prognosis with limited standard chemotherapy options. The PI-3Kinase signalling pathway is frequently dysregulated in BTC and preclinical studies using mTOR inhibitors have shown activity in BTC cell lines. This exploratory phase II study aims to evaluate the clinical activity and safety of the mTOR inhibitor RAD001 (everolimus) in BTC, as well as to evaluate potential biomarkers of response in vivo and in vitro. **Methods:** Inclusion criteria included advanced BTC, no prior chemotherapy, adequate organ function and written informed consent. Treatment involved everolimus (10mg/d) and continued until tumour progression. The primary endpoint was disease control (DC) at 12 weeks (w). Secondary endpoints were response rate, progression free survival (PFS), overall survival (OS) and adverse events (AE). The two-stage study allowed progression to stage 2 when $>3$ of 9 patients had DC at 12w and would be declared active when $>13$ of 27 had DC. Correlative in vitro studies evaluated biomarkers predictive of benefit to everolimus and exploratory endpoints include correlation with these biomarkers in vivo. **Results:** 27 eligible patients (median age 64 y) were enrolled between 2009 and 2011. At 12w, 48% had SD, 8% PR and 56% had DC. Median PFS was 6.0 months (95% CI, 2.1-11.2), median OS was 9.5 months (95% CI, 5.5-16.6) and DCR 76%. Treatment was well tolerated with stomatitis (63%) and rash (52%) being the most frequent AEs. The most common grade 3/4 AEs were infection (26%), pain (15%), hyperglycemia and hypercholesterolemia (11%). After progression, 26% received 2$^{nd}$ line chemotherapy. In vitro studies showed that *k-ras* mutation was associated with everolimus resistance ($p=0.03$). There was significant negative correlation between basal pAKT: tAKT and drug resistance regardless of *k-ras* status ($r=-0.57$, 95% CI -0.81 to -0.17, $p=0.007$). Mutation profiling for Ras and PIK3Ca mutations in tumour tissue from the trial is ongoing. **Conclusions:** Single agent everolimus demonstrates activity as monotherapy in advanced BTC, with an acceptable side effect profile. Two potential predictive biomarkers have been identified in vitro and are undergoing evaluation in vivo. Clinical trial information: NCT00973713.

**4102 General Poster Session (Board #189), Sat, 8:00 AM-11:45 AM**

**Randomized phase II trial of intravenous RO5137382/GC33 at 1600 mg every other week and placebo in previously treated patients with unresectable advanced hepatocellular carcinoma (HCC; NCT01507168).** *Presenting Author: Chia-Jui Yen, Internal Medicine Department, National Cheng Kung University Hospital, Tainan, Taiwan*

**Background:** RO5137382/GC33 (GC33) is a humanized monoclonal antibody against GPC3 that is frequently expressed in HCC. GC33 interacts with CD16/Fc$\gamma$R3 and triggers antibody-dependent cytotoxicity. GC33 was compared with placebo in a randomized phase II study in advanced HCC patients (pts) who had failed prior systemic therapy. **Methods:** Pts with advanced HCC who had failed prior systemic therapy, $\geq$18 years, ECOG 0-1, Child-Pugh A were randomized in a 2:1 ratio to GC33 1600 mg Q2W after two weekly doses versus placebo. Prior to randomization, pts were assigned into 3 cohorts based degree of GPC3 immunohistochemical expression: A (GPC3 2-3+), B (GPC3 1+) and C (GPC3 no expression). Primary endpoint was progression free survival (PFS). Secondary endpoints include overall survival (OS), time to progression (TTP), tolerability, and pharmacokinetics (PK). Tumor assessment was based on RECIST1.0 criteria and safety on CTCAE 4.0. **Results:** Between February 2012 to March 2013, 185 pts were enrolled: 121 received GC33 and 64 placebo: Median age 64/63, 85/75% male, 46/42% Asian, ECOG 0 65/63%, 74/77% having vascular invasion and/or extra-hepatic metastasis. 49/41% had prior single agent sorafenib. Drug exposure was 98.6% of planned dose, with an identical adverse events profile between the 2 groups. The median PFS, OS, and TTP in the GC33 vs placebo groups in months were: 2.6 vs 1.5 (HR 0.97, $p=0.87$), 6.8 vs 6.7 (HR 0.99, $p=0.97$), and 2.9 vs 1.7 (HR 0.96, $p=0.85$). A subsequent exposure-efficacy analysis showed that increased exposure based on projected $C_{trough}$at cycle 3 day 1 was associated with prolonged PFS and OS. Median PFS for high GC33 exposure group ($n=60$) was 4 vs 1.5 months for placebo ($n=60$), and OS 9.7 vs 6.7 months, respectively. Combining higher exposure with Fc$\gamma$R3A-158V polymorphism or CD16 expression intensity may correlate with improved PFS and OS. **Conclusions:** GC33 did not show a clinical benefit in this advanced, previously treated HCC population, potentially due to suboptimal dosing. Further studies are needed to investigate whether higher GC33 drug exposure and a favored CD16/FcgR3 immune environment may help. Clinical trial information: NCT01507168.

**4103 General Poster Session (Board #190), Sat, 8:00 AM-11:45 AM**

**Final results of a phase II trial of stereotactic body radiotherapy (SBRT) in patients with hepatocellular carcinoma (HCC) with Child-Pugh class A (CPC-A).** *Presenting Author: Foster D Lasley, Indiana University Department of Radiation Oncology, Indianapolis, IN*

**Background:** After confirming the safety and appropriate radiation dose in phase I dose escalation trial, a phase II trial was completed to evaluate the efficacy of SBRT for HCC in CPC-A patients. **Methods:** Thirty-eight patients with HCC in the context of liver cirrhosis, CPC-A, were treated with SBRT in a Phase II trial at Indiana University. All patients received three fractions, 1,600 cGy per fraction (total dose 4800 cGy), 1-2 fractions per week. Dose was prescribed to the 80-90% isodose line covering the planning target volume (PTV). Demographics, clinical variables, treatment –related toxicities within 90 days of end of treatment, and local control at 6 months were tabulated and 95% exact binomial confidence intervals for local control (LC) at 6 months was calculated. A modified RECIST criteria was used to determine local failure. Progression Free Survival (PFS), and Overall Survival (OS) estimates were calculated using Kaplan-Meier methodology. **Results:** Median follow-up time was 31.0 months (2.8-64.4 months). There were 28 males and 10 female; median age of 61 years (range 24-86). Thirty-six (94.7%) patients had stage T1 disease and one patient each (2.6%) with T2 and T3 disease. Pre-treatment AFP ng/ml median (range): 8.3 (1.5-2931.9). All patients had 1 treated lesion. Median (range) for gross tumor volume (cc) was 30.9 (2.0-79.1); PTV volume (cc) was 99.1 (20.8-196.0); and uninvolved liver volume (cc) was 1607.3 (939.0-3214.0). There was 1 grade 4 toxicity of elevated GGT and 3 grade 3 toxicities including, 1 each of GGT, increased INR, and thrombocytopenia. Of the 38 patients enrolled, 1 did not return for their 6 month follow-up. Of the 37 evaluable patients, 35 (94.6%), 95% C.I. (81.8%, 99.3%) had LC at 6 months. Median PFS was 30.9 months (95% CI: 13.9 months, 64.4 months). Median OS is 38.3 months (95% CI: 28.2 months, 64.4 months). OS at 1, 2 and 3 years was 94%, 77% and 52% respectively. **Conclusions:** In selected patients with hepatocellular carcinoma in the context of CPC-A liver cirrhosis, SBRT is an effective therapy with good toxicity profile. Clinical trial information: NCT00243841.

**4104 General Poster Session (Board #191), Sat, 8:00 AM-11:45 AM**

**Role of FDG-PET-CT (PET) in predicting outcome of advanced hepatocellular carcinoma (aHCC) patients (pts) treated with sorafenib (SB): A prospective controlled study.** *Presenting Author: Roberto A. Pazo Cid, Medical Oncology Department, Miguel Servet University Hospital, Zaragoza, Spain*

**Background:** SB remains since 2007 the only drug that improves overall survival (OS) of aHCC pts. Predicting early response to SB could save costs and toxicity. PET has never been properly tested as biomarker in this setting. **Methods:** This prospective study recruitedaHCC pts eligible for first-line SB therapy. RECIST response to treatment was evaluated by CT scan every 6 weeks, and metabolic PET response after two weeks on SB (1999 EORTC criteria). PET response cut-off: a minimum of 15% reduction in the sum of SUVmax of up to 5 target lesions. CT (CR+PR+SD *vs* PD) and PET (CR+PR *vs* SD+PD) responses were categorized as dichotomous variables. OS and time to progression (TTP) were calculated by the Kaplan–Meier test and statistically evaluated by the log-rank test. Association between OS/TTP and several meaningful clinical variables (including PET and CT response) were evaluated using univariate Cox proportional hazards regression analysis and significant parameters were included in a multivariate analysis. **Results:** Accrual: 55pts Characteristics: Median age: 71 years. Male 62%. PS 0-1/2(%) 60/40. Cirrhosis etiology: HCV/HBV/Alcohol/Other/unknown(%) 34/18/20/11/17. Child-Pugh A/B(%) 75/25. Extrahepatic spread(%) yes/no 60/40. Macroscopic vascular invasion(%) yes/no 30/70. Median AFP level 24.0 (range 2.0-85520.0). BCLC stage B/C(%) 12/88. CLIP stage 0/1/2/3/4(%) 13/25/25/23/12. Baseline PET+/-(%) 86/14. SB median dose: 400mg/d. Second-line therapy (Bevacizumab): yes/no(%) 44/56. Median TTP/OS 3.7 and 7.3 months (95%CI 2.30-5.12/ 4.87-9.77). Multivariate analysis showed that CLIP stage and CT and PET responses were independent prognostic factors for TTP. For OS CLIP stage, second-line therapy and PET response retained significance but not CT response. **Conclusions:** Early metabolic response strongly predicted survival benefit from first-line SB therapy in aHCC pts. Clinical trial information: NCT01157013.

| **Cox analysis TTP** | **p** | **HR** | **95%CI** |
|---|---|---|---|
| **PET** | 0,005 | 0,292 | 0,123-0,693 |
| **CLIP** | 0,022 | 1,482 | 1,060-2,073 |
| **CT** | 0,048 | 0,376 | 0,143-0,991 |
| **Cox analysis OS** | **p** | **HR** | **95%CI** |
| **CLIP** | 0,000 | 2,047 | 1,418-2,954 |
| **Second-line therapy** | 0,000 | 0,087 | 0,032-0,240 |
| **PET** | 0,004 | 0,253 | 0,099-0,650 |

**4105 General Poster Session (Board #192), Sat, 8:00 AM-11:45 AM**

**A phase I trial of of cixutumumab (C) (IMC-A12) and sorafenib (S) for treatment of advanced hepatocellular carcinoma (HCC).** *Presenting Author: Anthony B. El-Khoueiry, USC Norris Comprehensive Cancer Center, Los Angeles, CA*

**Background:** The insulin growth factor (IGF) pathway is activated in hepatocarcinogenesis. C is a monoclonal antibody against insulin-like growth factor-1 receptor (IGF-1R). *In vivo* HCC models showed activated IGF signaling and antitumor effects due to C. Given the cross-talk between the IGF and VEGF pathways, the combination of C and S was chosen. **Methods:** This study evaluated the safety of C (2, 4 or 6 mg/kg) IV weekly with standard doses of S (400 mg po bid) in patients (pts) with HCC. Eligibility criteria included: no prior systemic therapy for HCC, Child-Pugh score of A or B7, ECOG 0 or 1, platelets > 75,000/mm3, and albumin > 2.8 g/dl. The study used a standard 3+3 design. One cycle was 28 days. **Results:** A total of 21 pts (17 males and 4 females) were enrolled; mean age was 63 years (43-85); 10 Asian, 4 Hispanic, 5 White, 1 Black, and 1 Native American. There were 3 dose limiting toxicities (DLTs); grade 3 hyperglycemia, grade 3 hypophosphatemia, and grade 5 peritonitis (see table). The maximum tolerated dose (MTD) was C 4 mg/Kg and S 400 mg BID. 18 of 21 (86%) pts had ≥grade 3 toxicities attributable to treatment. Grade 3 adverse events that occurred in ≥ 2 pts were: diarrhea (4; 19%), hypertension (4; 19%), thrombocytopenia (3; 14%), palmar-plantar erythrodysesthesia (2; 10%), hyperglycemia (2; 10%), and fatigue (2; 10%). There was 1 grade 4 colonic perforation and 1 grade 5 peritoneal infection in the same pt. The median number of cycles was 4 (0-19 cycles). Sixteen of the 21 pts completed 2 cycles and were evaluated for response. 13 of the 16 (81%) (95% CI: 54%-96%) achieved stable disease. The median event free survival was 3.8 months (95%CI: 1.9, 11.3). The median OS was 13.1 months (95% CI: 7.6, undefined). An increase of 0.5 in baseline natural log of hepatocyte growth factor and insulin growth factor binding protein 3 were associated with risk of death (log rank p value 0.01 and 0.03). **Conclusions:** The majority of adverse events in pts treated with the combination of C and S were typical of sorafenib toxicity. There was preliminary evidence of efficacy as seen in the median OS. Clinical trial information: NCT01008566.

| Dose level | Pts treated | Pts evaluable for dose escalation | DLT |
|---|---|---|---|
| **1** | 8 | 6 | 1 (gr 3 hyperglycemia) |
| **2 (MTD)** | 6 | 5 | None |
| **3** | 7 | 5 | 2 (gr 3 hypophosphatemia, gr 5 peritonitis) |

**4106 General Poster Session (Board #193), Sat, 8:00 AM-11:45 AM**

**Prognostic factors of overall survival of stage III or IV adrenocortical carcinomas (ACC): A multicenter ENS@T study.** *Presenting Author: Rossella Libe, Hopital Cochin, Paris, France*

**Background:** Several reports suggest heterogeneity of advanced ACC.The primary objectives of our study were to provide evidence for an improved staging and grading system and refine the prognostic classification of stage III-IV ACC**. Methods**: 444 patients registered with the ENS@T ACC database (diagnosed 2000-2009) were enrolled (210 stage III; 234 stage IV). Inclusion criteria were: age>18 yrs, pathological review, synchronous stage III-IV, follow-up available. Primary endpoint was overall survival. Parameters captured were: age, modality of diagnosis, TNM, pathological grading (Weiss score,Ki 67%), R status at first surgery. Univariate and multivariate analyses were performed according two models. Model 1 "prior surgery"; model 2 "post surgery." **Results:** 301 patients (68%) died due to ACC (median follow-up: 55.2 mo). Median overall survival was 24 mo. N positive status, but not venous invasion, was confirmed to behave like stage IV. A modified ENSAT (mENSAT) classification was therefore used: stage III in case of invasion in surrounding tissues/organs or vena renalis/cava; stage IVa, IVb, IVc if the number of metasatic organs (including N positive status) was 2, 3 or >3, respectively. ACC tumors with Ki 67>20% and/or Weiss score>6 was confirmed to behave significantly more aggressively. At multivariate analysis within model 1: age>50 years (HR:1.6,P<0.0001), presence of tumor- (HR:1.6, P=0.01) or hormone-related symptoms (HR: 1.6, p=0.03), mENS@T stage, (HR:2.6, HR:3.8 or HR:4.9 for stage IVa, IVb, or IVc respectively, all P<0.0001) were found significant. Within multivariate model 2: age>50 years (HR:1.1,P<0.01), presence of tumoral- (HR:1.7,P=0.01) or hormone-related symptoms (HR: 1.6,P=0.04), mENS@T stage, (HR:2.1,HR:2.7 or HR:3.7 for stage IVa, IVb, IVc respectively, all P<0.0001), R status (for R1/2/x HR:1.7,P=0.0006), grade (Weiss >6 and Ki67> 20%, HR:1.3,P=0.06) were found significant. By combining the different parameters 2 years-OS for mENSAT stage IV ranges between 17-67% in model 2. **Conclusions:** This largest prognostic study on advanced ACC patients allows to refine the prognostic stratification and future therapeutic management of advanced ACC patients.

**4107^ General Poster Session (Board #194), Sat, 8:00 AM-11:45 AM**

**Progression-free survival (PFS) with lanreotide autogel/depot (LAN) in enteropancreatic NETs patients: The CLARINET extension study.** *Presenting Author: Martyn E. Caplin, Neuroendocrine Tumour Unit, Royal Free Hospital, London, United Kingdom*

**Background:** The CLARINET core study showed that the long-acting somatostatin analog (SSA) LAN 120 mg significantly prolonged PFS vs placebo (PBO) in patients (pts) with metastatic enteropancreatic NETs (p=0.0002). Median PFS not reached with LAN vs 18.0 months with PBO. This study was the first randomized PBO-controlled trial investigating PFS with an SSA in a population that included pts with pancreatic NETs and pts with grade G2 tumors (Ki-67 <10%). Here, we report PFS data and safety findings from the open-label extension (OLE) to CLARINET. **Methods:** Pts enrolled in CLARINEThad: well/moderately differentiated non-functioning enteropancreatic NETs with Ki-67 <10%; no prior SSAs, or other medical therapies in last 6 months; metastatic disease. In CLARINET, pts were randomized to LAN 120 mg (n=101) or PBO (n=103) every 28 days for 96 wks or until death/disease progression (PD; according to RECIST 1.0). LAN pts with stable disease and PBO pts with/without PD could then enter the single-arm (LAN) OLE (NCT00842348, max. expected duration 5 yrs). The primary objective of the OLE was safety (safety population). The main efficacy endpoint was PFS (i.e. time from randomization in core study to death/PD) for the core study intent-to-treat population, using survival analysis based on Kaplan–Meier estimates. **Results:** 88 pts from the CLARINET core study (LAN arm, 41; PBO arm, 47) participated in OLE. At core study enrollment, 96% of OLE patients did not have tumor progression; 38% had pancreatic primary tumors, 39% had midgut, and 8% hindgut. The median PFS for LAN was reached during the OLE: 32.8 months. For subset of pts who had PD while on PBO in the core study, median time to further PD with LAN in the OLE was 14.0 months. During the OLE, 27% who continued LAN vs 40% switched to LAN had treatment-related adverse events (TRAE); most frequent TRAE was diarrhea. No new safety concerns were identified in the extension. **Conclusions:** CLARINET extension data suggest there were antitumor effects with LAN 120 mg in enteropancreatic NET patients with progressive disease. Long-term safety/tolerability of lanreotide in the extension was consistent with its known profile. Clinical trial information: NCT00842348.

**4108 General Poster Session (Board #195), Sat, 8:00 AM-11:45 AM**

**The association between octreotide dose and tumor control in gastroenteropancreatic neuroendocrine tumors (NETs).** *Presenting Author: Sally Chui Mei Lau, University of British Columbia, Vancouver, BC, Canada*

**Background:** Gastroenteropancreatic NETs represent a heterogeneous group of cancers that are associated with an indolent, protracted course. Octreotide has been used as a mainstay in the symptom management of these tumors. However, the recent PROMID study showed that octreotide 30 mg contributed to disease stabilization in well-differentiated midgut NETs, but a meaningful survival analysis was limited due to insufficient events. Our aim was to examine the relationship between octreotide dose and overall survival (OS) in a population-based setting. **Methods:** Patients diagnosed with NETS from 1987 to 2013, referred to any 1 of 5 regional cancer centers in British Columbia, and who initiated octreotide were reviewed. To account for variations in the duration of therapy, we determined the mean octreotide dose per 28-day cycle and compared OS based on dose of octreotide. Dose was dichotomized into high vs. low based on the median as well as 30mg as per the PROMID study. **Results:** A total of 170 patients were included: mean age 60 years (SD=13) and 54% were men. NETs most commonly originated from the midgut (47%) and the pancreas (21%). A significant proportion had unresectable, metastatic disease (81%) among whom the majority (87%) had hepatic involvement. Carcinoid symptoms that included diarrhea, flushing and wheezing were prevalent (72%). Octreotide was offered to patients with the intent of symptom management (71%), disease stabilization (23%), and tumor marker control (6%). The mean dose per 28-day cycle was 27 mg (SD=9). After accounting for symptoms and tumor burden, patients who received > 27 mg (n=78) experienced significantly longer median OS when compared to those who received </= 27 mg (n=92) of octreotide (82 vs. 39 months, respectively, p<0.0001). Likewise, median OS was also superior among those who were given > 30 mg (n=65) of octreotide as per the PROMID study, relative to those on </= 30 mg (n=105) of the drug (83 vs. 46 months, p=0.0001). **Conclusions:** Our findings suggest that higher doses of octreotide may confer OS benefits in selected patients with gastroenteropancreatic NETs and that titration of this drug to manage symptoms may not represent the optimal treatment strategy for all patients.

**4109 General Poster Session (Board #196), Sat, 8:00 AM-11:45 AM**

**Study of the gastroenteropancreatic neuroendocrine tumor (gep-net) microenvironment beyond angiogenesis: The role of lysyl oxidase-like 2 (LOXL2).** *Presenting Author: Jorge Barriuso, Translational Oncology and Pathology Group. La Paz University Hospital-IdiPAZ / Molecular Cancer Group. Faculty of Life Sciences. University of Manchester, Manchester, United Kingdom*

**Background:** A better understanding of the tumour microenvironment beyond angiogenesis of this heterogeneous group of malignancies remains a challenge. In this study, we present an exploratory analysis of the microenvironment protein expression and its relation with prognosis and previously described biomarkers. **Methods:** Formalin-fixed and paraffin embedded samples (FFPEs) of patients (pts) who underwent surgery for gep-net and their clinical data were collected consecutively from 1980 to 2012.Tissue microarrays were constructed from non-necrotic areas of tumour foci. Microenvironment related proteins (LOXL2, LOX, CXCR4, TWIST, $\beta$-catenin and E-cadherin) were studied by inmunohistochemistry and compared to the expression of SSTR2, ATRX and members of the mTOR pathway. The study was approved by the local Ethic Committee. Univariate (UVA) and multivariate analysis (MVA) was performed. Kaplan-Meier method, log rank test and cox regression was used to study disease free survival (DFS) and overall survival (OS). **Results:** A total of 115 FFPEswere analysed**.** Median age was 46 years; female/male ratio 1:1; 78 were intestinal. Grades were: G1 64.3%, G2 11.3%, G3 7 %, unknown 17.4%. Median follow up was 12 years. Stage and grade were statistically significant for DFS and OS ($p<0.001$) and remain so in the MVA. LOXL2 over expression was associated with better DFS and OS ($p<0.001$). $\beta$-catenin nuclear expression (BCAT) was related to worst DFS and OS ($p<0.001$). PTEN presence was associated with better DFS ($p<0.001$). MVA for DFS showed BCAT ($p=0.019$) and PTEN presence ($p=0.024$) as independent factors and LOXL2 ($p=0.024$) and BCAT ($p=0.004$) were significant for OS after adjustment for stage and grade. LOXL2 expression was associated with SSTR2 ($p=0.004$). **Conclusions:** LOXL2 is a druggable novel biomarker candidate for gep-nets.

| | UVA for DFS | MVA for DFS | UVA for OS | MVA for OS |
|---|---|---|---|---|
| **LOXL2** | 0.3 (0.1-0.7) | ns | 0.2 (0.1-0.5) | 0.2 (0.04-0.8) |
| **BCAT** | 9.2 (2.3-37.5) | 10.5 (1.5-75.7) | 12.8 (3.3-50.5) | 11.9 (2.2-65.4) |
| **PTEN** | 0.2 (0.1-0.6) | 0.2 (0.04-0.8) | ns | - |
| **LOX** | 0.3 (0.1-0.7) | ns | ns | - |

Cox regression for presence vs absence or nuclear localization vs non-nuclear. Hazard ratios and 95%CI. Abbreviations: Ns, non-significant.

**4110 General Poster Session (Board #197), Sat, 8:00 AM-11:45 AM**

**Antiproliferative activity of octreotide LAR in advanced neuroendocrine tumors.** *Presenting Author: Christos Toumpanakis, Neuroendocrine Tumour Unit, Royal Free Hospital, London, United Kingdom*

**Background:** The antiproliferative activity of Octreotide LAR in Neuroendocrine Tumors (NETs) has been demonstrated by small retrospective studies and confirmed by a prospective phase III trial (PROMID). However, there are limited data about the duration and predictors of response. The aim of our retrospective study was to determine the time to radiological progression (TTRP) of disease and the factors that were associated with better response **Methods:** Overall, 254 patients with advanced NETs and positive somatostatin receptor scintigraphy were included. Radiological assessment was based on RECIST criteria. Univariate and multivariate analyses were used to identify predictive factors. Median TTRP and 95% confidence intervals were calculated using Kaplan-Meier analysis. **Results:** The patients' mean age was 60.5 +/- 12.8 years. Male to female ratio was 1.1. Mean follow-up was 42 months. The location of primary was in small bowel in 204, pancreas in 22, lungs in 14, rectum in 7 and unknown in 7 patients. Tumors were well-differentiated, G1 (71%) and G2 (29%). Octreotide LAR was commenced for functional symptoms in 68%, radiological progression in 13%, whilst 29% of patients were asymptomatic with stable disease and started treatment on the basis of PROMID data. Partial response occurred in 5%. For all patients, the median TTRP was 37 months (95% confidence interval, CI: 32-52 months). There was a statistically significant shorter TTRP in patients with pancreatic primary (p: 0.001), G2 tumors (p: 0.001), high hepatic tumor volume (p: 0.006), and baseline Chromogranin-A (CgA) levels >10 times the upper normal limit (p: 0.006). Mean time to progression was longer in patients with stable disease at presentation (53 months). Age, mesenteric mestastases, desmoplasia and previous resection of primary did not affect progression. Female sex and skeletal metastases had some negative, but no statistically significant, effect. **Conclusions:** The duration of anti-proliferative effect of Octreotide LAR seems to be longer than previously reported. Small bowel primary and G1 tumors, as well as low hepatic tumor volume, lower CgA levels and stable disease at the time of commencement of treatment seem to be associated with a more favorable response.

**4111^ General Poster Session (Board #198), Sat, 8:00 AM-11:45 AM**

**Lanreotide autogel/depot (LAN) treatment for carcinoid syndrome (CS) symptoms: Patient-reported outcomes (PROs) from the SYMNET study.** *Presenting Author: Philippe B. Ruszniewski, Beaujon Hospital, Clichy, France*

**Background:** Somatostatin analogs can provide CS symptom relief, but associated PROs in clinical practice, in particular patient (pt) treatment satisfaction, are less clear. **Methods:** SymNET was a large multinational observational study of PRO after >3 months' LAN for CS-related diarrhea (NCT01234168). At a routine clinic visit (CV), 273 pts reported their satisfaction with diarrhea control (primary endpoint) on a 5-point Likert scale. Secondary endpoints included health-related quality of life (HRQoL) assessed with EORTC QLQ-C30 and G.I.NET 21 questionnaires completed by pts. HRQoL scores were transformed for some items/scales so that all had a range 0–100. Summary statistics were derived from evaluable data (enrolled population). **Results:** 58% (157/273) of pts were >60 yrs, 66% (176/267) had small-bowel primary tumors, and 80% (217/271) had liver metastases. At the CV, median LAN treatment duration was 11 months and 76% (203/268) [95% CI: 70–81%] were satisfied with diarrhea control (primary endpoint). QLQ-C30: problematic symptoms were fatigue, insomnia, diarrhea and, to a lesser extent, pain; in contrast, the majority of pts had no problems with other symptoms, levels of functioning were high, and global QoL only slightly lower (Table). G.I.NET 21: problematic symptoms were disease-related worries, social function, and muscle/bone pain and, to a lesser extent, gastrointestinal and endocrine symptoms; the majority of pts had no problems with other symptoms, including treatment-related effects. **Conclusions:** High levels of pt satisfaction with LAN for CS-related diarrhea were generally accompanied by high levels of HRQoL functioning. These data show HRQoL levels that are currently attained in a real-world setting and may help guide future efforts in CS management. Clinical trial information: NCT01234168.

| Functioning scales (higher score=better QoL) | Median score |
|---|---|
| **Physical** | 85 |
| **Role; cognitive; social** | 83 |
| **Emotional** | 75 |
| **Global QoL** | 67 |
| **General symptoms scale (lower score=better symptoms)** | |
| **Nausea and vomiting** | 0 |
| **Pain** | 17 |
| **Fatigue** | 33 |
| **Specific symptoms scale (lower score = better symptoms)** | |
| **Dyspnea; appetite loss; constipation; financial difficulties** | 0 |
| **Insomnia; diarrhea** | 33 |

**4112 General Poster Session (Board #199), Sat, 8:00 AM-11:45 AM**

**Octreotide LAR (OCT-L) among elderly patients with stage IV neuroendocrine tumors (NETs): A survival analysis of SEER-Medicare data.** *Presenting Author: Chan Shen, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** OCT-L is approved in the US for the management of secretory syndromes among patients with NETs. Two placebo-controlled studies have recently demonstrated that somatostatin analogues delay time to progression. The effect of OCT-L on overall survival (OS) has not been evaluated. **Methods:** Stage IV NET patients diagnosed between 1/1999 and 12/2009 were identified from the SEER-Medicare database. Those under age 65, with poorly differentiated histology, enrolled in HMOs, or without continuous enrollment were excluded. HCPCS codes, J2352 and J2353, were used to identify OCT-L use. Current analysis compares the OS of those who started OCT-L within 12 months of diagnosis to those who did not receive OCT-L during the observation period. Presence of secretory syndrome was defined as having ≥ 2 claims for carcinoid syndrome, flushing, diarrhea, or malignant islet cell neoplasm either before the start of OCT-L for those who received it; or within 12 months of diagnosis for those who did not receive OCT-L. Analyses included Kaplan-Meier estimation and Cox proportional hazard modeling with covariates including age, gender, race, region, comorbidity score, urban/rural status, tumor characteristics, other treatments received, neighborhood socioeconomic status and year of diagnosis. **Results:** Among 1,149 patients, 231 (20%) received OCT-L within 12 months of diagnosis, 394 (34%) had secretory syndrome. Median OS from diagnosis among patients who started OCT-L within 12 months (35.4 [95%CI, 28.3 – 49.3] months) was longer than those who did not receive OCT-L during the observational period (20.3 [95%CI, 17.3 – 24.2] months; $P<0.001$). Multivariate Cox proportional hazard regression showed that OCT-L was associated with significant improvement in survival both for the whole study group ($HR=0.69$, $P<0.001$) and in the subgroups with ($HR=0.64$, $P=0.003$) and without ($HR=0.56$, $P=0.002$) secretory syndrome. Other significant predictors were age, gender, race, comorbidity score, primary tumor site, and surgery. **Conclusions:** This population-based study suggests potential survival benefits for use of OCT-L among elderly stage IV NET patients with or without secretory syndrome.

**4113 General Poster Session (Board #200), Sat, 8:00 AM-11:45 AM**

**Profiling of 1,350 neuroendocrine tumors for identification of multiple potential drug targets.** *Presenting Author: Igor A. Astsaturov, Fox Chase Cancer Center, Philadelphia, PA*

**Background:** Identification of new drug targets may extend treatment options for neuroendocrine tumors (NET) regardless of histologic classification or primary organ site. **Methods:** 1,350 cases of infradiaphragmatic neuroendocrine tumors (all grades and sites) were identified among >60,000 cases profiled in a CLIA-certified laboratory. Biomarker profiling utilized multiple platforms: gene sequencing (next generation sequencing [NGS], Sanger or pyrosequencing), gene copy number (*in-situ*hybridization), and protein expression (immunohistochemistry [IHC]). The results are shown relative to the total number of tests performed. **Results:** Overall, drug therapy-relevant alterations were identified in 1255 of 1350 (93%) of cases. Low or absent (0 or 1+ by IHC) expression of MGMT a biomarker of sensitivity to alkylating agents, was found in 149/243 pancreatic cases (61%), and in 488/1015 (48%) of non-pancreatic NET. Low or absent (0 or 1+ by IHC) expression of RRM1, a biomarker of gemcitabine sensitivity, was found in 927/1193 of NET (78%) and low or absent thymidine synthase, TS, a biomarker of fluoropyrimidines sensitivity, was shown for 950/1187 (80%) of NET by IHC. Sequencing of tumors showed oncogenic mutations in BRAF (6/446 (V600E in 4, and G596R in 2), CTNNB1 (3/223), KIT (4/357), EGFR (1/245), FGFR2 (2/224), GNAS (1/224), HRAS (2/192), PIK3CA (10/418), RB1 (4/222) VHL (2/203), KRAS (23/472), NRAS (2/349), and APC (14/224) and amplifications of EGFR (46/688) and MET (4/306. Therapies guided by mechanism-based biomarkers produced durable responses in documented cases: partial response (PR) >1 year to imatinib in a patient with KIT-mutant metastatic NET, and in cases of $MGMT^{low}/TS^{low}$treated with streptozocin or temozolomide plus fluoropyrimidine chemotherapy, thus supporting the clinical relevance of target profiling in NET. **Conclusions:** Comprehensive multiplatform profiling of a large series (n=1350) of NET, despite low frequency of individual biomarkers, identified clinically relevant targets in >90% of patients.Given the increasing utilization of chemotherapy for NET, our results provide the basis for future clinical trials to assess the efficacy of biomarker-based therapy for NET.

**4114 General Poster Session (Board #201), Sat, 8:00 AM-11:45 AM**

**Defining the neuroendocrine tumors landscape: A 15-year population-based analysis of incidence, outcomes, and therapies.** *Presenting Author: Julie I. Hallet, Odette Cancer Centre, Sunnybrook Health Sciences Centre; University of Toronto, Toronto, ON, Canada*

**Background:** Neuroendocrine Tumors (NETs) are poorly understood malignancies. We sought to define epidemiologic characteristics and outcomes, and describe systemic, interventional and surgical therapies use for NETs. **Methods:** We conducted a population-based retrospective cohort study of all adult patients with NETs in Ontario from 1994 to 2009, linking propsective databases linked at the Institute of Clinical Evaluative Sciences. We looked at incidence, proportion of metastatic disease, overall survival (OS), and use of systemic therapy (ST), liver embolization (LE), and surgery. **Results:** We identified 5619 NET cases. Incidence of NETs increased from 2.48 to 5.86 per 100 000 per year over 15 years. Synchronous metastases were found in 20.8% and metachronous metastases in 38%. Incidence and metastases varied according to primary NET site. Around time of diagnosis (60 days pre/post diagnosis), 56.8% did not consult a surgeon and 97.2% did not see a medical oncologist. Initial primary site resection was performed in 63.9% broncho-pulomnary (BP), 57.1% gastrointestinal (GI) and 46.4% pancreas (PA) NETs (p <0.001). 53.7% of all liver metastases were resected. ST was used in 46% of PA, 23.2% GI and 25.4% BP NETs, and LE in 8.1% BP, 11.9% GI, and 19.2% PA NETs. 10-year OS was 42.8%, with independent predictors of worse OS being: advanced age, male gender, low socioeconomic status, rural living, and pancreas and small intestine sites. **Conclusions:** NETs incidence has markedly increased over 15 years, with outcomes disparities based on demographics, social, and tumor characteristics. Patterns of care for NETs were irregular and sporadic. Numerous NETs were not assessed by a surgeon or medical oncologist, indicating worrisome potential under treatment and non-optimal management. Future work is needed to define mechanisms explaining this portrait in order to improve outcomes through early diagnosis, more frequent surgical referrals and standardization of therapies.

**4115 General Poster Session (Board #202), Sat, 8:00 AM-11:45 AM**

**Retrospective analysis of CA19-9 decrease in patients with metastatic pancreatic carcinoma (MPC) treated with FOLFIRINOX or gemcitabine (gem) in a randomized phase III study (ACCORD11/PRODIGE4).** *Presenting Author: Marie Robert, Institut de cancérologie de l'Ouest, Nantes, France*

**Background:** RECIST criteria remain the reference for tumor response evaluation. Carbohydrate antigen 19-9 (CA19-9) is known to be a sensitive and specific serum marker in pancreatic cancer. Its determination could be helpful to assess early therapeutic efficacy (MPACT trial, ASCO 2013, abstract 4058). Our retrospective analysis aims to evaluate CA19-9 decrease in patients included in the randomized phase III study ACCORD11/PRODIGE4 comparing FOLFIRINOX and gem in MPC. **Methods:** 342 patients were treated in the ACCORD11/PRODIGE4 study. CA19-9 levels were available at inclusion for all patients and 283 had abnormal values. CA19-9 measures were performed at 8 weeks ± 2 for 160 patients (gem arm, 75 patients and FOLFIRINOX arm, 85 patients). In this retrospective study, best CA19-9 decrease, or 8-week CA19-9 decrease ≥ 20 % were analysed. According to these CA19-9 rates, efficacy parameters, progression free survival (PFS) and overall survival (OS) were estimated. **Results:** FOLFIRINOX superiority compared with gem is confirmed in this population subgroup with a better PFS (6.7 vs 3.9 months; HR 0.52, IC95%: 0.36-0.73, p<0.001) and OS (12.0 vs 7.6 months; HR 0.55; IC95%: 0.38-0.79, p=0.001). 8-week CA19.9 decrease ≥20% was correlated with a better OS [10.3 vs 7.8 months; HR 0.57, (IC95%: 0.40-0.81); p=0.002] and PFS [6.1 vs 3.0 months, HR=0.58 (IC95%: 0.42-0.81), p=0.001]. A higher proportion of patients in the FOLFIRINOX arm had an 8-week CA19-9 and a best CA 19-9 decreases ≥20%. Median OS, PFS and ORR for those patients were improved (Table). **Conclusions:** CA19-9 response was increased in patients treated with FOLFIRINOX regimen and correlated with OS, PFS and ORR. CA19-9 could be considered as a potential early surrogate marker and therefore help to evaluate the efficacy of FOLFIRINOX and gem regimen.

| | FOLFIRINOX n=85 | Gem n=75 |
|---|---|---|
| **Best CA19-9 decrease, n (%)** | 60 (70,6) | 42 (56,0) |
| **ORR, %** | 45,0 | 21,4 |
| **Median OS, mo** | 13,7 | 8,6 |
| **1-year OS, %** | 59,6 | 31,5 |
| **HR (95%CI)** | 0,49 [0,31-0,79] | |
| **p value** | 0,003 | |
| **8-week CA19-9 decrease ≥20%, n (%)** | 50 (58,8) | 39 (52,0) |
| **ORR, %** | 44,0 | 23,1 |
| **median OS, mo** | 13,5 | 8,6 |
| **1-year OS, %** | 54,4 | 30,0 |
| **HR (95%CI)** | 0,55 [0,33-0,91] | |
| **p value** | 0,021 | |

**4116 General Poster Session (Board #203), Sat, 8:00 AM-11:45 AM**

**A phase I trial of the γ-secretase inhibitor (GSI) MK-0752 in combination with gemcitabine in patients with pancreatic ductal adenocarcinoma (PDAC).** *Presenting Author: Natalie Cook, Cancer Research UK, Cambridge Research Institute, University of Cambridge, Cambridge, United Kingdom*

**Background:** The Notch pathway is frequently activated in cancer. Pathway inhibition by GSIs has been shown to be effective in models of PDAC, in combination with gemcitabine (GEM). **Methods:** A multi-centre, non-randomised Bayesian adaptive design study of MK-0752, administered p.o. weekly (starting dose; 1,200mg), and GEM i.v. on days 1, 8 and 15 (28 day cycle) at 800 or 1000 mg/m$^2$, is being performed to determine the safety (using CTCAE v4.02) of combination treatment and recommend a Phase 2 dose (RP2D) combination. Other objectives are tumor response (RECIST 1.1), plasma and tumor MK-0752 concentration, and inhibition of the Notch pathway in hair follicles (expression profiling) and tumor (IHC). **Results:** 29 patients (pts) were registered on the study, of whom 27 received treatment (17 WHO PS 1; 10 PS 0). All patients received GEM/MK-0752 as first line treatment for metastatic disease. The RP2D of both single agents could be administered in combination (MK-0752 1800mg and GEM 1000 mg/m$^2$). As no DLTs were experienced at this dose combination, the Bayesian algorithm allowed further dose escalation, but dose limiting toxicity (G3 hypokalaemia) was observed at MK-0752 2,400mg in 1 pt. Gastrointestinal related adverse events (AEs) were common (diarrhoea 18 pts; nausea 19 pts; vomiting 17 pts). Other (>10% pts) AEs included fatigue, thrombocytopenia (G4 in 1 pt) and transaminitis. Tumor response evaluation was available after 10 weeks of treatment in 18 pts (6 withdrew early due to AEs, 1 pt was not evaluable, 2 pts still on treatment): 11/18 achieved stable disease and a confirmed partial response was observed at 12 weeks (time to subsequent progression 38 weeks). Plasma PK analysis revealed Cmax at 1,800mg of 61-104 μg/mL (n=7, Tmax, 4-8 hours) with a long half-life: quantifiable (>50 ng/mL) MK-0752 in plasma, 7 days after a single administration in 5/7 pts. A signature of Notch pathway inhibition was observed in 16/18 pts in hair follicles and paired biopsies (20 pts) are being analysed for tumor PK and Hes1 IHC. **Conclusions:** GEM and MK-0752, can be combined at full, single agent RP2Ds and the regimen is well tolerated. Clinical activity was seen, which will require confirmation in a Phase II trial. Clinical trial information: NCT01098344.

**4117 General Poster Session (Board #204), Sat, 8:00 AM-11:45 AM**

**Statin use and risk of pancreatic cancer: Results from a large clinic-based case-control study.** *Presenting Author: Evan J. Walker, University of California, San Francisco, School of Medicine, San Francisco, CA*

**Background:** Statins are cholesterol-lowering medications whose pleiotropic effects include alterations in growth signaling as well as immunomodulatory and anti-inflammatory effects that may alter cancer risk. Evidence from epidemiologic studies to date is conflicting as to whether statin use is associated with a reduced risk of pancreatic cancer (PC). The current case-control study investigates the association between statins and PC risk overall and by sex. **Methods:** Patients with a confirmed diagnosis of PC (cases) were recruited from medical and surgical oncology clinics at the University of California, San Francisco, with controls (frequency-matched by sex and age) recruited from general medicine clinics, from 2006-2011. Direct interviews were conducted using an epidemiological risk factor questionnaire covering topics such as lifestyle factors, diet, and medication usage. Adjusted multivariable logistic regression was used to compute odds ratios (OR) and 95% confidence intervals (CI) as estimates of the relative risk of PC. **Results:** Data were obtained from 536 cases and 869 controls. Ever use of statins was associated with 34% reduced PC risk (OR=0.66, 95%CI 0.47-0.92). In sex-stratified analyses, risk was statistically significantly reduced in men only (men: OR=0.51, 95%CI 0.32-0.80; women: OR=0.86, 95%CI 0.52-1.43). Duration of use was inversely associated with PC risk in men (long-term use: OR= 0.41, 95%CI 0.21-0.79; $p_{trend}$=0.005). Exploratory analyses of statins classified according to pharmacologic characteristics showed reduced PC risk in participants using statins with high compared to low bioavailability (p=0.01), whereas no significant differences were observed according to statin potency, solubility, or pattern of metabolism. **Conclusions:** This is the largest case-control study to demonstrate an inverse association between statin use and PC risk. Risk reduction from statins appears to be sex-specific and is more pronounced in long-term users. Further research is warranted to better characterize this association and clarify the role of underlying biologic mechanisms. If validated, statins could prove useful as preventive drug therapy for this disease. Supported by NIH R01 CA 109767.

**4118 General Poster Session (Board #205), Sat, 8:00 AM-11:45 AM**

**Serum procarboxypeptidase combined with CA19-9 and accuracy of detection of pancreatic cancer.** *Presenting Author: Michelle A. Orlowski, Princeton University, Princeton, NJ*

**Background:** Pancreatic cancer continues to have a dismal prognosis when diagnosed at an advanced stage. Thus, there is need for an early detection test. CA19-9 is the "gold standard", but fails as a means for detecting early stage disease. Previous studies have shown that pancreatic cancer, particularly in its early stages, is characterized by elevation in serum procarboxypeptidase A (PCPA) and high ratios of PCPA to free carboxypeptidase A (FCPA). The ratio can also enhance the diagnostic efficacy for some late stage tumors when the PCPA is within the normal range. The purpose of this study was to evaluate the performance of the assay alone and with CA19-9 in an independent cohort. **Methods:** Pre-treatment serum from 224 subjects recruited at Mayo Clinic were used (74 early and 75 late stage clinically and/or histologically proven pancreatic adenocarcinoma patients, and 75 healthy primary care controls). 111 cases had a head lesion and 38 had a body/tail lesion. All had CA19-9 measured. Blinded to clinical status, PCPA and FCPA were measured using a newly-automated method on the Beckman Coulter UniCel DxC 800 Synchron Clinical System. Patients were classified as having cancer if they had CA19-9 >55 and/or PCPA/FCPA ratio either <1 or >33, based on previous studies. **Results:** As single biomarkers, CA19-9 and PCPA/FCPA ratio have similar sensitivity (73.2 vs. 72.5, respectively), but specificity was higher for CA19-9 (98.7 vs. 78.7, respectively). A biomarker panel containing both the PCPA/FCPA ratio and CA19-9 improves sensitivity (73.2% to 87.2%, McNemar's test p-value < 0.0001) when compared to CA19-9 alone; specificity is decreased (98.7% to 82.7%, McNemar's test p-value = 0.0005). However, overall accuracy is increased relative to CA19-9 alone (81.7% to 85.7%). **Conclusions:** In a blinded, single draw independent sample, the combination of the PCPA/FCPA ratio and CA19-9 has demonstrated 87.2% sensitivity and 82.7% specificity for pancreatic cancer in a heterogeneous patient population. The addition of the PCPA assay may provide some promise for the development of a screening tool for the early detection of pancreatic cancer in high risk patients and studies are needed to further validate the utility of the assay.

**4119 General Poster Session (Board #206), Sat, 8:00 AM-11:45 AM**

**Treatment, outcomes, and clinical trial participation in very elderly patients (pts) with metastatic pancreas cancer (mPC).** *Presenting Author: Daneng Li, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** PC has a median age at diagnosis of 72 years. Aldoss et al. (Veterans Affairs Cancer Registry) and Vijayvergia et al. have reported that elderly pts are less likely to receive standard therapy compared to younger pts. Limited other studies in the very elderly (>80 years) with PC have been undertaken. **Methods:** A retrospective analysis on 237 pts with mPC >75 years of age who received care at Memorial Sloan Kettering Cancer Center between 2005 to 2013 was performed. Age groups: 75-79, 80-84, and 85+ years were analyzed and compared with respect to demographics, comorbidities, performance status, primary site of tumor, location and number of metastatic sites, laboratory data, treatment including type and number of systemic agents, clinical trial participation and overall survival (OS) after diagnosis. **Results:** A total of 196 (83%) pts received systemic therapy. The median OS of the entire cohort was 7 months. Use of therapy versus no therapy was significantly associated with longer OS (p<0.01). No significant difference was detected in survival between the different age groups among those receiving chemotherapy (p=0.49). Seventy-seven (32%) pts participated in a clinical study (biospecimen collection, psychosocial, therapeutic, etc); however, only 13 (5%) pts were enrolled in a therapeutic clinical trial with no pt age 85+ participating in a therapeutic study. **Conclusions:** Use of systemic therapy has a survival benefit in selected very elderly pts with mPC. While participation in any study was high, the number of very elderly pts enrolled in a therapeutic trial remains very low and similar to overall PC clinical trial participation (4.57%, Hoos et al. J Clin Oncol, 2013). In the future, therapeutic trials participation in this age group should be further encouraged.

| Age | Total cohort | 75-79 | 80-84 | 85+ |
|---|---|---|---|---|
| N | 237 | 114 | 84 | 39 |
| Male | 104 | 51 | 40 | 13 |
| Female | 133 | 63 | 44 | 26 |
| ECOG PS | | | | |
| 0-1 | 144 | 69 | 51 | 24 |
| 2 | 71 | 37 | 24 | 10 |
| 3+ | 22 | 8 | 9 | 5 |
| Charlson comorbid index (median) | 5 | 5 | 5 | 6 |
| Chemotherapy use | 196 (83%) | 101 (89%) | 70 (83%) | 25 (64%) |
| Clinical trial participation | 77 (32%) | 43 (38%) | 29 (34%) | 5 (13%) |
| Participation in a therapeutic trial | 13 (5%) | 9 (8%) | 4 (5%) | - |
| OS (median months) | 7.0 | 7.1 | 7.3 | 5.9 |
| Systemic therapy | 7.9 | 7.9 | 8.1 | 7.7 |
| No therapy | 2.3 | 1.4 | 2.7 | 4.7 |

**4120 General Poster Session (Board #207), Sat, 8:00 AM-11:45 AM**

**A phase II study of perioperative therapy for patients with resectable and borderline-resectable pancreatic adenocarcinoma.** *Presenting Author: Andrew L. Coveler, University of Washington, Seattle, WA*

**Background:** Most patients (pts) who undergo surgical resection (SR) for pancreatic ductal adenocarcinoma (PDA) relapse and die. Adjuvant chemotherapy (CT) improves survival compared to observation in randomized trials, but median disease-free survival (DFS) and overall survival (OS) are only 13.4m and 22.1m, respectively. Multiagent CT in the metastatic setting improves DFS and OS compared to gemcitabine (G) alone. Neoadjuvant (NA) treatment of resectable PDA is a rational though unproven strategy to improve standard results. We hypothesized NA multiagent CT and chemoradiotherapy (CRT) paired with SR and adjuvant CT would be manageable and improve the OS of pts with borderline (BR)/resectable (R) PDA. **Methods:** This was a prospective, single arm, single institution phase II trial. Eligibility included confirmed PDA, R/BR disease, ECOG ≤ 2, and adequate organ function. NA CT (3 cycles of GTX (G 750mg/m$^2$ over 75 minutes and docetaxel 30mg/m$^2$ days (d) 4 and 11, capecitabine (C) 750mg/m$^2$ BID d1-14)) followed by CRT (IMRT 3 Gy/fraction on days 1-5 and 8-12 (30 Gy total) with C 650mg/m$^2$ BID d1-14 and oxaliplatin (O) 60mg/m$^2$ d1 and 8. Adjuvant CT was 2m of GemOx (G 1000mg/m$^2$ and O 85mg/m$^2$ d1 every 14d) and 2m of standard G. The primary objective was to estimate the OS of pts treated in this fashion. Secondary objectives included DFS, Response Rate (RR), pathologic RR, SR completion and safety. **Results:** 35 pts were enrolled, 16 had BR disease and 16 were clinically node positive. One pt had progression during NA CT and 32 (91%) completed NA CRT. 31 (89%) pts went to surgery, 6 had occult metastases, 2 were locally advanced and 23 had SR (74% R0 and 26% R1). Pathology demonstrated 1 pCR and 87% N0. Among 35 pts enrolled, 21 (60%) are alive with a median follow-up of 23.6m. Median OS of all 35 patients is 31.1m and mDFS is 27.6m. Of 23 pts who underwent SR, 18 remain alive with a median follow-up of 25.7m. Estimated mDFS is 35.1m with a lower 95% confidence limit of 18.9m and mOS is not reached to date. **Conclusions:** In this phase II study, peri-operative multiagent CT and CRT was feasible and resulted in promising DFS and OS outcomes relative to historical controls. The current results are encouraging and warrant further evaluation. Clinical trial information: NCT00609336.

**4121 General Poster Session (Board #208), Sat, 8:00 AM-11:45 AM**

**Predictive cytokine biomarkers for survival in patients with advanced pancreatic cancer randomized to sequential chemoimmunotherapy comprising gemcitabine and capecitabine (GemCap) followed by the telomerase vaccine GV1001 compared to concurrent chemoimmunotherapy in the TeloVac phase III trial.** *Presenting Author: John P. Neoptolemos, University of Liverpool, Liverpool, United Kingdom*

**Background:** The TeloVac trial randomized 1,062 patients with advanced pancreatic cancer to a control chemotherapy Arm1, using GemCap; sequential chemoimmunotherapy Arm 2, GemCap for 8 wks followed by GV1001 and GMCSF (d1, 2, 5 during wk 9, then once on wks 10, 11, 12, 14, followed by once 4-wkly) with further GemCap given if there was PD at wk 8; and concurrent chemoimmunotherapy Arm 3, GemCap and GV1001 and GMCSF (d1, 2, 5 during wk1, then once on wks 2, 3, 4, 6, andthen once 4-wkly) . The final results (ASCO 2013) did not show improved survival with the addition of GV1001 to GemCap. A translational component examined predictive cytokine biomarkers **Methods:** 27 cytokines plus CRP were measured (Luminex) in 38 patients in Arm2 at baseline and in 50 at wk8 (after 2 cycles of GemCap, no vaccine) and in 41 patients in Arm3 at baseline and in 51 at wk10 (3rdcycle GemCap, 4 wks after the previous vaccine dose). The results at baseline and post-treatment were compared between the two arms and survival. **Results:** 19 cytokines showed a significant fall ($P<0.05$) between pre- and post-treatment in Arm2 (PDGF, IL1b, 1ra, 2, 4, 5, 7, 10, 12, 13 and 17, GCSF, IFNg, eotaxin, FGFb, MIP1b, RANTES, TNFa, VEGF; but not CRP, IL6, 8, 9, and 15, GMCSF, IP10, MCP1, MIP1a) and none in Arm3. Baseline eotaxin levels predicted median (95% CI) overall survival in Arm3 (high eotaxin=14.8 [10.1-20.5] mths; low eotaxin=7.9 [5.9-11.3] mths; p=0.0135) but not in Arm2 (high eotaxin=9.8 [5.5-11.8] mths; low eotaxin=6.2 [3.4-10.5] mths; p=0.1138 **Conclusions:** GemCap chemotherapy induced a fall of a distinct range of cytokines which was prevented by GV1001 given with GemCap. High eotaxin (CLL11) levels may predict improved survival in patients given GV1001 with GemCap but its role in advanced pancreatic cancer is subject to prospective trial validation Clinical trial information: 43482138.

**4122 General Poster Session (Board #209), Sat, 8:00 AM-11:45 AM**

**Gemcitabine(G)/erlotinib(E) versus gemcitabine/erlotinib/capecitabine(C) in the first-line treatment of patients with metastatic pancreatic cancer (mPC): Efficacy and safety results of a phase IIb randomized study from the Spanish TTD Collaborative Group.** *Presenting Author: Manuel Benavides, Hospital Universitario Carlos Haya, Malaga, Spain*

**Background:** G and E have shown a survival benefit in the 1st-line setting in mPC. The aim of this study was to assess whether combining C with G+E was safe and effective as compared with G-E in patients(pts) with mPC. **Methods:** Previously untreated pts with mPC were randomized in a 1:1 ratio to receive G(1000 mg/m2, d1,8,15)+E(100 mg, d1–28)+C(1660 mg/m2, d1-21) or G+E, q4-wk, until progression or unacceptable toxicity. Primary endpoint: progression-free survival (PFS); secondary endpoints: overall survival (OS), response rate (RR), relationship of rash with PFS/OS, and safety. A sample size of 118 pts was required for a hazard ratio(HR) of 0.63, assuming a median PFS of 6 months (m) in pts treated with GEC; unilateral $\alpha=0.05$; $\beta=0.8$. **Results:** 120 pts were randomized. Median age: 63 years; ECOG status 0/1/2(%), 33/58/8. Median follow-up was 16.5 m (95%CI:13.7-26.2). Median PFS was 4.3 m in the GEC arm and 3.8m in the GE arm (HR:0.88; 95%CI:0.58-1.31; p=0.52). The estimated median OS was 6.8 m in the GEC arm as compared with 7.7 m in the GE group (HR:1.09, 95%CI:0.72-1.63; p=0.69). Neutropenia grade 3/4 (GEC 43% vs GE 15%; p=0.0008) and mucositis (GEC 9% vs GE 0%;p=0.03), were the only statistically significant differences in grade 3/4 adverse events. PFS and OS were significantly longer in pts with rash (grade $\geq$ 1) vs no rash (grade=0): PFS 5.5 vs 2.0 m; HR=0.39 95%CI:0.26-0.6; $p<0.0001$ and OS: 9.5 vs 4.0 m; HR=0.51 95%CI:0.33-0.77; p=0.0014). **Conclusions:** PFS with GEC was not different to that with GE as it did not meet the criterion for statistical significance. Skin rash strongly predicted erlotinib efficacy, deserving further investigation for patient selection. Clinical trial information: NCT01303029.

**4123 General Poster Session (Board #210), Sat, 8:00 AM-11:45 AM**

**Nab-paclitaxel (nab-P) combined with FOLFOX for advanced pancreatic cancer: A phase I study.** *Presenting Author: Howard Safran, Brown University Oncology Research Group, Providence, RI*

**Background:** The contribution of irinotecan to the efficacy of FOLFIRINOX in pancreatic cancer is uncertain. The addition of irinotecan to gemcitabine was not superior to gemcitabine alone in pancreatic cancer, however nab-P demonstrates a survival benefit. This phase I study was designed to evaluate the addition of nab-P to fluorouracil, leucovorin, oxaliplatin (FOLFOX-A). **Methods:** Patients with metastatic or locally advanced pancreatic adenocarcinoma without prior treatment received oxaliplatin, 85 mg/m$^2$, leucovorin 400 mg/m$^2$ and 5-FU 2400 mg/m$^2$ with 3 dose levels of nab-P (125, 150 and 175 mg/m$^2$) every 2 weeks for up to 12 cycles. Patients with locally advanced disease could receive locoregional therapy after 6 cycles. The maximum tolerated dose (MTD) was established from dose limiting toxicities (DLTs) in the first 2 cycles of therapy. A study amendment, to include an expansion phase allowing a dose reduction of oxaliplatin to 68 mg/m$^2$for patients developing grade 2 neuropathy to facilitate administration of $>$ 10 cycles of FOLFOX-A, was activated after the MTD was determined. **Results:** 25 patients (pts) have been entered: Dose level 1 (n=6), dose level 2 (N=16), dose level 3 (N=3). The median age was 65 (35-82). Eighteen had metastatic and 7 had locally advanced disease. 15 pts were entered to determine the MTD. DLTs of nausea and fatigue occurred in 2 of 3 pts at dose level 3. Eight of the first 9 pts (89%) who received 10 or more cycles of FOLFOX-A had grade 2 or greater neuropathy including 2 of 9 (22%) with grade 3 neuropathy. None of the pts receiving less than 10 cycles of FOLFOX-A developed grade 2 neuropathy. One patient had grade 3 and one patient had grade 4 neutropenia. Eight of the first fifteen pts (53%) had a partial response. Following activation of the amendment allowing a dose reduction of oxaliplatin for grade 2 neuropathy, 10 additional pts have been enrolled. **Conclusions:** The MTD of nab-P is 150mg/m$^2$ every 2 weeks with FOLFOX. FOLFOX-A has substantial activity and may represent a promising regimen in pancreatic cancer. Supported by the Davis and Browning families and LIFEcycle. Clinical trial information: NCT01744353.

**4124 General Poster Session (Board #211), Sat, 8:00 AM-11:45 AM**

**Hent1 expression in patients with pancreatic cancer treated with gemcitabine after curative intended resection: Results from the CONKO-001 trial.** *Presenting Author: Marianne Sinn, Medical Department, Division of Hematology, Oncology and Tumor Immunology, Charité Universitätsmedizin Berlin, Berlin, Germany*

**Background:** High expression of human equilibrative nucleosid transporter 1 (hent1) is considered to predict disease-free (DFS) and overall survival (OS) in patients (pts) treated with adjuvant gemcitabine for pancreatic cancer. No standard evaluation system for immunohistochemical analysis (antibody, scoring system) is established so far. **Methods:** CONKO-001, a prospective randomized phase III study investigated the role of adjuvant gemcitabine (gem) as compared to observation (obs). Representative formalin-fixed, paraffin-embedded (FFPE) tumor samples of 156 patients were collected and tissue microarrays (TMA) built. TMA slides (4 $\mu$m) were evaluated by immunohistochemistry for expression of hent1 (rabbit monoclonal antibody SP120 Ventana Medical Systems). The analysis was performed by an experienced pathologist blinded to clinical outcome. Hent1 high was defined as unequivocal membranous staining in more than 50% of tumor cells, all other cases were classified as hENT1 low. Kaplan-Meier analyses for median DFS (mDFS) and median OS (mOS) were performed in dependence of hent1 expression. **Results:** For the 88 gem and 68 obs pts, mDFS (mOS) was 12.9 (22.7) months and 6.2 (19.1) months, respectively and thus comparable to the overall study population of CONKO-001 (mDFS gem 13.4 vs obs 6.7 months, mOS gem 22.8 vs obs 20.2 months). High hent1 expression was not associated with improved mDFS (high hent1 11.5 months vs low hent1 13.2 months, p= 0.5; HR 1.19, 95% CI 0.72-2.0) or mOS (high hent1 19.7 months vs low hent1 24.4 months, p=0.92; HR 1.03, 95% CI 0.63-1.68) in the gem group nor in the obs group (median DFS high hent1 5.9 months vs low hent1 6.2 months, p=0.83; median OS high hent1 20.4 months vs low hent1 17.7 months, p=0.65). **Conclusions:** Corresponding to previously available and contradictory data, we can not confirm a predictive role of hent1 in our study population. Reproducible standard procedures and further investigations are urgently needed prior to the implementation or exclusion of hent1 as predictive biomarker in the treatment of pancreatic cancer.

**4125 General Poster Session (Board #212), Sat, 8:00 AM-11:45 AM**

**A UGT1A1 genotype-guided dosing study of modified FOLFIRINOX (mFOLFIRINOX) in previously untreated patients (pts) with advanced gastrointestinal malignancies.** *Presenting Author: Manish Sharma, The University of Chicago Medicine, Chicago, IL*

**Background:** FOLFIRINOX improves survival compared with gemcitabine in advanced pancreatic cancer (PC), but at the cost of significant toxicity (Conroy, *NEJM*2011). UGT1A1 clears SN-38, the active metabolite of irinotecan (IRI); UGT1A1 gene polymorphisms that reduce enzymatic activity predispose to severe IRI toxicity. We hypothesized that dosing mFOLFIRINOX based on UGT1A1*28 genotype could prevent toxicity. Thus, the primary objective of this study (NCT01643499) was to determine whether genotype-guided dosing of IRI in mFOLFIRINOX is tolerable. A secondary objective was to describe objective response rates (ORR; by RECIST 1.1) in PC, biliary tract cancers (BTC), and gastric cancer (GC). **Methods:** mFOLFIRINOX was given every 14 days. CT scans were obtained every 8 weeks. UGT1A1 *1/*1, *1/*28, and *28/*28 pts received initial IRI doses of 180, 135, and 90 mg/m$^2$, respectively. 5-FU dose was 2400 mg/m$^2$ over 46 hours (no bolus); leucovorin 400 mg/m$^2$; oxaliplatin 85 mg/m$^2$. Prophylactic pegfilgrastim was not allowed in cycle 1 (28 days), unless clinically indicated. DLT during cycle 1 was defined as Grade (Gr) 3/4 neutropenia with fever; Gr 4 neutropenia lasting $\geq$ 5 days; Gr 4 thrombocytopenia, or Gr 3/4 non-hematologic toxicity despite optimal medical management. Doses were tolerable if the DLT rate during cycle 1 was $\leq$ 33% with 70-80% statistical confidence, which required $\leq$ 2 DLTs in 15 pts. **Results:** 40 pts were evaluable for tolerability: 19 PC, 14 BTC, 7 GC. DLTs were observed in 2 of 15 *1/*1 pts (both neutropenic fevers); 2 of 16 *1/*28 pts (Gr 3 fatigue, diarrhea; Gr 3 fatigue); and 3 of 9 *28/*28 pts (2 neutropenic fevers; Gr 3 abdominal pain). Neutropenic fever was the most common DLT (4/7; 57%). To date, 35 pts are evaluable for response. ORR: 10/18 (56%) PC; 4/13 (31%) BTC; 3/4 (75%) GC. **Conclusions:** mFOLFIRINOX is tolerable in UGT1A1*1/*1 pts at the standard IRI dose of 180 mg/m$^2$ and in *1/*28 pts at a reduced dose of 135 mg/m$^2$. *28/*28 pts cannot tolerate a reduced dose of 90 mg/m$^2$. Accrual is ongoing for expansion cohorts in PC and BTC with prophylactic pegfilgrastim. Clinical trial information: NCT01643499.

| UGT1A1 genotype | Initial IRI dose (mg/m$^2$) | # DLTs / # pts |
|---|---|---|
| ***1/*1** | 180 | 2/15 |
| ***1/*28** | 135 | 2/16 |
| ***28/*28** | 90 | 3/9 |

**4126 General Poster Session (Board #213), Sat, 8:00 AM-11:45 AM**

**Impact of gemcitabine (Gem)- or capecitabine (Cape)-based chemoradiation (CRT) on health-related quality of life (HRQL) in patients with locally advanced pancreatic cancer (LAPC): Outcomes from the randomized phase II SCALOP trial.** *Presenting Author: Somnath Mukherjee, Gray Institute for Radiation Oncology and Biology, University of Oxford, Oxford, United Kingdom*

**Background:** HRQL in pancreatic CRT trials have not been widely reported. In SCALOP, registered patients (n=114) received Gem and Cape induction chemotherapy (4 cycles) and non-progressing patients (n=74) were randomized to conformal RT (50.4Gy/28 fractions/5.5 weeks) in combination with Gem (300mg/m$^2$ weekly) or Cape (830mg/m$^2$ bd on days of RT). SCALOP demonstrated superior overall survival (15.2 mo vs 13.4 mo, HR 0.39, p=0.012) and lower Grade 3/4 hematological toxicity (18% v 0%, p=0.008) in the Cape-CRT arm (Mukherjee, Lancet Oncol, Apr 2013). The SCALOP trial was funded by Cancer Research UK (CR UK 07/040). **Methods:** HRQL was assessed with EORTC QLQ-C30 (generic domains) and EORTC PAN26 (pancreas specific) at Week 0 (pre-treatment), Week17 (pre-CRT), Week23 (post-CRT) and follow-up (Weeks 26, 39). The difference in change in function and symptom scores between trial arms from pre-CRT baseline (week 17) to later time-points were analysed using Wilcoxon rank sum tests. **Results:** HRQL form completion was 93%, 82%, 65%, 68% and 58% respectively across the time-points. Compared to pre-CRT baseline (week 17), at the end of CRT (week 23), patients on Cape-CRT arm experienced significantly better HRQL outcomes in terms of cognitive functioning (p=0.04), fatigue (p=0.05), bloating (p=0.04) and dry mouth (p=0.03). The differences were no longer significant at week 26 or 39 apart from cognitive function scores (p=0.01) and dry mouth (p<0.01), which remained significant at week 39. **Conclusions:** The better HRQL in the Cape-CRT arm complements the outcome from the main trial and further supports the use of Cape rather than Gem as concomitant chemotherapy with radiation in LAPC. Clinical trial information: NCT01032057.

**4127 General Poster Session (Board #214), Sat, 8:00 AM-11:45 AM**

**Association of recurrence patterns following resection of pancreatic adenocarcinoma with overall survival.** *Presenting Author: Jin He, The Johns Hopkins University School of Medicine, Baltimore, MD*

**Background:** Although recurrence is common after curative resection of pancreatic ductal adenocarcinoma (PDAC), little is known regarding the pattern of recurrence. **Methods:** We reviewed clinical data of 1,138 consecutive patients with PDAC who underwent pancreatectomy from 2000 to 2010 to document the pattern of recurrence based on CT and/or MRI and/or FDG-PET scan. Local recurrence (LR) was defined as cancer recurrence at the pancreatectomy site. Recurrence in the omentum, peritoneum, liver, lung, spine, pelvic or supraclavicular lymph nodes was considered as distal recurrence (DR). **Results:** The median follow up was 17 months (IQR 26 months). Of 845 patients with complete follow-up, 470 (55.6%) had recurrence with the following pattern: LR only in 111 (23.6%), liver recurrence only in 128 (27.2%), lung recurrence only in 55 (11.7%), local and DR in 84 (17.9%), and other recurrences in 92 (19.6%). 405 (86.2%) patients had only intra-abdominal recurrence. In the patients who recurred, 49.8% and 80.2% recurred within 1 year and 2 years from the resection respectively. The incidence of recurrence at different time after pancreatectomy was summarized in the Table. More patients with liver only recurrence occurred within 6 months after resection comparing to that with LR only (41% vs 9%, p<0.001). The median overall survival (OS) of the entire cohort is 22.6 month and varied significantly based on recurrence pattern (Table). The median OS of patients with lung only recurrence is longer than that with liver only recurrence (31.6 vs 16.7 months, p<0.001). **Conclusions:** The pattern of recurrence is associated with distinct survival and supports the observation that PDAC is genetically diverse. Our findings are important in selecting patients for personalized treatment combinations and laying the groundwork for defining the molecular basis behind the biological diversity of PDAC.

**The median OS and incidence of different recurrence pattern at different time after pancreatectomy.**

| | Time after pancreatectomy | | | | | | | | Median OS |
|---|---|---|---|---|---|---|---|---|---|
| | 6 mo | | 12 mo | | 24 mo | | 60 mo | | (m) |
| **Local only** | 10 | 9% | 44 | 40% | 82 | 74% | 106 | 95% | 25 |
| **Liver only** | 53 | 41% | 86 | 67% | 111 | 87% | 126 | 98% | 16 |
| **Lung only** | 7 | 13% | 15 | 27% | 35 | 64% | 55 | 100% | 32 |
| **LR and DR** | 17 | 20% | 47 | 56% | 72 | 86% | 84 | 100% | 20 |
| **Other** | 14 | 15% | 42 | 46% | 75 | 82% | 90 | 98% | 20 |

**4128 General Poster Session (Board #215), Sat, 8:00 AM-11:45 AM**

**Effect of molecular genotyping to predict outcomes in patients with metastatic pancreatic cancer.** *Presenting Author: Jason Edward Faris, Massachusetts General Hospital Cancer Center, Boston, MA*

**Background:** The majority (85-90%) of patients (pts) with MPC have mutations in KRAS. Pts with wild type (WT) KRAS, as well as pts with codon-specific KRAS mutations (KRASm) may be associated with distinct presentations and survival. We utilized a molecular genotyping test, SNaPshot, to detect tumor-specific mutations. **Methods:** The molecular genotypes of 150 pts with MPC that received treatment at the MGH Cancer Center were analyzed. The SNaPshot assay utilizes DNA extracted from formalin-fixed paraffin-embedded tissue and detects sequence variants in a panel of 14 cancer genes. Demographic and clinical characteristics were tabulated, and statistical analysis performed to evaluate correlations between genotype, demographics, clinical characteristics, and outcomes. Overall survival (OS) since diagnosis and OS since metastatic disease were analyzed using Kaplan Meier method and compared using log-rank test. Categorical variables were compared using chi-square test or Fisher's exact test. Continuous variables were compared using ANOVA or nonparametric test. **Results:** Median age was 63. There were 92 males and 58 females. 98 pts presented with tumors of the head/uncinate and 52 of the body/tail. 71 patients underwent Whipple surgery prior to development of MPC. There were 49 pts with G12D, 38 with G12V, 22 with G12R, and 13 with other KRASm. 28 pts were KRAS WT, including 24 pts without detectable mutations in any gene assayed. Median OS since metastatic disease for the entire cohort was 10 mo (CI: 8.6-12.2). Patients with KRAS G12R had superior OS since metastatic disease (15.6 months, CI 9.4-47.6 mo) relative to patients with G12D mutations (6.1 mo, CI 4.5-12.2 mo) and to patients with KRAS non-G12R mutations (8.9mo, CI 6.0-11.3mo) (p=0.02 for each comparison). 25 pts presented with lung-only metastatic disease at diagnosis, with median OS of 22.4 mo (CI, 10-47.5 mo); 10/25 (40%) were KRAS WT or KRAS 12R. **Conclusions:** Molecular genotyping of pancreatic cancer identified subgroups of patients with distinct clinical presentation and survival.

| KRAS mutation | n | OS since metastatic disease (mo) |
|---|---|---|
| **G12R** | 22 | 15.6 (9.4-47.6) |
| **WT** | 28 | 12.1 (9.5-17.1) |
| **Non-G12R** | 100 | 8.9 (6.0-11.3) |
| **G12V** | 38 | 8.2 (5.2-14.5) |
| **G12D** | 49 | 6.1 (4.5-12.2) |

**4129 General Poster Session (Board #216), Sat, 8:00 AM-11:45 AM**

**Phase II study of the MEK inhibitor refametinib (BAY 86-9766) in combination with gemcitabine in patients with unresectable, locally advanced, or metastatic pancreatic cancer: Biomarker results.** *Presenting Author: Hanno Riess, Charité Comprehensive Cancer Center and Department of Oncology and Haematology, Berlin, Germany*

**Background:** Refametinib is a potent oral allosteric MEK 1/2 inhibitor with both single-agent and synergistic activity in combination with gemcitabine in preclinical models of pancreas cancer (PC). A synergistic effect between refametinib and erlotinib was also reported in KRAS wild-type human PC in vitro (Diep et al, Clin Cance Res 2011). We report the biomarker results of a single-arm, open label, phase 2a study combining refametinib and gemcitabine in advanced PC. **Methods:** Refametinib was administered 50 mg bid in combination with gemcitabine. The primary objective was overall response rate (ORR). Secondary objectives included progression-free survival (PFS), overall survival (OS) and biomarker assessment. KRAS mutational analysis was performed from plasma collected at baseline on circulating tumor DNA (ctDNA) by BEAMing. Circulating miRNA were obtained from plasma collected at baseline and post-dose and analyzed by qPCR. Targeted tumor gene next-generation sequencing, gene expression analysis by RNA sequencing and the proliferation index were conducted. **Results:** Of the 60 patients treated, 39 (65%) had KRAS mutations. In the KRAS subgroups (mut/WT, respectively), the ORR, mPFS and OS were 28%/48% (p=0.136), 4.6/9.0 mo (HR 0.26) and 6.6/18.2 mo (HR 0.27). There was a trend correlating allele frequency with response. KRAS G12D, G12V and G12R were the most frequent mutations. Mutations of codon 38 or 436 were not observed. Tumor exome sequencing was performed from 16 patients, 15 of which had a KRAS mutation (G12D or G12V). The most frequent co-occurring somatic mutations or amplifications were TP53, CDKN2A, and cMYC. Tumor proliferation index and miRNA signatures were not correlated with response. Gene expression data were tested for correlation with response or the presence of published KRAS pathway signatures. Additional subgroup analyses were performed. **Conclusions:** The high prevalence of KRAS mutations in patients with PC has been confirmed using BEAMing. There was a trend towards improved response, mPFS and OS in the wild-type KRAS subset and for KRAS allele frequency to correlate with response. Clinical trial information: NCT01251640.

**4130 General Poster Session (Board #217), Sat, 8:00 AM-11:45 AM**

**Pharmacogenomic modeling of pancreatic cancer (PDAC) for prediction of chemotherapy response and resistance in second-line treatment setting.** *Presenting Author: Kenneth H. Yu, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

**Background:** PDAC is a leading and rising cause of cancer mortality. Despite this, modern cytotoxics (C) can induce tumor responses and extend life. Xenograft models have shown that pharmacogenomic (PGx) modeling of C can predict efficacy. We previously presented results supporting PGx profiling of circulating tumor and invasive cells (CTICs) to predict effective C in the 1st line setting. We now present results in the second-line setting. **Methods:** PGx models for five common PDAC C regimens were created from the GI50 data obtained from the NCI-60 cell lines. These PGx models were validated in a prospective study of 50 patients with unresectable PDAC. 10 mL of peripheral blood was collected prior to C and at disease progression. CTICs were isolated, total RNA extracted and gene-expression analysis performed. Gene and pathway analyses were performed comparing patients with short v long TTP and for an individual patient at baseline v at time of progression. **Results:** CTICs were isolated, and gene expression profiles were obtained in all 50 patients prior to initiating C and in 25 patients at first-line disease progression. In the 1st line setting, we previously presented that CTIC PGx profiling predicted effective versus ineffective C treatment. In the 2nd line setting, 15 patients were evaluable for C response. Clinical benefit was again seen for patients treated with C predicted to be effective versus ineffective (PFS 5.7 mo v 2.5 mo, p=0.027, HR 0.15; OS 8.6 mo v 3.4 mo, p=0.020, HR 0.14). Changes in PGx profiles at disease progression reflected resistance to first-line C treatment. Widespread dysregulation in 32 gene pathways was found in CTICs at disease progression. CTIC SMAD4, ATM and XPO1 expression levels correlated with TTP in the first-line setting. **Conclusions:** PGx profiling of CTICs from patients with unresectable PDAC can predict effective C, both in the first- and second-line setting. Repeat PGx profiling identifies key gene pathways associated with treatment resistance. Clinical trial information: NCT01474564.

| | Treatment response, PGx prediction | | |
|---|---|---|---|
| | Sensitive | Resistant | |
| **First Line (*n=35*)** | | | |
| **PFS (mo)** | 10.4 | 3.6 | *p = 0.0001*, HR 0.14 |
| **OS (mo)** | 17.2 | 8.3 | *p = 0.0249*, HR 0.29 |
| **Second Line (*n=15*)** | | | |
| **PFS (mo)** | 5.7 | 2.5 | *p = 0.027*, HR 0.15 |
| **OS (mo)** | 8.6 | 3.4 | *p = 0.020*, HR 0.14 |

**4131 General Poster Session (Board #218), Sat, 8:00 AM-11:45 AM**

**Patterns of chemotherapy (CT) use in a population-based US-wide cohort of patients (pts) with metastatic pancreatic cancer (MPC).** *Presenting Author: Thomas Adam Abrams, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Few population studies have examined the frequencies and durations of specific CT treatment regimens in MPC. **Methods:** We assessed 3,796 consecutive MPC pts who received CT between Jan 2005 and Aug 2013 at academic, private and community hospital-based practices participating in a US-wide CT order entry system that captures pt, provider and treatment data. Multivariate analyses of prospectively recorded pt and provider characteristics identified predictors of specific therapeutic approaches. **Results:** Among all pts, median age was 70; 55% male. In 1st-line CT, 48% of pts received gemcitabine (GEM) monotherapy, 16% received a GEM-based doublet (incl. GEM + nab-paclitaxel [NAB-P]), 9% received fluoropyrimidine (FU) + oxaliplatin (OX) + irinotecan (FOLFIRINOX), 9% received FU monotherapy, and 5% received FU + OX (FOLFOX). The remaining 13% received other regimens. GEM monotherapy use peaked at 58% in 2009 but declined to 28% in 2013. FOLFIRINOX use emerged in 2010 with 4% usage and peaked at 23% in 2012. Since 2012, GEM + NAB-P use has risen substantially, representing 20% of first-line therapy in 2013. GEM + cisplatin use declined steadily from 2010 (9%) to 2013 (3%). Pts under age 60 and those treated at academic centers were more likely to receive first-line FOLFIRINOX and less likely to receive GEM monotherapy (both p<0.05). Mean duration of all 1st-line treatments was 87 days. 31% of all pts received 2nd-line treatment, 13% third-line, and 5% fourth-line. Second-line CTs included GEM monotherapy (28%), FOLFOX (14%), FOLFIRINOX (7%) and GEM + NAB-P (6%). 37% of pts who received second-line GEM + NAB-P received 1st-line FOLFIRINOX. **Conclusions:** This population-based study provides insight into US MPC treatment patterns. Treatments vary significantly according to patient and practice characteristics.

**MPC first-line CT treatment trends (2005-2013).**

| | 2005-2009 | 2010-2011 | 2012 | 2013† |
|---|---|---|---|---|
| **# Pts** | 1,694 | 1,111 | 604 | 387 |
| **GEM (%)** | 57.6 | 48.1 | 33.0 | 28.4 |
| **GEM doublet‡ (%)** | 16.1 | 8.6 | 11.4 | 9.3 |
| **GEM + NAB-P (%)** | 0.2 | 2.1 | 4.0 | 20.4 |
| **FOLFOX (%)** | 2.3 | 5.8 | 8.9 | 2.3 |
| **FOLFIRINOX (%)** | 0.1 | 11.8 | 23.3 | 20.7 |
| **FU (%)** | 9.5 | 9.0 | 8.4 | 11.9 |
| **Other (%)** | 14.2 | 14.6 | 11.0 | 7.0 |

†Through Aug 31 (data through Dec 31, 2013 will be presented at the meeting).
‡Not including GEM + NAB-P.

**4132 General Poster Session (Board #219), Sat, 8:00 AM-11:45 AM**

**Use of first-line chemotherapy for advanced pancreatic cancer: FOLFIRINOX versus gemcitabine-based therapy.** *Presenting Author: Thomas H. Cartwright, Ocala Oncology, Ocala, FL*

**Background:** Pancreatic cancer (PC) is the fourth leading cause of death in the United States. It is estimated that 46,420 patients will be diagnosed in 2014 and 35,590 will die (Siegel, CA Cancer J Clin 2014). Gemcitabine has long been the standard of care chemotherapy. Recent advances in treatment created the combination regimens (oxaliplatin, irinotecan, leucovorin, fluorouracil [FOLFIRINOX]) and gemcitabine, nab-paclitaxel (GN) for patients with good Karnofsky performance status (PS) (Conroy, NEJM 2011; Von Hoff, NEJM 2013). This retrospective analysis was conducted as an update to results reported at ASCO 2013 (Cartwright, JCO 2013) to evaluate characteristics and overall survival (OS) of patients receiving FOLFIRINOX and gemcitabine-based treatments in a large outpatient community setting. This is the largest study describing FOLFIRINOX patients to date. **Methods:** Patients with advanced PC treated at practices in The US Oncology Network entered into the iKnowMed (iKM) database between June 2010 and November 2013 were included. Patterns of treatment were characterized by the median age at diagnosis, sex, PS, and first-line metastatic chemotherapy prescribed. The primary endpoints of the analysis were OS and uptake of FOLFIRINOX within The Network. **Results:** Compared to ASCO 2013 results, 700 additional patients were identified. Of the 2,422 total patients, 27% received FOLFIRINOX (24% in 2013) and 73% received gemcitabine-based therapy (76% in 2013). Increased utilization of FOLFIRINOX for good PS patients began in June 2010 and GN April 2013. For all patients (55% male), the median age at diagnosis was 67 and 95% had a PS of 70% or greater. When controlled for age and PS, the OS was significantly longer for FOLFIRINOX (11.2 mos) versus gemcitabine (7.2 mos) (p<0.0001). Median OS for GN (n=189) was 10.2 mos, despite shorter follow up time. **Conclusions:** Utilization of FOLFIRINOX and GN has continued to increase after the publication of phase III trials. Our data in a community setting continues to support a survival advantage for FOLFIRINOX as well as GN. The magnitude of benefit appears slightly better in the community; therefore, we agree that FOLFIRINOX should become a standard of care for good PS patients.

**4133 General Poster Session (Board #220), Sat, 8:00 AM-11:45 AM**

**A novel biomarker panel examining response to gemcitabine (G) with or without erlotinib (E) for pancreatic cancer (PA) therapy in NCIC clinical trials group PA.3.** *Presenting Author: David Shultz, Stanford University, School of Medicine, Stanford, CA*

**Background:** NCIC Clinical Trials Group PA.3 (NCIC CTG PA.3) was a randomized control trial that demonstrated an overall survival (OS) benefit in patients receiving E in addition to G for locally advanced or metastatic PA. Prior to therapy, patients had baseline plasma samples drawn and archived for future study. **Methods:** By using the multiplex capabilities and high sensitivity detection of the proximity ligation assay (PLA), a probe panel was built from commercially available antibodies capable of quantifying 35 key proteins, selected from a global genetic analysis of pancreatic caners followed by a k-means clustering, from 20 uLof patient plasma. To determine if any of these proteins independently associated with OS, multivariate Cox models adjusting for gender, age, race, stage, and pain intensity at baseline were used. **Results:** Of the 559 eligible patients, 483 had samples available for study. Samples were randomly allocated into training (T) (253) and validation (V) sets (230). Elevated levels of interleukin-8 (IL-8) was the only protein found independently associated with lower OS in patients treated with G alone in both T and V sets, while elevated levels of IL-8, carcinoembryonicantigen (CEA), and hypoxia-inducible factor 1-alpha (HIF-1 alpha) were the proteins in patients treated with G+E or among patients from both treatment arms. Conclusions**:** PLA is a powerful tool for identifying potential biomarkers from archived, small volume serum samples. These data suggest that pancreatic cancer patients with low IL-8, CEA, or HIF-1 alpha plasma levels were most likely to have longer OS from the addition of E to G while patients with lower IL-8 levels had improved survival when treated with G alone, which may also be useful to stratify patient outcomes regardless of therapeutic intervention.

| | OS hazard ratio (95% CI) of low to high level (using median as cutpoint) | | | | | |
|---|---|---|---|---|---|---|
| | G Alone | | G+E | | All | |
| Biomarker | T | V | T | V | T | V |
| IL-8 | 0.58 (0.39, 0.89) | 0.51 (0.33, 0.74) | 0.56 (0.37, 0.84) | 0.51 (0.30, 0.86) | 0.64 (0.48, 0.84) | 0.62 (0.45, 0.85) |
| CEA | - | - | 0.59 (0.39, 0.90) | 0.60 (0.37, 0.98) | 0.67 (0.50, 0.89) | 0.58 (0.43, 0.79) |
| HIF-1 alpha | - | - | 0.63 (0.43, 0.94) | 0.59 (0.37, 0.95) | 0.70 (0.54, 0.92) | 0.58 (0.43, 0.79) |

**4135 General Poster Session (Board #222), Sat, 8:00 AM-11:45 AM**

**A phase 2 trial of low-dose multiagent chemotherapy with gemcitabine, docetaxel, capecitabine, and cisplatin (GTX-C) in subjects with metastatic pancreatic cancer.** *Presenting Author: Dung T. Le, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

**Background:** Triplet chemotherapy has been shown to delay the emergence of resistance and extend survival in patients with metastatic pancreatic adenocarcinoma. Four drug regimens, even at low doses, may further improve survival by simultaneously targeting multiple oncogenic pathways. **Methods:** A phase 2 study of GTX-C (capecitabine 500 mg bid on days 1-14, and the combination of gemcitabine 500 mg/m2 [10 mg/m$^2$/min], docetaxel 20 mg/m$^2$ and cisplatin 20 mg/m$^2$ on days 4 and 11) was initiated in newly diagnosed untreated metastatic pancreatic cancer patients. The primary endpoint was progression-free survival rate at 6 months and designed such that the regimen would be considered active if the 6-month PFS rate was >75% and inactive if < 50%. **Results:** Twenty-eight patients were enrolled. All patients were ECOG 0-1. Eighty-six percent of patients had evidence of liver metastases and 25% had biliary stents in place at time of study initiation. Median CA19-9 was 6,159 U/mL (37-154,323 U/mL). Median length of follow-up was 10.1 months. Grade 3/4 related adverse events included: nausea/vomiting (7%), transaminitis (10%), anemia (14%), thrombocytopenia (24%), and neutropenia (55%). However, febrile neutropenia occurred in only 3 patients (10%) and not until cycles 6, 14, and 15. PFS rate at 6 months was 74.2% (95% CI: 53.3% - 86.8%). The partial response (PR) rate was 50%, stable disease (SD) rate was 39% and the disease control rate (DCR) was 89%. CA19-9 declines of >80% occurred in 77% of patients with measurable levels. Estimated median PFS was 8.4 months (95% CI: 6.1-10.6 months) and OS was 12.9 months (95% CI: 10.0-NA months) as of 11/14/2013. Ten additional patients have been enrolled onto an expansion cohort in which the period off between cycles has been changed from 7 to 14 days. **Conclusions:** GTX-C is highly active and well-tolerated in patients with metastatic pancreatic cancer and should be tested in a larger, comparative study. Clinical trial information: NCT01459614.

**4136 General Poster Session (Board #223), Sat, 8:00 AM-11:45 AM**

**Multiplatform molecular profiling of 2,400 pancreatic adenocarcinomas to identify targets for therapeutic intent.** *Presenting Author: Sherri Z. Millis, Caris Life Sciences, Phoenix, AZ*

**Background:** Pancreas adenocarcinoma (PC) is a challenging disease with overall single digit 5-year survivorship. Few validated biomarkers exist for directing treatment in PC. Only one targeted agent (erlotinib) is FDA-approved and was developed in an unselected population (Moore, et al, J Clin Oncol, 2007). Identification of individual PC genomic and phenotypic profiles may yield targets with novel therapeutic application. **Methods:** 2400 cases referred internationally to Caris Life Sciences were evaluated using a combination of sequencing (Sanger or next generation sequencing (NGS)), protein expression (immunohistochemistry), and/or gene amplification (CISH or FISH). **Results:** The published PC molecular profile (24 cases, Jones, et al, Science, 2008) is consistent with the 2400 cases evaluated; KRAS was the most common mutation N=1190/1460 (82%) followed by TP53, N=175/310 (56%), and SMAD4, N=39/324 (12%). Mutations in BRAF, EGFR, HER2, FLT3, HRAS, PDGFRA and PTEN were identified exclusively in KRAS WT cases. **Conclusions:** 18% of PC cases were KRAS WT, representing a significant minority of patients with PC. Aberrant signaling through the RAS/MAPK pathway through oncogenic mutations in HRAS, BRAF, EGFR, HER2 and PDGFR was found in a very small subset of KRAS WT cases (8%), and the likely benefit of anti-EGFR-based therapies is limited to those patients with KRAS wild-type tumors lacking downstream oncogenic activation of this pathway. IHC evaluation of certain markers, e.g., RRM1, SPARC, etc. may help select drugs and refine treatment decision making for certain patients. Evaluating these profiles with clinical outcomes will provide valuable insight into the clinical behavior in genomically defined subsets and will assist in developing rational combinations of targeted agents in PC.

| | IHC | | | ISH | Sequencing | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PR | RRM1 | SPARC | HER2 | BRAF | cKit | cMET | EGFR | HER2 | FLT3 | HRAS | PDGFRA | PTEN | SMAD4 | TP53 |
| KRAS MT (82%) | | | | | | | | | | | | | | | |
| Total N | 1099 | 1092 | 1092 | 603 | 451 | 346 | 254 | 278 | 252 | 250 | 216 | 248 | 247 | 250 | 242 |
| % Positive | 2 | 21 | 35 | 4.5 | - | 1 | 4 | - | - | - | - | - | - | 14 | 65 |
| KRAS WT (18%) | | | | | | | | | | | | | | | |
| Total N | 248 | 248 | 248 | 111 | 87 | 71 | 50 | 54 | 49 | 50 | 43 | 49 | 49 | 49 | 47 |
| % Positive | 8 | 19 | 38 | 7.3 | 8 | 3 | 8 | 2 | 2 | 2 | 5 | 4 | 2 | 6 | 21 |

**4137 General Poster Session (Board #224), Sat, 8:00 AM-11:45 AM**

**Infiltrating neutrophils and malignant progression in intraductal papillary mucinous neoplasms (IPMN): An opportunity for identification of high-risk disease.** *Presenting Author: Eran Sadot, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** There is a strong link between neutrophil infiltration and malignant progression. Inflammatory proteins (IP) released by these cells play a pivotal role in the crosstalk between neoplastic and inflammatory cells. We evaluated tumor associated neutrophils (TAN) and their association with malignant progression in IPMN, and studied the cyst fluid from these lesions for biomarkers of the inflammation-carcinogenesis association. **Methods:** We evaluated 78 patients with resected IPMN (2004-2013). Patients were divided into 3 groups: low-risk (low and moderate grade dysplasia: n=48), high grade dysplasia (HGD, n=21), and invasive carcinoma (n=9). TAN were examined in representative areas on 2 slides of a given tumor. The number of TAN was assessed using the mean value of high power fields. Areas with <10 TAN/100 tumor cells were considered 'negative' and areas with 11–15 TAN/100 tumor cells were designated as 'low' while those with >15 TAN/100 tumor cells were regarded as 'high'. A multiplexed protein assay (Luminex Corp.) was performed on cyst fluid to evaluate for inflammatory cytokines and tumor-associated markers. **Results:** Significant positive correlation between grade of dysplasia and TAN level was found. High TAN were identified in 2.1%, 33.3%, and 88.9% of patients from the low risk, HGD, and invasive carcinoma groups, respectively ($p$<0.001). Within the cyst fluid, IP(e.g. IFN-g, TIMP-1, MIF, TNF-a, and MMP-9) were also found to have positive correlation with higher grades of dysplasia. Higher levels of TAN correlated with increased cyst fluid concentrations of the IP (e.g. IL-1b, TNF-a, IFN-g, IL-4), and 90% of these proteins were also found to be associated with higher grades of dysplasia. Multivariate analysis of clinical, radiographic, and molecular findings identified cyst fluid MMP-9 and CA 72-4 to be independent predictors for higher grades of dysplasia. **Conclusions:** Tumor associated neutrophils are strongly associated with malignant progression in IPMN. Measurement of IP in the cyst fluid may be a surrogate marker for IPMN progression and allow for the identification of high-risk disease.

**4138 General Poster Session (Board #225), Sat, 8:00 AM-11:45 AM**

**FG-3019, a human monoclonal antibody to connective tissue growth factor (CTGF), with gemcitabine/erlotinib (G/E) in patients with locally advanced or metastatic pancreatic ductal adenocarcinoma (PDAC).** *Presenting Author: Vincent J. Picozzi, Virginia Mason Medical Center, Seattle, WA*

**Background:** CTGF is overexpressed in PDAC and facilitates local desmoplasia, tumor survival and metastasis. FG-3019 is a CTGF-specific monoclonal antibody that decreases tumor growth and metastases and prolongs survival in the KPC mouse model of pancreatic cancer. This study evaluated safety and efficacy of FG-3019 with G/E in patients (Pts) with PDAC. **Methods:** FG-3019 was combined with G/E in Pts with previously untreated, measurable, Stage 3 or 4 PDAC. Cohorts 1−6 received FG-3019 Q2W at 3, 10, 15, 25, 35 or 45 mg/kg. Cohort 7 received 35 mg/kg on Day 1, then 17.5 mg/kg QW. Cohort 8 received 45 mg/kg on Day 1, then 22.5 mg/kg QW. **Results:** 75 Pts were enrolled. Baseline characteristics: Stage 3 / 4 (11/64); ECOG=0/1 (30/45). Median of 9 FG-3019 doses were administered (range: 1-73). FG-3019 was well tolerated with no DLT. MTD is > 45 mg/kg. Median OS was 9.4 months in the per-protocol population. Best RECIST response was 2(3%) CR, 8(11%) PR, 39(52%) SD, 12(16%) PD, (14 no RECIST data). OS generally correlated with FG-3019 exposure in Cycle 1. Day 15 $C_{min} \geq 150$ ug/mL was associated with improved OS (p=0.03) and 1 year survival (p=0.03). CA 19.9 response was 52% ($C_{min} \geq 150$) and 38% ($C_{min} < 150$). Pts with ascites had low $C_{min}$ and poor OS. High FG-3019 doses with $C_{min}$ >150 ug/mL appeared to improve OS. Baseline plasma CTGF correlated inversely with OS (p=0.006). In bivariate analysis, Day 15 $C_{min} \geq 150$ ug/mL and baseline CTGF < median were associated with better survival (p=0.04 and 0.02 respectively). Greatest survival was in Pts with Day 15 $C_{min}$> 150 ug/mL and baseline CTGF < median. **Conclusions:** FG-3019 did not add to toxicity of G/E. Results suggest OS improves with increasing exposure to FG-3019, and the combination of baseline CTGF and plasma FG-3019 levels could be a predictor of efficacy. Given its advantageous safety profile, FG-3019 could be combined with other chemotherapeutic regimens. Clinical trial information: NCT01181245.

| FG-3019 Day 15 $C_{min}$ (ug/mL) | Baseline CTGF (ng/mL) | Median OS (months) | 1-year OS (%) |
|---|---|---|---|
| ≥150 | Any | 9.4 | 34% |
| < 150 | Any | 6.3 | 12% |
| Any | < median | 10.4 | 31% |
| | ≥ median | 4.8 | 13 % |
| ≥150 | < median | 11.2 | 42% |
| | ≥ median | 8.6 | 22% |
| < 150 | < median | 8.0 | 19% |
| | ≥ median | 3.8 | 6% |

**4139 General Poster Session (Board #226), Sat, 8:00 AM-11:45 AM**

**A phase I study of veliparib (ABT-888) in combination with low-dose fractionated whole abdominal radiation therapy (LDFWAR) in patients with advanced solid malignancies and peritoneal carcinomatosis.** *Presenting Author: Kim Anna Reiss, The Johns Hopkins University School of Medicine, Baltimore, MD*

**Background:** The combination of low-dose radiation therapy with poly (ADP-ribose) polymerase (PARP) inhibition has been shown to enhance anti-tumor efficacy through potentiating DNA damage in tumor cells. In this phase I study, we combined low dose fractionated whole abdominal radiation (LDFWAR) with escalating doses of veliparib (ABT-888), an orally available, small molecule PARP inhibitor, in patients (pts) with peritoneal carcinomatosis from advanced solid tumor malignancies. **Methods:** Pts were treated with escalating doses of veliparib, starting at 40mg PO BID on days 5-21 of the first 28-day cycle and on days 1-21 of the subsequent 2 cycles. LDFWAR consisted of 21.6Gy in 36 fractions, 0.6 Gy twice daily on days 1 and 5 for weeks 1-3 of each cycle. Circulating tumor cells (CTCs) were serially collected. Quality of life (QoL) was assessed using the EORTC-QLQ-C30 questionnaire. **Results:** 22 pts were treated. Treatment-related gr3 and 4 toxicites included lymphopenia (68%), anemia (9%), thrombocytopenia (14%), neutropenia (4%), leukopenia (9%), ascites (4%), vomiting (4%) and dyspnea (4%). Of 21 pts evaluable for response, disease stabilization (≥24 wks) was observed in 7 (33%) patients. Median progression free survival (PFS) was 4.7 months and overall survival (OS) was 15.5 months. In the subset of 8 ovarian and fallopian cancers (OV), median PFS was 6.9 months and OS was 17.6 months compared to PFS 2.9 months and OS 13.4 months in others. QoL data assessed at baseline and after cycle 2 showed no significant worsening with dose escalation. Pts with OV had better QoL over time than those with other cancers. Lower baseline CTCs trended towards improved OS. **Conclusions:** The combination of veliparib and LDFWAR is a well-tolerated regimen that results in remarkable disease stability in a refractory, pretreated pt population with advanced solid tumors and carcinomatosis, particularly in the OV subpopulation. Clinical trial information: NCT01264432.

| | Durable disease stability (≥24wk) No. pts (%) | PFS median, months (95% CI) | OS median, months (95% CI) |
|---|---|---|---|
| All patients (n=21) | 7/21 (33) | 4.6 | 15.5 |
| Ovarian (n=8) | 4/7 (57) | 6.9 | 17.6 |
| Non-ovarian (n=13) | 3/14 (21) | 2.9 | 13.4 |

**4140 General Poster Session (Board #227), Sat, 8:00 AM-11:45 AM**

**Cancer of unknown primary in adolescents and young adults: Clinicopathologic features, prognostic factors, and survival outcomes.** *Presenting Author: Kanwal Pratap Singh Raghav, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Cancer in adolescents and young adults (AYAs) (15-39 yrs) is increasingly recognized as a distinct clinical and biological entity. Cancer of unknown primary (CUP) although rare in young adults, poses a complex and unique challenge. Our study describes clinicopathologic features and outcomes in AYA-CUP patients (pts). **Methods:** We performed a retrospective review of 47 AYA pts diagnosed with CUP at The Univ. of Texas, MD Anderson Cancer Center, between 6/2006 and 6/2013. Data on demographics, imaging, pathology and treatment was collected from a prospectively maintained CUP database. Kaplan-Meier product limit method was used to estimate median overall survival (OS) and log-rank test was used for comparison. Cox proportional hazards model was used for multivariate analysis. **Results:** Median age was 35 years (19–39 yrs). Pts had comprehensive workup (CT 100%); PET scan, upper endoscopy, colonoscopy and mammography was performed in 60%, 51%, 47% and 40% pts, respectively; none yielding a primary diagnosis. Adenocarcinoma was the predominant histology (70%) with a median of 9 immunostains (range 2–29). Most common putative primary (tissue of origin) was biliary profile based on clinicopathologic parameters as well as gene expression profiling. Patients presented with a median of 2 metastatic sites, most common being lymph node (60%), lung (47%), liver (38%) and bone (34%). Systemic chemotherapy used included gemcitabine, fluorouracil, taxanes and platinum agents. Median OS for the entire cohort was 9.9 months. On multivariate analysis, elevated LDH (HR 3.86; 95%CI 1.58-9.44; P=0.003) and multiple metastatic sites (2 sites: HR 4.45; 95%CI 1.05-18.9; P=0.043; 3 or more sites: HR 8.5; 95%CI 1.9-37.9; P = 0.001) compared to 1 site were associated with poor OS. Culine CUP prognostic model (performance status, liver metastasis, LDH) was validated in this cohort (median OS: good risk 25.2 months vs. poor risk 6.1 months). **Conclusions:** AYA-CUP is associated with a poor prognosis. In the current "-omics" era collaborative research efforts towards understanding tumor biology and therapeutic targets in AYA-CUP is an unmet need, necessary for improving outcomes in young CUP patients.

**4141 General Poster Session (Board #228), Sat, 8:00 AM-11:45 AM**

**Molecular classification of ampullary adenocarcinoma: Comparative prognostic performance of the 92-gene assay versus histomolecular analysis.** *Presenting Author: Aaron Schueneman, MD Anderson Cancer Center, Houston, TX*

**Background:** As distinct epithelia coalesce within the ampulla (duodenal, pancreatic, and biliary), the exact epithelial origin of ampullary carcinomas remains unclear and in part contributes to the clinical heterogeneity for these cancers. Differential expression of CDX2 and MUC1 along with histological subtype [intestinal (INT), pancreaticobiliary (PB), and mixed] have been used to subclassify ampullary tumors by histomolecular phenotype (Chang et al. JCO 2013). We compared the ability of a 92-gene RT-PCR Assay (CancerTYPE ID, bioTheranostics. Inc.) and histomolecular phenotype to prognostically stratify ampullary adenocarcinomas. **Methods:** In this prospectively-defined, blinded study, ampullary adenocarcinoma samples (N=77) were evaluated by the 92-gene assay and histomolecular phenotype. A total of 54 ampullary adenocarcinomas were compared after the exclusion of 23 samples that failed QC. A reference diagnosis was established by independent histopathological review prior to sample blinding. Relapse-free survival (RFS) and overall survival (OS) for patients were evaluated by Kaplan-Meier analysis with log-rank P-values. **Results:** For tumor subtyping, the sensitivity of the 92-gene assay and histomolecular classification were similar for the intestinal subtype, however the 92-gene assay demonstrated higher sensitivity for the Pb subtype (P=0.045). While the 92-gene assay was prognostic for both RFS (HR=2.81, P=0.02) and OS (HR=2.49, median OS 114 m vs. 36.4 m, P=0.03), histomolecular classification failed to demonstrate a significant difference in RFS (HR = 1.02, P=0.96) or OS (HR=1.07, P=0.87). Stratification of the cohort to include lymph node status revealed three distinct prognostic groups for ampullary subtypes predicted by the 92-gene Assay (P=0.04), but not for histomolecular phenotype (P=0.39). **Conclusions:** Molecular classification of ampullary adenocarcinomas into intestinal and pancreaticobiliary subtypes is prognostically relevant and may have therapeutic implications. Further validation of this novel 92-gene assay in comparison to histomolecular phenotype in a larger ampullary adenocarcinoma dataset is needed.

**4142 General Poster Session (Board #229), Sat, 8:00 AM-11:45 AM**

**Comprehensive genomic profiling of gallbladder adenocarcinoma and frequent genomic-derived targets of therapy.** *Presenting Author: Phil Stephens, Foundation Medicine, Inc., Cambridge, MA*

**Background:** Metastatic gallbladder adenocarcinoma (GBCA) has a poor prognosis and systemic therapies are commonly extrapolated from those used in other gastrointestinal malignancies. In this study, next generation sequencing-based comprehensive genomic profiling of 83 clinical GBCA samples was performed to identify genomic-derived targets of therapy for patients with this lethal cancer. **Methods:** Hybridization capture of 3,769 exons from 236 cancer-related genes and 47 introns of 19 genes commonly rearranged in cancer was applied to ≥ 50ng of DNA extracted from 83 GBCA FFPE specimens and sequenced to high, uniform coverage. Potentially actionable alterations were defined as those identifying anti-cancer drugs on the market or in registered clinical trials. **Results:** Sequencing was performed on 34 primary and 49 metastatic GBCA biopsies, Grade I/II/III, 5, 55 and 23 cases, respectively. A total of 329 alterations were identified with an average of 4.0 alterations per tumor (range 1-15). The most frequently altered genes were: *TP53* (63%), *CDKN2A* (49%), *ARID1A* (18%), *ERBB2* (17%), *PIK3CA* (12%), *SMAD4* (11%) and *CCNE1* (11%). Forty-three additional genes were altered in multiple cases including: *BRCA2*, *CCND1*, *ERBB3*, *EGFR*, *FGFR3*, *GNAS*, *KRAS*, *MET*, *NF1*, *NF2*, *NRAS, PDGFRA*, *PTEN*, *STK11* and *TSC2*. One case of *FGFR3-TACC* fusion gene was noted. At least one alteration associated with agents that are FDA approved or being studied in clinical trials was identified in 71/83 (86%) of cases. Clinical follow up of a small subset of patients to date, revealed two patients with focal amplification of *EGFR* and *ERBB2* had sustained PR with erlotinib and trastuzumab, respectively. **Conclusions:** This is the largest known series of GBCA cases analyzed using next generation sequencing-based genomic profiling. The long tail of genomic-derived targets of therapy identified, necessitate broad diagnostic assays capable of accurately profiling tumors from limited biopsy material to maximize targeted treatment options. Our results indicate that genomic profiling can identify clinically meaningful alterations that can potentially guide targeted treatment decisions in the majority of patients with this orphan tumor.

**4143 General Poster Session (Board #230), Sat, 8:00 AM-11:45 AM**

**Potential actionable targets in appendiceal cancer detected by immunohistochemistry (IHC), fluorescent in situ hybridization (FISH), and mutational analysis.** *Presenting Author: Erkut Borazanci, TGen - Virginia G. Piper Cancer Center at Scottsdale Healthcare, Scottsdale, AZ*

**Background:** Appendiceal cancers are rare and consist of carcinoid, mucocele, pseudomyxoma peritonei, goblet cell carcinoma, lymphoma, and adenocarcinoma histologies. Current treatment involves surgical resection or debulking, but no standard exists for adjuvant chemotherapy or treatment for metastatic disease. **Methods:** Samples were identified from 60,000 global tumors analyzed at a referral molecular profiling CLIA-certified laboratory. 460 samples with appendix primary tumor sites were identified (male/female ratio of 2:3; mean age = 55). 62% of samples were adenocarcinomas (used for analysis); the rest consisted of 9% goblet cell, 15% mucinous; 6% pseudomyxoma, and less than 5% carcinoids and 2% neuroendocrine. Tests included sequencing (Sanger or next generation sequencing [NGS]), protein expression (immunohistochemistry [IHC]), and gene amplification (FISH or CISH). **Results:** % positive of total adenocarcinoma cohort are shown (see Table). **Conclusions:** Appendiceal adenocarcinomas show high levels of drug resistance proteins (BCRP and MRP1), which highlight the difficulty in treating these tumors and suggest an individualized approach to treatment. Therapeutic options include TOPO1 inhibitors (irinotecan/topotecan), PDGFR antagonists (regorafenib, axitinib), MGMT (temozolamide), and SPARC (nab-paclitaxel). These findings indicate the need to evaluate patient samples for patterns in marker expression and alteration, in order to better understand the molecular biology and formulate a personalized therapy approach in these difficult to treat cancers (supported by a grant from Caris Life Sciences).

| IHC (n=296) | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| BCRP | cKIT | cMET | EGFR | ERCC1 | MGMT | MRP1 | PDGFR | PGP | PTEN | RRM1 | SPARC | TLE3 | TOP2A | TOPO1 | TS | TUBB3 |
| 97 | 18 | 40 | 47 | 42 | 71 | 85 | 31 | 54 | 52 | 28 | 38 | 9 | 38 | 56 | 22 | 32 |
| Seq (n=54) | | | | | | | | | | | | | | | | |
| APC | | ATM | | FBXW7 | | GNAS | | KRAS | | PIK3CA | | SMAD4 | | TP53 | | |
| 11 | | 7 | | 6 | | 18 | | 52 | | 6 | | 20 | | 28 | | |

**TPS4144 General Poster Session (Board #231A), Sat, 8:00 AM-11:45 AM**

**NeoSCOPE: A phase II randomized comparison of neoadjuvant oxaliplatin/capecitabine versus carboplatin/paclitaxel-based chemoradiation in operable esophageal cancer.** *Presenting Author: Thomas Crosby, Velindre Hospital NHS Foundation Trust, Cardiff, United Kingdom*

**Background**: Both oxaliplatin/capecitabine-based chemoradiation (OXCAP-RT) and carboplatin-paclitaxel based radiation (CarPac-RT) are active regimens in oesophageal cancer, but no randomized study has compared their efficacy/toxicity. This study compares the two regimens to identify the optimum regimen to take forward to a phase III trial against neo-adjuvant chemotherapy, the current standard in the UK. **Methods**: Eligibility: Resectable adenocarcinoma of oesophagus and Type 1-2 Gastro-Osophageal Junction; ≥T3 and/or ≥N1 staged with EUS and PET-CT; PS 0-1. Intervention: Both arms receive 2 cycles induction OXCAP (oxaliplatin 130mg/m2 D1, Cape 625mg/m2 D1-21, q 3wk) followed by randomization to OXCAP-RT (oxali 85mg/m2 Day 1,15,29; cape 625mg/m2 on days of RT; RT-45Gy/25 fractions/5weeks) or CarPac-RT (Carbo AUC2 and paclitaxel 50mg/m2 Day 1,8,15,22,29; RT-45Gy/25 fractions/5weeks). Restaging CT/PET-CT 4-6 weeks after CRT, and 2-phase oesophagectomy with 2-field lymphadenectomy 6-8 weeks after CRT. Primary End-Point: Pathological complete response. Secondary: 1) Feasibility of recruitment; Toxicity; 30-day surgical morbidity/mortality; resection margin positivity rate; median, 3- and 5-yr OS. Statistics: Randomised phase II with 1:1 randomisation; planned accrual 76 patients (38/arm) over 18 months. In each arm, this sample size gives 90% power and one-sided type 1 error of 10% to detect that pCR is not <15% but could be >35%. Interim safety analysis: Toxicity analysis after 10 patients have completed treatment. RT Quality Assurance: Pre-trial: Detailed RT protocol and guidance document, RT workshop, central evaluation of test-case contours and adequacy of RT plan. On-trial: Real-time central review of contours and plans of first 20 patients on trial, 1st case from each centre, and 10% of cases selected at random. Current Status: Activation: September 2013; Centres open: 10, in set-up:10; Recruitment: 13. Funding: Cancer Research UK. Sponsor: Velindre NHS Trust. Trials Unit: Wales Cancer Trials Unit. Eudract No: 2012-000640-10. Clinical trial information: NCT01843829.

**TPS4145 General Poster Session (Board #231B), Sat, 8:00 AM-11:45 AM**

**ICORG 10-14: Neo-AEGIS: A randomized clinical trial of neoadjuvant and adjuvant chemotherapy (modified MAGIC regimen) versus neoadjuvant chemoradiation (CROSS protocol) in adenocarcinoma of the esophagus and esophagogastric junction.** *Presenting Author: Niamh Keegan, St. James's Hospital, Dublin, Ireland*

**Background:** Neoadjuvant therapy is increasingly the standard of care in the management of locally advanced adenocarcinoma of the esophagus and junction (AEG). The MAGIC and CROSS regimens were superior to surgery only in randomized controlled trials (RCTs) that included AEG but were not powered on this cohort, and no completed RCT has directly compared neoadjuvant chemotherapy and chemoradiation. This trial, uniquely powered on AEG, and including comprehensive modern staging, compares both these Level I regimens. **Methods:** This open label, phase III RCT randomizes patients in a 1:1 fashion to receive either pre and postoperative chemotherapy as per the MAGIC regimen [Etoposide, Cisplatin, Fluorouracil (Capecitabine)] or neoadjuvant chemoradiation as per the CROSS protocol (Carboplatin and Paclitaxel with concurrent radiotherapy, 41.4Gy/23Fr, over 5 weeks). The power calculation is a 15% difference in 3 year overall survival, power at 80%, two-sided alpha level of 0.05, requiring 366 subjects over a five year period, with analysis performed one year after last subject recruited. Eligibility includes: AEG, types I, II, and III, staged (CT-PET and EUS) as cT2-3, N0-3, M0 and surgically resectable, with good performance status and no major co-morbidities. The primary endpoint is overall survival, with a minimum 3 year follow up. Secondary endpoints include: disease free survival, recurrence rates, clinical and pathological response rates, toxicities of induction regimens, post-operative pathology and tumor regression grade, operative in-hospital complications, and health-related quality of life. Pre-treatment bio-resourcing of tumor and blood will enable correlative translational studies. Conduct to Date: The trial activated in February 2013 at the national center in Ireland, 35 patients are randomized to date. Other centers in Ireland and Europe will commence in 2014. Clinical trial information: NCT01726452.

**TPS4146 General Poster Session (Board #232A), Sat, 8:00 AM-11:45 AM**

**A phase III clinical trial of neoadjuvant chemoradiotherapy followed by surgery versus surgery alone for locally advanced squamous cell carcinoma of the esophagus.** *Presenting Author: Hong Yang, Sun Yat-Sen University Cancer Center, Guangzhou, China*

**Background:** Surgery is the main treatment of esophageal squamous cell carcinoma (ESCC), but the prognosis of patients with locally advanced ESCC is rather poor. Preoperative chemoradiotherapy followed by surgery seems to hopefully improve the survival of ESCC. Nevertheless, the results of different studies were inconsistent. We are to carry out a phased III clinical trial to investigate the effect of this multidisciplinary therapy for the overall survival of patients with locally advanced ESCC. **Methods:** This study is a multi-centered randomized controlled phase III clinical trial. According to Sixth Edition AJCC Cancer Staging, patients with IIB-III staged squamous cell carcinoma of the thoracic esophagus are randomly allocated to either preoperative chemoradiotherapy followed by surgery (arm A), or surgery alone(arm B). The intended number of randomized patients will be 430, 215 per arm. In the arm A, Chemotherapy and radiotherapy are performed concurrently. Patients received two cycles of vinorelbine and cisplatin. Vinorelbine at 25 mg/m$^2$ per day is administered in bolus infusion on d1, d8, d22 and d29. Cisplatin at 75 mg/m$^2$ is administered by intravenously infusion on d1 and d22 (or 25 mg/m$^2$days 1 to 4 and 22 to 25). A total radiotherapy dose of 40 Gy is delivered in 20 daily fractions of 2.0 Gy each (given 5 d/wk for 4 weeks). McKeown esophagectomy or Ivor Lewis esophagectomy will be performed 4-6 weeks after chemoradiotherapy. Two-field lymphadenectomy with total mediastinal lymph node dissection is performed during sugery. Primary outcomes are 3 and 5 years overall survival. From 2007 July to 2013 December, over 300 eligible patients were randomly assigned in eight cooperative cancer centers. The patient enrollment will be completed in 2014. Clinical trial information: NCT01216527.

**TPS4147 General Poster Session (Board #232B), Sat, 8:00 AM-11:45 AM**

**JAGUAR: A randomized phase II study of the AKT inhibitor ipatasertib (GDC-0068) versus placebo in combination with mFOLFOX6 chemotherapy in patients (pts) with locally advanced or metastatic HER2-negative gastric (G) or gastroesophageal junction (GEJ) adenocarcinoma.** *Presenting Author: Yung-Jue Bang, Department of Internal Medicine and Cancer Research Institute, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea*

**Background:** Activation of PI3K/Akt signaling occurs in greater than 60% of G/GEJ cancers by decreased PTEN and/or mutations or amplifications of *PIK3CA*, and may contribute to chemoresistance. Pts with G/GEJ cancers that have PI3K/Akt activation have been reported to have poor prognosis and decreased overall survival. Ipatasertib (GDC-0068) is an oral, potent ATP-competitive small molecule inhibitor of all three isoforms of Akt that specifically targets cancer cells with activated Akt. In preclinical models, ipatasertib synergistically combines with fluorouracil (5-FU) and platinum chemotherapy. In Phase Ib clinical studies, the combination of ipatasertib and mFOLFOX6 chemotherapy is well-tolerated; the most commonly reported adverse events associated with ipatasertib are grade 1-2 diarrhea, nausea, vomiting, fatigue, and decreased appetite. RECIST responses and prolonged stable disease were seen with the combination, including pts with tumors having PI3K/Akt activation. **Methods:** JAGUAR is a randomized, double-blind, placebo-controlled, global Phase II study in pts with previously untreated locally advanced or metastatic G/GEJ cancers. Approximately 120 patients with measurable HER2-negative or HER2-unknown G/GEJ cancer will be randomized (1:1) to receive mFOLFOX6 plus ipatasertib or mFOLFOX6 plus placebo. Patients will be stratified by PTEN status. A maximum of 8 cycles of mFOLFOX6 are permitted, and ipatasertib or placebo in combination with 5-FU and leucovorin will be continued until disease progression or intolerable toxicity. The primary endpoint is progression free survival. Additional endpoints include overall survival, objective response rate, duration of response, safety, pharmacokinetics, and correlative biomarkers. This study is open for accrual. Clinical trial information: NCT01896531.

**TPS4148 General Poster Session (Board #233A), Sat, 8:00 AM-11:45 AM**

**Randomized open-label phase 2 study of MM-111 and paclitaxel (PTX) with trastuzumab (TRAS) in patients with HER2-expressing carcinomas of the distal esophagus, gastroesophageal (GE) junction, and stomach who have failed front-line metastatic or locally advanced therapy.** *Presenting Author: Crystal Shereen Denlinger, Fox Chase Cancer Center, Philadelphia, PA*

**Background:** HER2 overexpression occurs in $\leq$ 20% of GE cancers, and front-line fluoropyrimidine/platinum with TRAS increases survival in HER2+ GE junction/gastric cancer patients. Weekly PTX has activity after front-line therapy in GE cancers. HER3 is overexpressed in $<$ 87% of GE cancers and expression is associated with poor prognosis. HER3 is activated by its ligand, heregulin, to form a potent signaling heterodimer with HER2 and is emerging as a key tumorigenic node and mediator of drug resistance. MM-111 is a novel molecule that inhibits heregulin-activated HER3 signaling in HER2+ tumors. In preclinical gastric cancer models, MM-111 potentiates the antitumor activity of TRAS and PTX, and also mitigates HER3-mediated resistance. MM-111 has been combined with PTX and TRAS in a multi-arm, dose escalation phase 1 trial. Most common dose-limiting toxicities include myelosuppression, GI toxicities, and electrolyte abnormalities. **Methods:** This is a randomized open-label multi-center Phase 2 study of PTX and TRAS +/- MM-111 in patients with HER2 expressing advanced GE adenocarcinoma. Arms are stratified for prior TRAS exposure, geographic region, and ECOG performance status. Patients are dosed with PTX at 80 mg/m$^2$ on days 1, 8, and 15 of a 28 day cycle; TRAS at 4 mg/kg loading dose then 2 mg/kg/weekly and MM-111 at 20 mg/kg/weekly. Pretreatment tumor biopsies and archived tumor tissue will be collected to explore the correlation of biomarkers associated with HER2, HER3 and heregulin signaling activity (1) between archived and pretreatment samples and (2) with clinical response. The primary objective is progression-free survival. Secondary objectives are overall survival, time to treatment failure, objective response rate, duration of response, safety, and health-related quality of life. Pharmacokinetic and immunogenicity analysis of MM-111 will be performed. Enrollment is ongoing. Clinical trial information: NCT01774851.

**TPS4149 General Poster Session (Board #233B), Sat, 8:00 AM-11:45 AM**

**Randomized phase III study of gemcitabine plus S-1 combination therapy versus gemcitabine plus cisplatin combination therapy in advanced biliary tract cancer: A Japan Clinical Oncology Group study (JCOG1113).** *Presenting Author: Chigusa Morizane, Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan*

**Background:** Gemcitabine plus cisplatin (GC) therapy is the standard of care for advanced biliary tract cancer (BTC). However, GC is considered to be toxic because of nausea, vomiting, appetite loss and inconvenient due to requiring hydration before and after cisplatin administration. Our previous JCOG0805 trial, a randomized phase II selection design study of gemcitabine plus S-1 combination therapy (GS) vs. S-1, demonstrated superiority of GS over S-1 in terms of 1-year survival with acceptable toxicity profile and showed GS to be a more promising regimen. This phase III study aims to confirm the non-inferiority of GS to GC in terms of overall survival in patients with recurrent or unresectable BTC. **Methods:** Eligibility criteria include chemotherapy-naïve patients with recurrent or unresectable biliary tract adenocarcinoma (gallbladder, intrahepatic biliary tract, extrahepatic biliary tract, or ampulla of Vater), an Eastern Cooperative Oncology Group performance status of 0–1, and adequate organ function. Eligible patients are randomized into either GC arm or GS arm. In the GS arm, 1000 mg/m$^2$ of gemcitabine is infused on days 1 and 8, and 30 mg/m$^2$ of S-1 is administered orally twice a day from days 1 to 14; the regimen is repeated every 3 weeks. In the GC arm, 1000 mg/m$^2$ of gemcitabine and 25 mg/m$^2$ of cisplatin are infused on days 1 and 8 and repeated every 3 weeks. The primary endpoint is overall survival and the secondary endpoints are progression-free survival, %response rate, %planned dose, adverse events, clinically relevant adverse events defined as any of grade 2 or more fatigue, appetite loss, nausea, vomiting, mucositis, diarrhea, and serious adverse events. The sample size was calculated to be 350 (175 patients per arm), with a one-sided alpha of 5%, a power of $>$=80%, assumed median survival time of 11.2 months in GC and of 13 months in GS, an non-inferiority margin of 1.155 in terms of hazard ratio, an accrual period of 4 years, and a follow-up period of 1 year. Twenty-eight institutions are participating in this study. The study was activated in May 2013. Clinical trial information: UMIN000010667.

**TPS4150 General Poster Session (Board #234A), Sat, 8:00 AM-11:45 AM**

**Phase 3 randomized, double-blind, controlled study of cabozantinib (XL184) versus placebo in subjects with hepatocellular carcinoma who have received prior sorafenib (CELESTIAL; NCT01908426).** *Presenting Author: Ghassan K. Abou-Alfa, Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

**Background:** Currently, there are no approved systemic therapies for patients with advanced hepatocellular carcinoma (HCC) who fail sorafenib. Cabozantinib is an oral receptor tyrosine kinase inhibitor (TKI) with activity against tyrosine kinases including MET, RET and VEGFRs. MET and VEGFR signaling have been implicated in tumor neo-angiogenesis and invasion. MET is overexpressed in HCC compared with non-tumor liver tissue, with higher MET expression linked to poor prognosis. Cabozantinib prolonged survival in a MET-driven transgenic mouse model of HCC, and has demonstrated clinical activity in multiple solid tumor types, including 41 subjects with advanced HCC treated in a phase 2 randomized discontinuation study. **Methods:** This phase 3, randomized, double-blind study evaluates the efficacy and safety of cabozantinib compared with placebo in subjects with advanced HCC previously treated with sorafenib and have progressed following 1-2 prior systemic treatments for HCC. Subjects must be $\geq$ 18 year old, have Child-Pugh Score of A and ECOG PS $\leq$ 1. Subjects are randomized 2:1 to receive either cabozantinib or placebo. Stratification factors are etiology of disease, geographic region and the presence of extrahepatic spread of disease and/or macrovascular invasion. The primary endpoint is overall survival. Secondary endpoints are progression-free survival and objective response rate by RECIST 1.1. Additional endpoints include safety, tolerability, circulating tumor cells, serum bone markers and plasma biomarkers, effects on bony disease assessed by bone scan and health-related quality of life (HRQoL) using the EuroQol Health questionnaire (EQ-5D-5L). Enrollment was initiated in September 2013. Target recruitment is 760 subjects. A total of 621 events planned with 2 interim analyses (at 311 and 466 events) would provide 90% power to detect a 31.6% increase in OS (HR=0.76). Clinical trial information: NCT01908426.

**TPS4151 General Poster Session (Board #234B), Sat, 8:00 AM-11:45 AM**

**A multicenter, randomized, phase Ib/II trial of the oral c-Met inhibitor MSC2156119J as monotherapy versus sorafenib in Asian patients with MET-positive (MET+) advanced hepatocellular carcinoma (HCC) and Child-Pugh Class A liver function.** *Presenting Author: Shukui Qin, Medical Oncology Department, Nanjing Bayi Hospital, Nanjing, China*

**Background:** Patients (pts) with HCC have a poor prognosis. Effective treatments are limited, particularly in Asia, which carries about 80% of the HCC burden. In a Phase I trial (Falchook et al. *J Clin Oncol* 2013:31(Suppl): 2506), the highly selective c-Met inhibitor MSC2156119J showed promising antitumor activity and a recommended Phase II dose was determined (RP2D; 500 mg/d). This Phase Ib/II, multicenter, open-label trial evaluates the efficacy of MSC2156119J monotherapy in first-line treatment vs sorafenib in pts with MET+ advanced HCC (NCT01988493). **Methods:** Primary objectives are to confirm the RP2D of 500 mg MSC2156119J in HCC pts (Phase Ib) and to assess efficacy of MSC2156119J monotherapy vs sorafenib, as determined by time to progression (TTP) per independent read (Phase II). Secondary objectives include pharmacokinetics, preliminary antitumor activity of MSC2156119J (Phase Ib), safety, tolerability, and antitumor activity of MSC2156119J vs sorafenib (Phase II: progression-free survival and TTP per investigator read, overall survival, time to symptomatic progression, objective response, and disease control). Adults with confirmed, advanced HCC of BCLC Stage C, Child-Pugh Class A liver function, life expectancy >3 mo, and ECOG status 0–2 (Phase II only: MET+, defined as moderate or strong protein overexpression determined by immunohistochemistry, eligible for sorafenib treatment, and measurable disease according to RECIST v1.1) are recruited in mainland China, South Korea, Taiwan, and other Asian countries. Key exclusion criteria: prior treatment with a c-Met/HGF pathway-targeting agent or systemic anticancer therapy (Phase II only), history of liver transplant or neoplasms other than HCC, impaired cardiac function, and chronic gastrointestinal disease. Up to 18 pts are planned for the Phase Ib part (3+3 design; 300 or 500 mg MSC2156119J p.o./d; 21-d cycle). In the Phase II part, 140 pts are planned to be randomized 1:1 to receive either MSC2156119J at the RP2D p.o./d or 400 mg sorafenib p.o./twice daily (21-d cycle). Enrollment began on Jan 9, 2014. Clinical trial information: NCT01988493.

**TPS4152 General Poster Session (Board #235A), Sat, 8:00 AM-11:45 AM**

**A randomized controlled trial comparing modified gemcitabine plus oxaliplatin (mGEMOX) to gemcitabine plus cisplatin in management of unresectable gall bladder cancer.** *Presenting Author: Atul Sharma, All India Institute of Medical Sciences, New Delhi, India*

**Background:** Gemcitabine and platinum compound have become preferred regimen for treatment of advanced/unresectable gall bladder cancer (Best supportive care compared with chemotherapy for unresectable gall bladder cancer:A randomized controlled study. Sharma A, Dwary A D, Mohanti B K,et al. *J Clin Oncol*. 2010; 28: 4581-4586; Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. J W Valle, H S Wasan, D D Palmer, et al. *N Eng J Med*. 2010; 362:1273-81). This ongoing equivalence study has been planned to see whether the combination of gemcitabine and oxaliplatin (mGEMOX) is equivalent to gemcitabine and cisplatin (GemCis). **Methods:** Primary end point of the study is overall survival in subjects receiving mGEMOX or GemCis regimen. Secondary end points are: A-Comparison of progression free survival in 2 groups, B- Response rates in two groups,C-Identification of genes predictive of responses in a subset of patients, D-To evaluate role of PET CT in GBC patients predicting disease activity Sample size was calculated taking median survival of 9.5 months in our previous study with mGEMOX and 11.7 months with GemCis. For this total of 216 patients are required (108 in each arm); to make for major protocol violation and lost to follow up additional 22 patients in each arm will be enrolled. Thus in total 260 patients (130) in each arm will be recruited. This will have alpha and beta values of 0.05 and 0.20 respectively. So far 152 patients have been enrolled. Treatment protocol: Cycles will be repeated every 3 weeks Arm A- mGEMOX Inj Oxaliplatin 80 mg/m$^2$ 2 hours infusion in Dextrose 5% Day 1 and 8 Inj Gemcitabine 900 mg/m$^2$ IV 30 minutes infusion day1 and 8 maximum of 6 cycles Arm B-GEMCIS Inj Cisplatin 25 mg/m$^2$ PO Days 1 and 8 Inj Gemcitabine 1,000 mg/m$^2$ IV 30 minutes infusion day 1 and 8 maximum of 8 cycles. Clinical trial information: CTRI/2010/091/001406.

**TPS4153 General Poster Session (Board #235B), Sat, 8:00 AM-11:45 AM**

**A multicenter, open-label, phase 3 trial to compare the efficacy and safety of lenvatinib (E7080) versus sorafenib in first-line treatment of subjects with unresectable hepatocellular carcinoma.** *Presenting Author: Richard S. Finn, Geffen School of Medicine at UCLA, Los Angeles, CA*

**Background:** Lenvatinib (L, E7080) is an oral multi-targeted tyrosine kinase inhibitor of VEGFR1-3, FGFR1-4, PDGFR$\beta$, RET and KIT. Given the role of angiogenesis in hepatocellular carcinoma (HCC), a phase 1/2 open-label study evaluated the safety and efficacy of L in 46 patients with advanced disease and Childs-Pugh (CP) A liver function status (Kudo ILCA 2013). Patients were treated with a starting dose of L 12 mg qd (28-d cycles) until disease progression or development of unmanageable toxicities. Median time to progression (TTP) was 12.8 months (mo; 95% confidence interval [CI] 7.23–14.7) and median overall survival (OS) was 18.7 mo (95% CI 12.8–25.1). The most common adverse events were hypertension 76% (Gr3 54%), palmar-plantar erythrodysesthesia syndrome 61% (Gr3 7%), proteinuria 59% (Gr3 20%), anorexia 57% (Gr3 2%), thrombocytopenia 50% (Gr3 33%), and fatigue 48% (Gr3 0%). Overall response rate (ORR) was 37%; 45.7% had stable disease. **Methods:** Based on these phase 2 data, a global, randomized, open-label phase 3 trial was designed to determine if L is non-inferior or superior compared to sorafenib (S) in advanced HCC. Eligible patients (N=940) with Barcelona Clinic Liver Cancer Stage B or C HCC, CP A status, and ECOG 0-1 will be randomized 1:1 to either L 12 mg or 8 mg orally qd (based on body weight [BW]) or S 400 mg orally bid. Patients will be stratified by region; macroscopic portal vein invasion, extrahepatic spread, or both; ECOG-PS; and BW ($<$60 vs $\geq$60 kg). The primary endpoint is OS. Secondary endpoints include progression-free survival, TTP, ORR (modified RECIST criteria), safety and PK/PD. Given an estimated median OS for S of approximately 10 mo, a 2.5 mo improvement was derived to achieve a hazard ratio (HR) of 0.8. Statistical study power (using a non-inferiority test by the 95% CI lower-limit method on log HR for OS) was determined based on this HR and a non-inferiority margin of 1.08, corresponding to 60% retention of S effect vs placebo. Based on these assumptions, the study power to declare non-inferiority or superiority is approximately 97% and 82%, respectively. The overall false positive rate is 0.05 (2-sided). Clinical trial information: NCT01761266.

**TPS4154 General Poster Session (Board #236A), Sat, 8:00 AM-11:45 AM**

**Sorafenib in combination with local microtherapy guided by gadolinium-EOB-DTPA enhanced MRI in patients with inoperable hepatocellular carcinoma (SORAMIC).** *Presenting Author: Jens Ricke, Otto von Guericke University of Magdeburg, Magdeburg, Germany*

**Background:** Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality with an increasing incidence. For the individual patient tumor stage , liver function and general health status are the principal prognostic factors. The clinical management of HCC requires a comprehensive, multidisciplinary approach. In early HCC curative treatment can be achieved by local ablation, resection or liver transplantation. In intermediate stages patients with HCC are offered locoregional treatment with palliative intent. Yttrium-90-radioembolisation (SIRT)) is currently evaluated in this setting with promising results. In advanced disease systemic therapy with sorafenib is standard of care in patients with preserved liver function. Studies on the combined use of locoregional and systemic therapy with their potential of a beneficial synergism are few and conducted in a small number of patients. The critical question is whether the combination is more benefit or more harm. **Methods:** This phase II-study is composed of three substudies with the following primary objectives: 1. In patients in whom local ablation is appropriate to determine if sorafenib in combination with RFA prolongs the time-to-recurrence in comparison with RFA plus placebo. Primary endpoint: time to recurrence, n = 290 patients 2. In patients in whom RFA is not appropriate (palliative treatment group) to determine if the combination of SIRT and sorafenib improves the overall survival in comparison to sorafenib alone. Primary endpoint: overall survival, n = 375 patients 3. To confirm in a 2-step procedure that Gd-EOB-DTPA enhanced MRI is non-inferior or superior compared with contrast-enhanced multislice CT for stratification of patients to a palliative or a local ablation treatment strategy. Primary endpoint: correct stratification of patients to a palliative versus local ablation treatment strategy; n = 830 patients The trial has started in December 2010 as a multinational and multicentric study. 349 patients have been enrolled until January 31$^{st}$ 2014 with 200 patients randomized in the palliative arm and 57 patients treated in the curative arm. Clinical trial information: 01126645.

**TPS4155 General Poster Session (Board #236B), Sat, 8:00 AM-11:45 AM**

**OPTIMIS: An international observational study to assess the use of sorafenib after transarterial chemoembolization (TACE) in patients with hepatocellular carcinoma (HCC).** *Presenting Author: Markus Peck-Radosavljevic, Medizinische Universitaet Wien, Vienna, Austria*

**Background:** TACE is currently recommended for the treatment of patients with intermediate-stage HCC (Barcelona Clinic Liver Cancer [BCLC] stage B). However, it remains unclear which patients are most likely to benefit from TACE, or when TACE should be stopped and alternative treatments considered. The multikinase inhibitor sorafenib is the only systemic therapy currently approved for the treatment of advanced HCC. The aim of this observational study is to prospectively collect data from patients with HCC who either receive or do not receive sorafenib subsequent to TACE. **Methods:** Patients are eligible if ≥18 years of age, have histologically/cytologically documented or radiographically diagnosed HCC classified as BCLC stage B or higher, have a life expectancy of ≥8 weeks, and a decision to treat with TACE has been made at the time of study enrollment (one prior TACE treatment is allowed if performed at the same center and all required data about the procedure are available). Treatment decisions made before a patient is enrolled, and during the observation period, must be according to investigators' regular practice. Exclusion criteria include any systemic anti-cancer therapy prior to the first TACE, or participation in an interventional study of locoregional or systemic therapy. The primary objective is evaluation of overall survival in patients who received sorafenib subsequent to TACE non-eligibility (early sorafenib) compared with those who did not (non-early sorafenib). The non-early sorafenib group includes patients who did not receive sorafenib or received it at a later point. Secondary objectives include progression-free survival, time to progression, tumor response, and safety. Planned enrollment is approximately 1600 patients from about 30 countries across Europe, Latin America, and Asia-Pacific, and from Canada. One interim analysis is planned once 500 patients have been observed for at least 6 months. Final analysis will be performed once the last enrolled patient has been followed for 18 months, has been lost to follow-up, or has died. The study began in October 2013 and 69 patients have been enrolled as of January 2014. Clinical trial information: NCT01933945.

**TPS4156^ General Poster Session (Board #237A), Sat, 8:00 AM-11:45 AM**

**RESORCE: An ongoing randomized, double-blind, phase III trial of regorafenib (REG) in patients with hepatocellular carcinoma (HCC) progressing on sorafenib (SOR).** *Presenting Author: Jordi Bruix, BCLC Group, Liver Unit, Hospital Clinic, University of Barcelona, Barcelona, Spain*

**Background:** No standard treatment options are available for patients with HCC that has progressed despite SOR treatment. The oral multikinase inhibitor REG has been shown to have an acceptable safety profile and evidence of antitumor activity in patients with SOR-pretreated HCC (Bruix *et al. Eur J Cancer* 2013): disease control was achieved in 26/36 patients (72%), and median time to progression (TTP) was 4.3 months; median overall survival (OS) was 13.8 months. On the basis of these results, a phase III trial was designed. **Methods:** This randomized, double-blind, placebo (Pbo)-controlled, multinational study (ClinicalTrials.gov identifier NCT01774344) will compare the efficacy and tolerability of REG *vs* Pbo in adults with HCC that has progressed on SOR. Inclusion criteria include Barcelona Clinic Liver Cancer stage B or C disease that cannot benefit from established treatments, Child–Pugh Class A liver function, and Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1. Patients discontinuing SOR >10 weeks before study entry or who received other previous systemic therapy for HCC will be excluded. Patients are randomized 2:1 to receive REG 160 mg or Pbo once daily for weeks 1–3 of each 4-week cycle; all patients also receive best supportive care. Treatment continues until disease progression, death, intolerable toxicity, or patient/investigator decision to stop. Doses of study drug may be delayed or reduced to manage clinically significant drug-related toxicities. The primary endpoint is OS; secondary endpoints are TTP, progression-free survival, objective tumor response, disease control, and safety. Analysis will be according to randomized group, stratified by geographic region (Asia *vs* rest of world), ECOG PS (0 *vs* 1), alfa-fetoprotein level (<400 *vs* ≥400 ng/ml), extrahepatic disease (yes *vs* no), and macrovascular invasion (yes *vs* no). In addition, blood, plasma, and archival tissue will be assessed for pharmacokinetic and biomarker analyses, and health-related quality of life will be measured. As of February 2014, 137 out of the planned 530 patients have been randomized. Clinical trial information: NCT01774344.

**TPS4157 General Poster Session (Board #237B), Sat, 8:00 AM-11:45 AM**

**A phase II trial of cabozantinib in patients with carcinoid and pancreatic neuroendocrine tumors.** *Presenting Author: Jason Edward Faris, Massachusetts General Hospital Cancer Center, Boston, MA*

**Background:** Neuroendocrine tumors are highly vascularized cancers. Sunitinib, a multitargeted tyrosine kinase inhibitor (TKI), whose targets include vascular endothelial growth factor receptors (VEGFRs) and stem-cell factor receptor (c-KIT), was recently approved for the treatment of patients with pancreatic neuroendocrine tumors (PNET). PNETs often express c-KIT, and more than half of PNET metastatic to lymph nodes or liver express MET, which is a putative mechanism of resistance to VEGF inhibitors. We are conducting a phase II trial of cabozantinib, a TKI with activity against VEGFRs, MET, RET, and KIT, which is approved for advanced medullary thyroid cancer. Cabozantinib has been demonstrated to inhibit development of hepatic metastases, with improved survival compared to VEGF inhibitor treatment in the RIP-Tag2 transgenic mouse model of PNET. **Methods:** The study is an open-label Phase II trial, with planned enrollment of 35 patients to each of two cohorts for patients with carcinoid and PNET. Eligible patients must have well or moderately differentiated tumors, and patients must be receiving or have progressed on octreotide if a carcinoid tumor. Patients receive 60mg of cabozantinib daily in 28-day cycles. The primary objective of this study is to evaluate the activity of cabozantinib in patients with PNET and carcinoid tumors as assessed by overall response rate (ORR). Secondary objectives include evaluation of progression free survival and overall survival, as well as correlative studies of circulating tumor cells and pro-angiogenic biomarkers at baseline and on-treatment. Imaging is performed every two cycles for the first three months, followed by every three cycles. For both cohorts, we hypothesize that cabozantinib will have an ORR≥12%. A sample size of 35 in each cohort achieves >80% power to detect a difference of 10% in ORR using a one-sided binomial test, with type I error of 3% and population proportion under the null hypothesis of 2%. Results and Conclusions: As of January 26, 2013, 31/70 (44%) of planned patients have been enrolled: 18 with carcinoid, and 13 with PNET. Clinical trial information: 01466036.

**TPS4158 General Poster Session (Board #238A), Sat, 8:00 AM-11:45 AM**

**NEONAX: Neoadjuvant plus adjuvant or only adjuvant nab-paclitaxel plus gemcitabine for resectable pancreatic cancer—A phase II study of the AIO Pancreatic Cancer Group.** *Presenting Author: Thomas Jens Ettrich, Ulm University Hospital, Ulm, Germany*

**Background:** Resectable pancreatic cancer still has an unfavourable prognosis. Neoadjuvant or perioperative therapies might improve the prognosis of these patients. Recently, two phase III trials demonstrated for the first time, a substantial improvement in overall response, PFS and OS in patients with metastatic pancreatic cancer compared to standard gemcitabine (FOLFIRINOX and nab-paclitaxel/gemcitabine). The combination of nab-paclitaxel/gemcitabine has a more favourable toxicity profile compared to the FOLFIRINOX protocol and appears applicable in a perioperative setting. **Methods:** NEONAX is a study for patients (to be enrolled: n=162) with resectable ductal adenocarcinoma of the pancreas ≤ T3 in two arms: Arm A (perioperative arm): 2 cycles nab-paclitaxel (125 mg/m2)/ gemcitabine (1000 mg/m2, d1, 8 and 15 of an 28 day-cycle) - tumor surgery - 4 cycles nab-paclitaxel/gemcitabine, Arm B (adjuvant only arm): tumor surgery - 6 cycles nab-paclitaxel/gemcitabine. NEONAX is an interventional, prospective, randomized, controlled, open label, two sided phase II study with an unconnected analysis of the results in both experimental arms against a fixed survival probability (38% at 18 month with adjuvant gemcitabine). The randomization (1:1) is eminent to achieve two comparable patient groups. Primary objective is DFS at 18 months after randomization. Key secondary objectives are 3-year OS and DFS, progression during neoadjuvant therapy and QoL. In the perioperative group tumor tissue will be collected prior to and post-surgery and subjected to microdissection and exome sequencing of tumor tissue. Tumor regression will be assessed both in the perioperative and the adjuvant group, respectively. In addition, circulating tumor-DNA will be analyzed in patients with the best and the worst responses to the neoadjuvant treatment Start of trial will be in II/2014 in 20 high-volume centers for pancreatic surgery in Germany. Clinical trial information: NCT02047513.

**TPS4159 General Poster Session (Board #238B), Sat, 8:00 AM-11:45 AM**

**A phase 2b, randomized, controlled, multicenter, open-label study of the efficacy and immune response of GVAX pancreas vaccine and CRS-207 compared to chemotherapy or to CRS-207 alone in adults with previously treated metastatic pancreatic adenocarcinoma (ECLIPSE Study).** *Presenting Author: Dung T. Le, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

**Background:** A heterologous prime-boost vaccination strategy using GVAX pancreas vaccine and CRS-207 is showing promise in patients with metastatic pancreatic adenocarcinoma (PDA). GVAX is composed of lethally-irradiated, allogeneic pancreatic cancer cells modified to express GM-CSF and induces a broad response against multiple tumor antigens. GVAX is given with low-dose cyclophosphamide (CY) to inhibit regulatory T cells. CRS-207 is live-attenuated *Listeria monocytogenes* engineered to express the tumor-associated antigen mesothelin. CRS-207 boosts responses against mesothelin and is unique in its capacity to stimulate both innate and adaptive immunity by activating T cells and NK cells. Results from a phase 2 study demonstrated the CY/GVAX plus CRS-207 combination improved overall survival (OS) compared to CY/GVAX alone (p-value<0.05; Le, GI ASCO 2014). **Methods:** This is a phase 2b study comparing CY/GVAX and CRS-207 to chemotherapy or to CRS-207 alone in adults with previously-treated metastatic PDA. Subjects will be enrolled in two cohorts: 150 subjects into a primary cohort of patients with at least two prior treatment regimens for metastatic disease (3$^{rd}$+ line) and 90 subjects into an exploratory cohort of patients with only one prior treatment regimen for metastatic disease (2$^{nd}$ line). Subjects will be randomized in a 1:1:1 ratio to receive either 2 doses of CY/GVAX and 4 doses of CRS-207 (Arm A), six doses of CRS-207 (Arm B) or physician's choice of select single-agent chemotherapy (Arm C). The primary objective is to compare OS in the primary cohort between Arms A and C. Secondary/exploratory objectives include: comparison of OS in both primary and exploratory cohorts between all treatment arms, assessment of safety and clinical responses (tumor assessments and CA19-9 levels) and correlation of *Lm*- and mesothelin-specific T cell and other immunological responses with OS, progression-free survival and best overall response. (Sponsor: Aduro BioTech, Inc.). Clinical trial information: NCT02004262.

**TPS4160 General Poster Session (Board #239A), Sat, 8:00 AM-11:45 AM**

**A phase 2, multicenter study of FOLFIRINOX followed by ipilimumab in combination with allogeneic GM-CSF transfected pancreatic tumor vaccine in the treatment of metastatic pancreatic cancer.** *Presenting Author: Rina Khatri Patel, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

**Background:** Combinatorial strategies aimed at priming tumor antigen-specific T cells while simultaneously blocking negative immune checkpoints may improve immunotherapy for immune tolerant cancers such as pancreatic adenocarcinoma (PDA). In a previously reported trial, concurrent administration of an allogeneic GM-CSF transfected pancreatic tumor vaccine and the cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibody, ipilimumab (IPI), which blocks an inhibitory signal on T cells resulted in both CT scan regressions and CA19-9 declines in heavily preteated patients. This proposal will test vaccine + IPI in patients with metastatic PDA who have stable disease (SD) with upfront FOLFIRINOX (5-FU/ irinotecan/oxaliplatin) chemotherapy. Integrating immunotherapy after upfront chemotherapy has several advantages. Chemotherapy can debulk the tumor and predispose cancer cells to cell death mediated by immune cells. Immunotherapy can take weeks to months to be effective and is therefore more likely to work in patients with SD. Vaccine + IPI showed promise in heavily pre-treated patients and giving it immediately after front line chemotherapy may improve activity. **Methods:** This is a phase 2, multicenter, randomized, controlled, open-label trial in patients with metastatic PDA who have SD after 8-12 doses of FOLFIRINOX. 92 patients will be randomized 1:1 to Arm A (vaccine + IPI) or Arm B (continue chemotherapy per standard of care). Patients on Arm A will receive vaccine + IPI (10mg/kg) every 3 weeks for 4 doses then every 8 weeks. The primary objective of the study is to compare the overall survival (OS) of Arm A vs Arm B. Secondary objectives include: assessment of safety, progression-free survival (PFS), immune-related PFS, duration of response, objective response rate by RECIST and immune-related response criteria, and tumor marker kinetics (CA 19-9). Exploratory objectives include: identification of predictors of response and toxicity using proteomic techniques, assessment of T cell responses and genomic and IHC analyses of tumor tissue. (FDA Office of Orphan Products Development, R01FD004819-01). Clinical trial information: NCT01896869.

**TPS4161 General Poster Session (Board #239B), Sat, 8:00 AM-11:45 AM**

**A phase 2, open-label study of rucaparib in patients with pancreatic cancer and a known deleterious BRCA mutation.** *Presenting Author: Susan M. Domchek, Basser Research Center for BRCA, University of Pennsylvania, Philadelphia, PA*

**Background:** Approximately 5% of unselected pancreatic cancer (PC) patients (pts), 10% of PC pts of Ashkenazi Jewish descent, and up to 19% of familial PC families, harbor a germline BRCA mutation. PARP inhibitors (PARPi) have exhibited clinical activity in pts with a BRCA mutation. Rucaparib, an oral PARPi, is being developed for treatment of cancers associated with homologous recombination repair (HRR) deficiency due to a BRCA mutation or other HRR pathway defect. Rucaparib has demonstrated clinical activity (RECIST and CA-125 responses) in pts with BRCA$^{mut}$ pancreatic, ovarian, or breast cancer in an ongoing Phase 1/2 study (NCT01482715). Clinical activity of PARPi in BRCA$^{mut}$ PC combined with the paucity of active 2$^{nd}$-line therapies support evaluation of rucaparib in PC pts with a deleterious BRCA mutation. **Methods:** Study CO-338-023 (NCT02042378) is a single-arm, open-label Phase 2 trial of continuous rucaparib in up to 100 pts with pancreatic ductal adenocarcinoma (or related subtype) and a known deleterious BRCA mutation (germline or somatic). Pts must have received at least 1, but no more than 2, prior regimens for locally advanced or metastatic disease and have relapsed disease, or are no longer able to tolerate chemotherapy due to toxicity and radiologic assessment confirms no response to such treatment. Other key inclusion criteria include measurable disease, ECOG PS 0 or 1, and adequate organ function. Pts with endocrine tumors or prior PARPi treatment are excluded. Pts will take rucaparib continuously and be evaluated for safety every 2–4 wks, disease status (CT scans, CA19–9) every 4–8 wks until disease progression, and then survival every 4 wks. Blood and archival tumor tissue (if available) will be collected from all pts. The primary endpoint is ORR by RECIST v1.1. Key secondary endpoints include duration of response, PFS, OS, and safety. Exploratory analyses include gene sequence and structural rearrangements of tumor DNA, and evaluation of circulating tumor DNA. A group sequential interim monitoring plan will be implemented to stop the study early for either superior efficacy or futility. Interim analyses will occur after every 10$^{th}$ pt enrolled has sufficient disease assessment data available. Clinical trial information: NCT02042378.

**TPS4162^ General Poster Session (Board #240A), Sat, 8:00 AM-11:45 AM**

**APACT: A phase 3 randomized, open-label, multicenter trial evaluating the use of adjuvant *nab*-paclitaxel (*nab*-P) plus gemcitabine (G) versus G alone in patients (pts) with surgically resected ductal pancreatic adenocarcinoma (PDA).** *Presenting Author: Margaret A. Tempero, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

**Background:** Resection is the only curative treatment for PDA. Adjuvant chemotherapy following resection is associated with improved disease-free survival (DFS), median overall survival (OS), and 5-year survival for pts with resectable PDA. Despite these improvements, recurrence rates are still high, and survival rates remain poor, requiring more effective adjuvant therapies. In the phase 3 MPACT trial, *nab*-P plus G was manageable and demonstrated superiority to G alone for OS (median 8.5 vs 6.7 months; HR 0.72; 95% CI, 0.617 - 0.835; $P < 0.001$) and all secondary efficacy endpoints in pts with metastatic PDA [Von Hoff et al. *N Engl J Med*. 2013]. The current phase 3 trial (APACT) will evaluate the efficacy and safety of *nab*-P plus G vs G alone as adjuvant chemotherapy in pts with surgically resected PDA. **Methods:** Approximately 800 eligible pts will be randomized 1:1 (stratified by resection status [R0 vs R1], lymph node status [positive vs negative], and region) to receive *nab*-P 125 mg/m$^2$ plus G 1000 mg/m$^2$ or G 1000 mg/m$^2$ on days 1, 8, and 15 of a 28-day cycle for 6 cycles. Eligibility criteria include histologically confirmed resected PDA with macroscopic complete resection (R0 and R1); surgical staging T 1-3, N0-1, M0; ECOG PS 0 or 1; acceptable hematologic function; and no prior neoadjuvant therapy or radiation for PDA. Pts will be assessed by CT scan every 8 weeks for the first 24 weeks, every 12 weeks for the first 3 years, and every 24 weeks thereafter until disease recurrence for up to 5 years. The primary endpoint is DFS by independent review. Secondary endpoints include: OS and safety. Exploratory endpoints include tumor markers and quality of life by EORTC QLQ-C30 and QLQ-PAN26. One interim analysis for safety and 2 interim analyses for efficacy are planned. This design provides 90% power to detect a hazard ratio of 0.74 for DFS, with a 2-sided 5% significance level, which represents a 36% improvement in median DFS with *nab*-P plus G vs G alone. Biospecimen collection will be integrated with the trial process to ensure a high yield of material for biomarker discovery. Clinical trial information: NCT01964430.

**TPS4163 General Poster Session (Board #240B), Sat, 8:00 AM-11:45 AM**

**A randomized, double-blinded, placebo-controlled phase II trial of gemcitabine (gem) plus nab-paclitaxel (n-pac) combined with OGX-427 (apatorsen) or placebo in patients (pts) with metastatic pancreatic cancer (mPaCa): The Rainier Trial.** *Presenting Author: Johanna C. Bendell, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN*

**Background:** Hsp27 (heat shock protein 27) is over-expressed in a variety of tumor types causing initiation, growth, and metastasis of cancer cells. OGX-427 (apatorsen) is an antisense oligonucleotide that binds to Hsp27 mRNA, inhibiting production of the Hsp27 protein. Pts with pancreatic adenocarcinoma have significantly higher levels of Hsp27 than healthy individuals. Preclinical studies with apatorsen showed inhibited proliferation, induced apoptosis, and enhancement of the effect of chemotherapy in pancreatic cancer models. This randomized, phase II trial evaluates the efficacy of gem/n-pac chemotherapy with or without apatorsen in patients with mPaCa. The primary endpoint is overall survival. Secondary endpoints include progression-free survival, objective response rate, CA19-9 response, and safety. Archival tissue will be collected and assessed for expression of Hsp27, PTEN (protein expression by IHC), and a panel of gene mutations for correlative analyses. **Methods:** A total of 130 patients are planned to be randomized in a 1:1 ratio to Arm A (gem, n-pac, apatorsen) or Arm B (gem, n-pac, placebo). Three loading doses of apatorsen 600 mg or placebo are given prior to start of chemotherapy. Apatorsen 600 mg or placebo IV is then administered weekly in 28 day cycles. Gem 1000 mg/m$^2$ and n-pac 125 mg/m$^2$ are administered IV on days 1, 8, and 15. Patients will be re-staged every 2 cycles per RECIST v 1.1 and will continue treatment until disease progression or other reasons for discontinuation. Key eligibility includes: stage IV pancreatic adenocarcinoma, ECOG PS of 0 or 1, adequate bone marrow and organ function, and no known CNS metastases or clinically significant cardiac disease. Serum Hsp27 levels will be collected at screening, baseline, and during treatment. Correlative analyses of clinical outcomes and between Hsp27 expression/percentage of tumors expressing Hsp27 will be explored. This trial is currently open to enrollment. Clinical trial information: NCT01844817.

**4500 Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**Final results of EORTC intergroup randomized phase III trial comparing immediate versus deferred chemotherapy after radical cystectomy in patients with pT3T4 and/or N+ M0 transitional cell carcinoma (TCC) of the bladder.** *Presenting Author: Cora N. Sternberg, Hospital San Camillo-Forlanini, Rome, Italy*

**Background:** Patients (pts) with muscle invasive TCC of the bladder have poor overall survival (OS) due to systemic disease at diagnosis. This randomized intergroup phase III trial compared immediate vs deferred chemotherapy after radical cystectomy in pts with pT3T4 and/or N+ M0 TCC of the bladder. **Methods:** Within 90 days after cystectomy, pts were randomized to 4 cycles of GC, HD-MVAC or MVAC adjuvant chemotherapy or 6 cycles of deferred chemotherapy at relapse. Main endpoint was OS with PFS a secondary endpoint. Analysis was by intent-to-treat using Cox models stratified by group and adjusted for T stage (pT1T2 vs pT3T4) and nodal status (N- vs N+). **Results:** 284 of 660 pts were enrolled in 63 sites from 13 countries from 4/2002 to 8/2008 when the trial closed for poor accrual. Follow up (f/u) continued for 5 yrs to 8/2013. Pt characteristics were well balanced in the treatment groups; median age was 61 yrs with similar pT and nodal status (70% N+). Most received GC. Median and maximum f/u is 7.0 and 10.4 yrs in the immediate and 7.2 and 10.6 yrs in the deferred arm. An IDMC reviewed the trial twice and recommended continuation. 176 pts (62.0%) progressed or died, 73 (51.8%) on the immediate and 103 (72.0%) on the deferred arm. Median and 5 yr PFS are 2.9 yrs and 46.8% on the immediate and 0.9 yrs and 29.5% on the deferred arm ($p< 0.0001$). 148 pts (52.1%) died, 66 (46.8%) on the immediate and 82 (57.3%) on the deferred arm. Median and 5 yr OS are 6.8 yrs and 53.6% on the immediate and 4.6 yrs and 47.7% on the deferred arm, HR=0.78 (95.09% CI: 0.56, 1.10, $p=0.13$). Grade 3/4 AEs in the immediate arm included myelosuppression (26%), neutropenia (38%) and thrombocytopenia (28%). One pt died due to toxicity in the immediate arm. **Conclusions:** This is the largest reported randomized trial of adjuvant chemotherapy in pts with muscle invasive bladder cancer. Immediate adjuvant cisplatin based combination chemotherapy led to a statistically significant improvement in the secondary endpoint PFS and a non-significant decrease of 22% in the risk of death after radical cystectomy, the primary endpoint. The 2005 IPD meta-analysis should be updated. Clinical trial information: NCT00028756.

**4501 Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**Effect of cabozantinib on immunosuppressive subsets in metastatic urothelial carcinoma.** *Presenting Author: Andrea Borghese Apolo, National Cancer Institute at the National Institutes of Health, Bethesda, MD*

**Background:** Myeloid-derived suppressor cells (MDSC) and regulatory T cells (Treg) are major components of the immune suppressive tumor microenvironment. Both cell types promote effector T-cell dysfunction and tumor progression. The effect of cabozantinib, a tyrosine kinase inhibitor primarily targeting MET and VEGFR2 on specific immunosuppressive subsets, is unclear. In this study we assess MDSC and Tregs in patients undergoing treatment with cabozantinib and correlate with clinical response to therapy. **Methods:** Peripheral blood samples were obtained from patients with advanced/refractory metastatic urothelial carcinoma undergoing treatment with cabozantinib under a clinical trial at the National Cancer Institute (NCT01688999). MDSC (CD11b+CD33+CD14-) and Tregs (CD4+CD25hi Foxp3+) were measured in 24 patients at baseline and after 2 cycles of continuous cabozantinib treatment. MDSC and Tregs were further analyzed for CD40 and PD-1, respectively, as suppressive functional markers. **Results:** Patients with low Tregs at baseline had an improved partial response (PR) rate ($p=0.014$), progression free survival (PFS) ($p=0.059$) and overall survival (OS) ($p=0.0071$). Tregs decreased with cabozantinib treatment ($p=0.015$). Overall, PD-1 expression in Tregs increased after cabozantinib ($p=0.011$). However, patients with a PD-1 change below the median showed a strong trend to improved PFS compared to those with increased PD-1 above the median ($p=0.035$). The percent MDSC did not change with treatment. However, MDSC CD40 expression was increased after cabozantinib treatment compared to baseline ($p=0.0005$). Though, a decrease in MDSC CD40 expression after treatment was associated with an improved PFS ($p=0.020$). **Conclusions:** Treg levels prior to cabozantinib treatment are predictive of therapeutic responsiveness and OS. Changes in Treg PD-1 expression and MDSC CD40 expression may be prognostic markers in patients with advanced/refractory metastatic urothelial carcinoma treated with cabozantinib.

**4502 Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**Validation of a 16-gene signature for prediction of recurrence after nephrectomy in stage I-III clear cell renal cell carcinoma (ccRCC).** *Presenting Author: Bernard J. Escudier, Institut Gustave Roussy, Villejuif, France*

**Background:** New molecular diagnostics are needed to improve assessment of recurrence risk after nephrectomy in ccRCC. The 16-gene (11 cancer-related, 5 reference) Recurrence Score (RS) was previously developed in a cohort of 931 stage I-III ccRCC patients (pts) from Cleveland Clinic, requiring validation in an independent study. **Methods:** A prospective clinical validation study of the Onco*type* DX RS in stage I-III ccRCC pts treated with nephrectomy from 1995 to 2007 was conducted by a French consortium. Genes, algorithm, endpoints, methods, and analysis plan were pre-specified and locked prior to merging clinical and molecular data. Gene expression was quantitated by RT-PCR in fixed paraffin-embedded primary ccRCC tissue without knowledge of pt clinical characteristics or outcomes. Recurrence-free interval (RFI, primary endpoint), renal cancer-specific survival (RCSS), disease-free survival (DFS) and overall survival (OS) were analyzed using Cox PH regression stratified by stage with data censored at 5 years, and Kaplan-Meier methods. **Results:** RT-PCR was successful in 626/645 pts (97%): 398 stage I, 54 stage II, 174 stage III. Median follow up was 5.5 yrs. 5-yr recurrence risk was dependent upon stage (7%, 16% and 30% in stage I, II and III). Continuous RS predicted recurrence risk (HR per 25 point increase in RS (HR/25) = 3.9, 95% CI 2.6-5.8, $p<0.001$). RS predicted RCSS, DFS and OS (all with $p<0.001$). In multivariable analyses, RS continued to predict recurrence (HR/25 =2.7, 95% CI 1.6-4.5, $p<.001$) after adjustment for tumor size, Fuhrman grade and necrosis. RS identified 39% of stage I pts with an average 5-yr recurrence risk of 2% (95% CI 0-7%) and 15% of pts with a 23% (95% CI 13-39%) risk. In stages II-III, RS identified 19% of pts with a 2% (95% CI 0-16%) and 44% of pts with a 39% (95% CI 29-50%) recurrence risk. **Conclusions:** The 16-gene Onco*type* DX RS is validated as a predictor of clinical outcome in pts with stage I-III ccRCC and provides significant information beyond conventional clinical and pathologic characteristics. The RS may be useful to select patients for adjuvant treatment trials, for active surveillance of small renal masses, and for surveillance strategies after surgery.

**4503 Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**Genome-wide association study (GWAS) of efficacy and safety endpoints in pazopanib- or sunitinib-treated patients with renal cell carcinoma (RCC).** *Presenting Author: Toby Johnson, GlaxoSmithKline, Hertfordshire, United Kingdom*

**Background:** Pazopanib and sunitinib are angiogenesis inhibitors approved for treatment of advanced RCC, but there is substantial heterogeneity in response to either treatment. We hypothesized that patient's germline genetic variation may affect treatment efficacy or safety endpoints. **Methods:** N=1099 patients, from the COMPARZ study (NCT00720941, NCT01147822, N=374 pazopanib, N=355 sunitinib) and three other phase II/III pazopanib studies (NCT00244764, NCT00334282, NCT00387764, N=370), provided consent for pharmacogenetic research. GWAS analyses used normal, ordinal, and Cox regression models to test 30M genetic variants (genotyped or imputed) for association with progression free survival (PFS), overall survival (OS), and best response (BR) in pazopanib or sunitinib treated patients, and with safety endpoints in pazopanib treated patients (bilirubin elevation, transaminase elevation, blood pressure change, hand foot syndrome [HFS], diarrhoea, fatigue, cardiotoxicity, hypothyroidism, proteinuria). **Results:** At the GWAS significance level for common variants ($P\leq 5\times10^{-8}$), combined analysis of PFS, OS and BR identified an association with a common variant intronic in *LOXL2* and *ENTPD4* ($P=1.7\times10^{-8}$). No common variants reached $P\leq 5\times10^{-8}$ for individual efficacy endpoints, but hypothesis-generating efficacy associations approaching GWAS significance ($P\leq 5\times10^{-7}$) were observed in and near biologically plausible genes for RCC (e.g. *IL2RA, LRRC2*). For safety endpoints, common variants near *UGT1A1* were associated with bilirubin elevation in pazopanib treated patients ($P=2.9\times10^{-17}$), consistent with our previous candidate gene analysis results. A common variant intergenic between *ANAPC4* and *SLC34A2* was associated with HFS ($P=4.6\times10^{-8}$). **Conclusions:** To our knowledge, this is the largest GWAS for response and toxicity to anti-angiogenesis therapies in RCC reported to date. We identified genetic markers associated with combined efficacy endpoints as well as safety endpoints. If replicated in independent studies, these associations may provide insight into biological mechanisms underlying differential outcome to treatment.

**4504 Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**Phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC).** *Presenting Author: Hans J. Hammers, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

**Background:** There is a need for agents that result in durable responses and improved tolerability in patients (pts) with mRCC. Nivolumab, a fully human IgG4 programmed death-1 (PD-1) immune checkpoint inhibitor antibody, has shown activity in mRCC. Combining nivolumab + ipilimumab, a fully human monoclonal antibody to CTLA-4, showed encouraging clinical activity and acceptable safety in advanced melanoma. We report preliminary results of the combination in mRCC. **Methods:** Pts with mRCC (favorable/intermediate MSKCC score; Karnofsky performance status ≥80%; untreated or any number of prior therapies) were randomized to receive nivolumab 3 mg/kg + ipilimumab 1 mg/kg (arm N3 + I1) or nivolumab 1 mg/kg + ipilimumab 3 mg/kg (arm N1 + I3) IV Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W until progression/toxicity. The primary objective was to assess safety/tolerability; secondary objective was to assess antitumor activity. **Results:** Pts were randomized to N3 + I1 (n=21) and N1 + I3 (n=23). Most pts (n=34; 77%) had prior systemic therapy (N3 + I1: 16; N1 + I3: 18). Treatment-related adverse events (AEs) were seen in 39/44 pts (89%); 7 pts (16%; N3 + I1: 2; N1 + I3: 5) discontinued due to any-grade related AEs. Grade 3–4 related AEs occurred in 19 pts (43%; N3 + I1: 5; N1 + I3: 14), most commonly ↑ lipase (16%, n=7), ↑ ALT (11%, n=5), diarrhea (9%, n=4), colitis (5%, n=2), ↑ amylase (5%, n=2). No grade 3–4 pneumonitis was seen. Objective response rate (ORR) was 29% (N3 + I1) and 39% (N1 + I3) (Table). Duration of response (DOR) was 4.1+ to 22.1+ wks (all 6 responses ongoing) in N3 + I1, and 6.1+ to 18.3+ wks (8/9 responses ongoing) in N1 + I3. Responses occurred by first tumor assessment (wk 6) in 67% of responding pts in both N3 + I1 and N1 + I3. Stable disease (SD) was seen in 7 (33%) pts (N3 + I1) and 9 (39%) pts (N1 + I3). **Conclusions:** Nivolumab + ipilimumab showed acceptable safety and encouraging antitumor activity in mRCC, with most responses ongoing. Follow-up, expansion cohorts at these doses and an additional dose cohort (nivolumab 3 mg/kg + ipilimumab 3 mg/kg) are being assessed. Clinical trial information: NCT01472081.

| | Arm N3 + I1 n=21 | Arm N1 + I3 n=23 |
|---|---|---|
| **ORR, n (%)** | 6 (29) | 9 (39) |
| **SD, n (%) [duration, wks]** | 7 (33) [6+ to 25+] | 9 (39) [6+to 26.1] |
| **DOR, range (wks)** | 4.1+ – 22.1+ | 6.1+ – 18.3+ |
| **PFS, range (wks)** | 4.7+ – 28.1+ | 4.3 – 26.1 |

**4505 Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**Everolimus versus sunitinib prospective evaluation in metastatic non-clear cell renal cell carcinoma (The ESPN Trial): A multicenter randomized phase 2 trial.** *Presenting Author: Nizar M. Tannir, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** In a single-arm phase II trial of sunitinib in non-clear cell RCC (nccRCC) we previously reported (Tannir et al. Eur Urol 2012), objective response rate [ORR] was 5% and median progression-free survival [PFS] was 2.7 months. Temsirolimus was previously shown to produce overall survival (OS) benefit in poor-risk RCC including nccRCC (Hudes et al. NEJM 2007). **Methods:** This is a randomized phase II trial of everolimus (E) vs. sunitinib (S) with crossover design in metastatic nccRCC. Primary endpoint was PFS in first-line (1L). Secondary endpoints were PFS in second-line (2L), safety, and OS. A sample size calculation of 108 pts (54/arm) was based on an assumption of improved median PFS from 12 weeks with S to 20 weeks with E. Pts were stratified by histology (papillary vs. others), and MSKCC risk groups. Kaplan-Meier curves were used to estimate unadjusted time-to-event distributions. Stratified log rank tests were used to compare each time-to-event variable between groups. **Results:** Seventy-three pts were enrolled. Sixty-eight pts were eligible and evaluable (median age 59, 43 males [63%], 52 pts [77%] had prior nephrectomy). Twenty-seven pts had papillary, 11 pts had chromophobe, 9 pts had unclassified, 7 pts had translocation, 13 pts had sarcomatoid, and 1 pt had oncocytic RCC. Thirty-five pts received E (good-risk 4, intermediate-risk 29, poor-risk 2). Thirty-three pts received S (good-risk 4, intermediate-risk 29). ORR with S in 1L was 12% (2 pts had chromophobe, 1 pt had papillary type 1 and 1 pt had 99% sarcomatoid); ORR with E in 1L was 0%. Median PFS in 1L with S was 6.1 mos (95% CI: 4.7, 10.8) and 4.1 mos with E (95% CI: 2.7, 7.4); p = 0.25. Thirty-eight pts received 2L therapy (S 19, E 19). Median PFS in 2L with S was 1.8 mos (95% CI: 1.5, NA) and 4.3 mos with E (95% CI: 1.4, NA). A total of 27 pts have died (8 had S and 19 had E). Median OS with E in 1L was 10.5 mos (95% CI: 7.4, NA); median OS with S in 1L was not reached; p=0.01. Toxicity was consistent with previous reports of E and S. **Conclusions:** Based on futility analysis for PFS and inferior OS with E compared to S in 1L, the DSMB recommended termination of further pt accrual on this trial. E cannot be recommended as 1L option in nccRCC.

**4507 Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**International randomized, double-blind, placebo-controlled, phase 3 study of linsitinib (OSI-906, L) in patients (pts) with locally advanced or metastatic adrenocortical carcinoma (ACC).** *Presenting Author: David I. Quinn, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA*

**Background**: ACC is an uncommon but frequently fatal cancer. For pts with metastatic or recurrent nonoperable ACC, there are very limited treatment options. Insulin-like growth factor 2 (IGF2) overexpression occurs in >90% of ACC, hence the IGF pathway is a potential therapeutic target. We assessed the activity of a potent IGF-1 receptor TKIlinsitinib in ACC. **Methods:** In a double-blind phase III trial accruing over 21 months, pts with measurable locally advanced or recurrent ACC following 1st- or 2nd-line treatment were randomly assigned to linsitinib 150mg BID orally or best supportive care & placebo (P), in a 2:1 ratio, respectively. The primary endpoint was overall survival (OS; power 80% for ñOS from 9 to 15.6 months); secondary endpoints: PFS, disease-control & objective response rate (blinded central review by RECIST 1.1), QoL & safety/toxicity (CTCAEv4.02). **Results**: 139 pts (median age 50yrs, 67% female, ECOG 0/1: 44.6, 51.1%) were enrolled with 90 assigned to linsitinib & 49 to P. Prior therapies included surgery: 90.6%; radiotherapy: 30.9%; mitotane: 100% & cytotoxic chemotherapy: 73.4%. The median time from diagnosis to trial initiation was 26.5 months. There was no difference between linsitinib and placebo in overall survival (median 323 days (10.8 months) vs 356d (11.8); p=0.77, HR 0.94); PFS (44 vs 46d; p=0.3, HR 0.83) & DCR (32.2 vs 34.7%). However, 3 pts on linsitinib experienced PR and 8 had prolonged PFS >100d (4 on drug >400d), whereas these events did not occur with placebo. Dose modification: L: 43.3, P 29.2%. Treatment-emerged adverse events (TEAEs) occurred in 97.8 vs 93.8%, grade 5: 5.6 vs 10.4%, gr 4: 10.1 vs 2.1%, gr 3: 45.6 vs 31.3% for L vs P respectively. Common TEAEs: fatigue (33.3 vs 22.9%), nausea (26.7 vs 31.3%), vomiting (20.0 vs 20.8%), abdominal pain (20.0 vs 20.8%), QTc prolonged (20 vs 6.3%) for L vs P. **Conclusions:** Targeting the IGF pathway with linsitinib did not improve overall or progression-free survival in adrenocortical cancer patients, although a small subgroup of patients seemed to benefit from this drug. Timely and efficient accrual to phase III trials in rare cancers is internationally feasible. Clinical trial information: NCT00924989.

**4508 Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**Management of clinical stage I seminomatous testicular cancer: A report from SWENOTECA.** *Presenting Author: Torgrim Tandstad, The Cancer Clinic, St. Olavs University Hospital, Trondheim, Norway*

**Background:** Clinical stage I seminoma testicular cancer is the most frequent presentation of testicular cancer. Current treatment option include surveillance (SURV) or adjuvant chemotherapy. Following a large randomized phase III study, 1 course of adjuvant carboplatin (AC) AUC7 became the preferred adjuvant treatment option. **Methods:** A risk-adapted protocol (SWENOTECA VII) was initiated in 2007, based on the proposed risk factors; invasion of rete testis and tumor size >4cm. Patients with 0-1 risk factor were recommended SURV, but could choose 1 course of AC (AUC7). Patients with 2 risk factors were recommended 1 course of AC, but could choose SURV. We also report treatment results from patients treated with AC in an earlier protocol during 2004-2007. **Results:** 839 patients were included in the SWENOTECA VII protocol. In addition 225 patients were treated with AC before 2007. Median follow-up is 4.0 years, 3.6 years for patients on SURV and 4.2 years for patients treated with AC. In total 675 patients were treated with AC, and 389 patients chose SURV. Complete information regarding risk factors was available in 946 patients. The relapse-rate (RR) following AC was 6.2 %; in patients without risk factors 2.7 % compared to 9.4 % in patients with 1-2 risk factors. In patients followed by SURV the RR was 10 %; in patients without risk factors 2.9 %, compared to 21.7 % in patients with 1-2 risk factors. **Conclusions:** In this modern, large, population-based prospective study we confirm the low relapse rate previously reported for patients with 0 risk factors on SURV, thus patients with no risk factors should be followed by SURV. The RR with AC was somewhat higher than reported in MRC TE19/EORTC 30982. This may be due to the risk-adapted approach, with a higher proportion of patients with 1-2 risk factors treated with AC. The RR following AC indicated a relatively modest effect in preventing relapse. Data regarding exact doses are being collected to assess if inadequate dosing may have affected the RR following AC.

**4509 Poster Highlights Session (Board #1), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Comprehensive molecular profiling of urothelial bladder cancer at the DNA, RNA, and protein levels: A TCGA project.** *Presenting Author: John N. Weinstein, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Urothelial carcinoma (UC) is a major cause of mortality with no approved molecularly targeted agents or good treatment options beyond cisplatin-based chemotherapy. **Methods:** For The Cancer Genome Atlas (TCGA), we profiled muscle-invasive UCs for mutations, DNA copy number variants (CNVs), mRNA and microRNA expression, protein expression and phosphorylation, DNA methylation, transcript splicing, gene fusion, viral integration, pathway perturbation, clinical correlates, and histopathology. The finding here are based on the first 131 tumors, but >250 more are being processed as of 1/2014. **Results:** Whole-exome sequencing revealed 29 recurrently mutated genes. Potential therapeutic targets included altered PIK3CA, ERBB2, FGFR3, TSC1, and ERBB3, plus mutated chromatin-regulating genes MLL, MLL2, MLL3, CREBBP, CHD7, SRCAP, ARID1A, KDM6A (UTX), and EP300. There were 27 focal CNVs, including CDKN2A deletion in 47%. Low-pass whole-genome sequencing identified 3 tumors with FGFR3-TACC3 fusions. Viral DNA was found in 6% (CMV, HHV6B, HPV16, BK polyoma), and viral transcripts were identified in 4% (CMV, BK polyoma, HPV16). mRNA-seq showed 4 tumor clusters: (I) papillary morphology, FGFR3 dysregulation. (I and II) high HER2 (ERBB2), estrogen receptor beta signaling signature (like Luminal A breast cancer). (III) similar to basal-like breast and squamous cell head and neck. Integrated analyses confirmed changes in cell cycle regulation (93%), kinase and PI3-K signaling (72%), and epigenetic regulation (histone-modifiers: 89%; SWI/SNF nucleosome remodeling complex: 64%). Recurrent defects in PI3-kinase/AKT/mTOR (42%) and RTK/RAS (44%) pathways may be actionable. **Conclusions:** This study and others identify druggable targets in UC. FGFR3 is activated by mutation, gene fusion, and overexpression, suggesting trials of FGFR3 inhibitors. PI3-kinase/mTOR/AKT/TSC1 pathway defects are frequent, and mutations in TSC1 suggest trial of mTOR inhibitors. ERBB2 amplifications and activating mutations suggest agents such as trastuzumab, trastuzumab-DM1, lapatinib, and neratinib. The mutations in epigenetic regulatory genes suggest potential for chromatin modifying agents.

**4510 Poster Highlights Session (Board #2), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Association of somatic *ERCC2* mutations with cisplatin sensitivity in muscle-invasive urothelial carcinoma.** *Presenting Author: Jonathan E. Rosenberg, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Cisplatin-based combination chemotherapy is the standard of care for patients with muscle invasive urothelial carcinoma. Pathologic downstaging to pT0/pTis after neoadjuvant cisplatin-based chemotherapy is associated with improved survival, although the molecular determinants of cisplatin sensitivity are incompletely understood. Recent reports have identified somatic mutations in ERCC2, a nucleotide excision repair gene, in 7-12% of bladder cancers. Preclinical evidence suggests that defects in the nucleotide excision repair (NER) pathway mediate cisplatin sensitivity. **Methods:** We performed whole exome sequencing of pre-treatment tumor and germline DNA from 51 patients with muscle invasive urothelial carcinoma who received neoadjuvant cisplatin-based chemotherapy followed by cystectomy (26 pT0/pTis "responders", 25 pT2+ "non-responders"). Computational methods were employed to identify somatic mutations that occurred preferentially in cisplatin responders. Functional validation of significantly enriched mutations was performed using cellular cisplatin and UV sensitivity assays. **Results:** Somatic *ERCC2* mutations were observed in 38.5% of responders and 0% of non-responders ($q < 0.01$). *ERCC2* was the only gene enriched in the cisplatin responders compared with non-responders. *ERCC2* mutations clustered within or near conserved helicase domains required for ERCC2 function. Expression of the identified *ERCC2* mutants in an *ERCC2*-deficient cell line failed to rescue cisplatin and UV sensitivity compared to wild-type *ERCC2*. **Conclusions:** Somatic *ERCC2* mutation is associated with cisplatin sensitivity in muscle invasive urothelial carcinoma. These results may inform the use of cisplatin-containing regimens in muscle invasive urothelial carcinoma, and potentially other *ERCC2*-mutated tumors.

**4511 Poster Highlights Session (Board #3), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Somatic copy number abnormalities (SCNAs) and mutations in PI3K/AKT pathway as prognostic factors for overall survival (OS) in platinum-treated locally advanced or metastatic urothelial tumors.** *Presenting Author: Joaquim Bellmunt, Bladder Cancer Center, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA*

**Background:** An integrative analysis was conducted to identify genomic alterations and mutational status on the gene pathway level that could predict OS in pts with urothelial cancers (UC) treated with platinum chemotherapy. **Methods:** DNA was extracted from FFPE samples from invasive UC and screened for mutations and CNAs. Of those, complete clinical data was available from 85 pts. Mutations were analyzed by a mass-spectrometry based genotyping platform (Oncomap v3) and genomic imbalances were detected by comparative genomic hybridization (CGH) analysis. Regions with threshold of $\log^2$ ratio $\geq 0.4$, or $\leq -0.3$ were defined as either having copy number gain or loss with significant CNAs determined using a GISTIC analysis.To better define the co-occurrence pattern of mutations and CNAs, we grouped genes into 3 core signal transduction pathways: 1) TP53 pathway; 2) RTK-RAS-RAF pathway including ERBB2, FGFR3, MET, FGFR1, KRAS BRAF, RAF1 and NF1; 3) PI3K/AKT pathway including PTEN, PIK3CA, AKT1, TSC1 and MTOR. OS was measured from treatment to time of death or censored. Cox regression was used to assess pathways abnormalities and mutations with outcome. **Results:** 35 out of 94 samples (41%) platinum treated pts with advanced UT, harbored mutations on at least 1 gene, mainly *TP53* (16%), *PIK3CA* (9%), *FGFR3* (2%), HRAS/KRAS (5%) and CTNNB1 (1%). 66%of pts had some sort of CNA. PI3K/AKT was the most affected pathway and was associated with shorter overall survival (hazard ratio (HR) 2.3, 95% CI: 1.3-4.2). There was no significant association between mutational status and OS. PIK3CA/AKT pathway alteration (mutations +CNV) may have the greatest impact on OS (p=0.055). Over-expression of CTNNB1 (p=0.0008) and PIK3CA (p=0.02) was associated with decreased OS. Among other individual genomic alterations, TP53 mutations (p=0.07) ,mTOR gain (p=0.07) and PTEN over expression (p=0.08) were marginally significant negative impact on OS. **Conclusions:** Our results suggest that targeted therapies focusing on the PIK3CA pathway alterations can generate the greatest impact in the overall patient population of metastatic UC.

**4512 Poster Highlights Session (Board #4), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Comparative effectiveness of gemcitabine plus cisplatin (GC) versus methotrexate, vinblastine, doxorubicin, plus cisplatin (MVAC) as neoadjuvant therapy for muscle-invasive bladder cancer (MIBC).** *Presenting Author: Matt D. Galsky, The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY*

**Background**: GC has been adopted as a standard neoadjuvant regimen for MIBC, supported by practice guidelines, despite a lack of prospective (randomized) data in this setting. Given the historical difficulties completing perioperative chemotherapy trials in MIBC, an adequately powered clinical trial to definitively address whether GC is comparable to regimens supported by Level I evidence (MVAC, CMV) may not be completed and additional levels of evidence are needed to support or refute current practice. **Methods:** Data were collected via an electronic data capture platform from 25 international centers. Eligible pts had cT2-4aN0M0 urothelial cancer of the bladder and received neoadjuvant GC or MVAC prior to cystectomy. Logistic regression was used to compute propensity scores as the predicted probabilities of patients being assigned to MVAC vs. GC given their: age, calculated creatinine clearance (CrCl), number of cycles of chemotherapy, pure versus mixed histology, Eastern Cooperative Oncology Group performance status, year of diagnosis, cT-stage, and gender. These propensity scores were then included in a log binomial model used to estimate an adjusted relative risk comparing the probability of complete pathologic response (pCR) between patients who received MVAC vs. GC. Survival between the two groups was analyzed as an exploratory endpoint. **Results:** 244 patients met eligibility for the analysis (GC: 175, MVAC: 69). Patients were median age 64, predominantly male (77%), had a median CrCl of 72, and received a median of 3 cycles of neoadjuvant chemotherapy. The pCR rate, adjusted for propensity scores, is shown in the Table. Overall survival was not significantly different between the groups. **Conclusions:** Neoadjuvant GC and MVAC achieved comparable rates of pCR, in this large retrospective cohort, providing additional evidence to support current practice.

**pCR adjusted for propensity scores.**

| pCR | GC N=175 | MVAC N=69 | Relative risk [95% CI] P value |
|---|---|---|---|
| Yes | 47 (27%) | 19 (28%) | 0.97 [0.60-1.56] |
| No | 128 (73%) | 50 (72%) | P=0.9 |

**4513 Poster Highlights Session (Board #5), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Neoadjuvant dose-dense gemcitabine and cisplatin (DDGC) in patients (pts) with muscle-invasive bladder cancer (MIBC): Final results of a multicenter phase II study.** *Presenting Author: Elizabeth R. Plimack, Fox Chase Cancer Center, Philadelphia, PA*

**Background**: Neoadjuvant cisplatin (cis) based chemotherapy prior to radical cystectomy (RC) is standard of care for localized MIBC. Combination gemcitabine (gem) and cis is frequently used, but has not been tested prospectively. We sought to evaluate the activity of this combination when given in a dose dense fashion. **Methods**: Pts with MIBC, cT2-T4a, cN0-N1 with CrCl >=50 were eligible. Pts received 3 cycles of DDGC (gem 1200 mg/m2, cis 70mg/m2) on day 1, with pegfilgrastim 6 mg day 2 or 3, every 2 wks. Pts with CrCl 50-60 could receive cis split over 2 days. RC with lymph node dissection was to be performed 4-8 weeks after the last dose of DDGC. Primary endpoint was pathologic complete response (pT0) rate. **Results**: 32 pts were enrolled at 2 institutions (FCCC, TJU) over 14 months. One withdrew consent prior to receipt of DDGC. Among the 31 evaluable pts, median age was 69 (range 51 – 82). Baseline clinical stage was T2N0M0 (11), T3N0M0 (15), T4aN0M0/TxN1M0 (5). 25 pts received all 3 cycles of DDGC, with 1/25 requiring dose reduction of gem for thrombocytopenia. 6 discontinued DDGC early due to gr 3/4 vascular (3), gr 2/3 renal (2), or gr 3 hematologic (1) toxicity. Analysis of toxicities among the first 13 pts revealed 2 pts with MI (1 in cycle 1 (C1) with resulting CHF precluding surgery, 1 D#3 post-op) and 2 pts with VTE (1 PE in C2, 1 DVT D#15 post-op), and 1 pt who required CABG between DDGC and RC. The protocol was then amended to require cardiac clearance prior to study entry. Despite this, further vascular toxicity was seen with 1 DVT in C3 and 1 CVA in C1. The study was thus closed prior to target accrual of 44 pts. 30/31 pts underwent RC, 28 within 8 weeks of last DDGC. Median time from start of DDGC to RC was 9.3 weeks (range 5-29). 10/31 pts had pT0 (32%, 95% CI 16-48%). An additional 4 (13%) were downstaged to non-muscle invasive disease. Median f/up is 36 wks. 4 pts have recurred. 5 pts have died, 2 due to metastases. **Conclusions**: DDGC yielded pT0 rates similar to those reported with Accelerated MVAC. However significant vascular toxicity precluding, delaying or increasing the risk of surgery was noted, leading to early study closure. Clinical trial information: NCT01611662.

**4514 Poster Highlights Session (Board #6), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Patient eligibility and trial design for the salvage therapy of advanced urothelial carcinoma (UC) based on the impact of prognostic factors.** *Presenting Author: Guru Sonpavde, The University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL*

**Background:** The prognostic impact of number of lines of prior chemotherapy, prior perioperative chemotherapy, prior platinum agent and site of primary tumor in salvage trials for advanced UC is unknown. This knowledge can inform trial design, stratification and eligibility criteria. **Methods:** Ten phase II trials of salvage therapy for advanced UC were pooled for data on the number of prior lines, prior perioperative chemotherapy, prior platinum (cisplatin, carboplatin) and site of primary (bladder vs. other) in addition to TFPC (time from prior chemotherapy), Hb (hemoglobin), PS (performance status), and LM (liver metastasis) status. Cox proportional hazards regression was used to evaluate the association of variables with overall survival (OS). Trial was included as a stratification factor. **Results:** The trials evaluated vinflunine (N=151), docetaxel +/- vandetanib (N=148), paclitaxel-gemcitabine (N=98), sunitinib (N=77), volasertib (N=50), nab-paclitaxel (N=48), everolimus (N=45), pazopanib (N=43), cetuximab +/-paclitaxel (N=39) and paclitaxel-cyclophosphamide (N=32). Of 731pts, 711 were evaluable for prior number of lines and perioperative chemotherapy, 663 for prior platinum and 512 for site of primary. The number of prior lines of therapy were 1 in 559 (78.6%), 2 in 111 (15.6%), and ≥3 in 41 (5.8%) pts. Prior perioperative chemotherapy was given to 277 (39.1%) and chemotherapy for metastatic disease to 454 (64.1%) pts. Prior platinum was cisplatin in 501 (75.6%), carboplatin in 216 (32.6%) and both in 57 (8.6%). Bladder was the primary site in 388 (75.8%). On univariate analyses, shorter TFPC, low Hb, low PS, LM, prior carboplatin and non-administration of prior perioperative chemotherapy were associated with worse OS ($p<0.05$ for all). On multivariate analyses, TFPC, Hb, PS and LM were significantly associated with OS, but none of the other factors were independently significant. **Conclusions:** These data imply that randomized trials in previously treated pts with advanced UC should stratify for TFPC, Hb, PS and LM status and may allow prior perioperative chemotherapy and not limit eligibility to only one prior therapy.

**4515 Poster Highlights Session (Board #7), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Molecular profiling of testicular cancer.** *Presenting Author: Carsten Bokemeyer, Department of Oncology, Hematology and BMT with Section of Pneumology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

**Background:** The incidence of testicular cancer (TC) has been increasing in many western countries for several decades. For 2013, about 7900 new TC cases with 370 deaths are estimated in the United States. While the overall prognosis in metastatic TC is excellent, treatment options for patients (pts) relapsing with cisplatin-refractory disease are limited. A personalized approach to therapy based upon molecular diagnostic tools to predict response to specific therapeutic agents may help pts in whom standard chemotherapy has failed. **Methods:** Eighty-five TC cases referred to Caris Life Sciences between 2009 and January 2014 were evaluated; diagnoses were collected from referring physicians and classified at intake based on pathology and clinical history. Specific testing was performed per physician request and included a combination of sequencing (Sanger, NGS or pyrosequencing), protein expression (immunohistochemistry), gene amplification (CISH or FISH), and/or RNA fragment analysis. **Results:** In this cohort of pts with advanced / refractory TC, the most commonly observed changes in protein expression were upregulation of TOPO2A (66%), TLE3 (45%), SPARC (44%), and TS (42%) and downregulation of PTEN observed in 40% of patients. PIK3CA gene amplification was observed in a single case tested, amplification of EGFR, cMET, and HER2 was observed in 14%, 7%, and 7% of cases, respectively. In 16 cases analyzed by NGS, KRAS was the most common mutation (13%) followed by TP53 (7%) and cKIT mutations (7%). No NRAS or HRAS mutations were found. Further 5 KRAS mutations were detected by PCR or sanger sequencing. Two of seven pts with KRAS mutations also had HER2 amplification, one had a cKIT mutation. All pts with TP53 mutations also had a loss of PTEN protein expression but no other mutations. Pathway profiling revealed that with the exception of loss of PTEN, 93% of patients were predominantly ERK and mTOR pathway wildtype, and activation of the ERK pathway only occurred through the presence of mutations in the KRAS gene. **Conclusions:** A low prevalence of mutations was observed in advanced / refractory TC. Predictive biomarkers may be used to guide treatment decisions. Targeting the cKIT, HER2 or cMET pathways may warrant treatment options in single pts.

**4516 Poster Highlights Session (Board #8), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Tumor genomic mutation profiling of germ cell tumors using "Profile".** *Presenting Author: Elizabeth O'Donnell, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Malignant germ cell tumors (GCTs) are the most common solid malignancy affecting males between the ages of 15 and 35. To date, little is known about the genomic landscape of GCTs. **Methods:** We used "*Profile*", an enterprise-wide mutation detection protocol. OncoMap, the platform used for this work detects 471 mutations in 41 well characterized oncogenes in formalin-fixed paraffin-embedded (FFPE) tissue samples including KIT, KRAS and BRAF which have previously been described in GCT. After informed consent, tumor DNA isolation from 33 unique patients, and a battery of quality assurance tests, the samples were run on the OncoMap platform. **Results:** 33% (11/33) tumor samples harbored mutations. 9/11 were orchiectomy specimens from newly diagnosed patients and 2/11 were samples from metastatic disease sites in relapsed disease. One mutation was noted in each of the 11 samples. Somatic oncogene mutations were found in *NRAS (4), KIT (3), MET (2), KRAS (1),* and *p53 (1).* 9/16 seminoma specimens had mutations (8 cured with orchiectomy, 2 cured with radiation therapy, and 6 cured with chemotherapy). 2/17 non-seminoma GCT pts had metastatic disease and mutations and both were cured with chemotherapy. **Conclusions:** Genomic analysis of tumor DNA extracted from FFPE orchiectomy specimen is feasible and may provide novel insights into GCT biology. Sequenom analysis using OncoMap details presence of genetic mutations in some GCT pts and supports the feasibility and rationale for further analysis (more samples and sequencing).

**4517 Poster Highlights Session (Board #9), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Phase 2 trial of bevacizumab (BEV)/high-dose chemotherapy (HDC) with autologous stem-cell transplant (ASCT) for refractory germ-cell tumors (GCT).** *Presenting Author: Yago Nieto, Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** HDC is curative therapy for relapsed GCT. The Beyer model identifies groups with poor (5% EFS at 1-year post-HDC), intermediate (25% EFS), or good risk (≥50% EFS). Given high VEGF expression in metastatic GCT and BEV-chemotherapy synergy, we studied concurrent BEV/HDC and the efficacy of a novel regimen of infusional gemcitabine, docetaxel, melphalan, carboplatin (GDMC) (BBMT 2005;11:297) in refractory GCT. **Methods:** Eligibility: GCT in poor/interm-risk 1t relapse or in ≥2nd relapse. Patients (pts) received tandem HDC/ASCT with BEV (5 mg/kg) 1 week before each cycle. HDC#1: GDMC; HDC#2: ifosfamide/carboplatin/etoposide. Trial powered to distinguish an expected 1-yr EFS of 15% from a goal of 50%. **Results:** We treated 42 pts, median age 22 (19-45) (Table). HDC#1 main toxicities: mucositis (31 G3, 11 G2) and rash (3 G3, 12 G2). Among 7 pts with marginal renal function, there were 4 HDC-related deaths (3 sepsis, 1 fungal pneumonia). Protocol was amended to reduce HDC doses by 15% in 8 subsequent pts with high creatinine (1.5–1.8 mg/dl), with no more deaths. Tumor markers normalized in 83% pts. Surgery of residual lesions (N=9) showed necrosis (5), mature teratoma (1), necrosis+teratoma (2) and teratocarcinoma (1). Median follow-up from HDC#1 for alive pts is 22 (1-69) months. The 1- and 2-yr EFS rates are both 63% (95% CI, 49-81%). The 1- and 2-yr OS rates are 72% (59-89%) and 65% (50-84%), respectively. **Conclusions:** Tandem HDC with BEV/GDMC followed by BEV/ICE showed promising EFS in pts with heavily pretreated and refractory GCT, exceeding the expected results with carboplatin/etoposide and no BEV, and warrants testing in less heavily pretreated pts. Clinical trial information: NCI-2011-01631.

| | N |
|---|---|
| **Beyer group** | Poor (23), interm (19) |
| **Origin** | Testic (35), mediast (4), retroperit (3) |
| **Cisplatin sensitivity** | Refractory (16), absolutely refractory (20) |
| **Prior surgery for metastases** | Retroperit (17), liver (1), other abdomen (5), lung (3), bone (1), brain (2), mediast (1) |
| **Prior xRT** | 9 |
| **Tumor markers at relapse /PD** | B-HCG (18), AFP (17), both (5) |
| **Median # prior regimens** | 4 (2-8) |
| **Histol** | Embryonal (6), chorio (6), yolk sac (4), teratoma (1), mixed (24) |
| **Metast** | Lungs (30), liver (12), bone (8), brain (6), retroperit (23), mediast (11) |
| **PD at HDC** | 22 |

**4518 Poster Highlights Session (Board #10), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Impact of long-term serum platinum on neuro- and ototoxicity, cardiovascular disease, and hypogonadism in testicular cancer survivors.** *Presenting Author: Line veronika Hjelle, Department of Oncology, Univesity Hospital of North Norway, Tromsø, Norway*

**Background:** Previous studies have identified several long-term complications following cisplatin-based treatment in testicular cancer survivors (TCS). We evaluated the impact of long-term serum levels of platinum (Pt) on neuro- and ototoxicity (NTX), cardiovascular disease (CVD) and hypogonadism in TCS. **Methods:** 292 cisplatin-treated TCS (1980-1994) participated in a national follow-up study (2007-2008), including laboratory tests and a questionnaire. Serum Pt was quantified by Inductively Coupled Plasma-Mass Spectrometry. Symptoms of NTX were assessed with Scale for Chemotherapy-Induced Neurotoxicity (SCIN), with each symptom categorized in 4 categories ranging from 0, "not at all" to 3, "very much". Total SCIN score was the sum of six scores, ranging from 0 to 18, and categorized into quartiles. Information about CVD (validated) and medication were retrieved from the questionnaire. Hypogonadism was defined as using testosterone substitution and/or having testosterone <10nmol/l. Associations between NTX and long-term Pt levels were analyzed with ordinal logistic regression. Cox regression was performed to evaluate the risk for CVD, and logistic regression for hypogonadism according to levels of Pt and cisplatin dose. The results are presented as odds ratio (OR) or hazard ratio (HR) with 95% confidence intervals (CI), and are adjusted for age. **Results:** Median follow-up was 20 years (range 11-28). Median Pt was 86 ng/L (range 0-725). There was a significant association between the highest Pt quartile (yes/no) and quartiles of total SCIN-score (OR 1.67, 95% CI 1.03-2.70), tinnitus (OR 1.77, 95% CI 1.08-2.89) and hearing impairment (OR 1.79, 95% CI 1.10-2.92). In total 24 (8.2%) TCS had a CVD event during follow-up. Increasing cisplatin dose, per 100 mg, was significantly associated with CVD (HR 1.14, 95% CI 1.01- 1.28) and hypogonadism (OR 1.09, 95% CI 1.00-1.19). No association was found between residual Pt versus CVD and hypogonadism. **Conclusions:** 20 years after chemotherapy, residual serum Pt was significantly associated with NTX. The risk of CVD and hypogonadism increased with higher cisplatin dose, but was not associated with serum Pt.

**4519 Poster Highlights Session (Board #11), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Association of higher institutional volume with improved overall survival in clinical stage III testicular cancer: Results from the National Cancer Data Base (1998-2011).** *Presenting Author: Claudio Jeldres, Virginia Mason Medical Center, Seattle, WA*

**Background:** Improvements in survival have been achieved with the introduction of cisplatin-based chemotherapy and refinements of local therapies, such as post-chemotherapy retroperitoneal lymphadenectomy (PC-RPLND) in the setting of metastatic testicular germ cell tumors (TGCT). However, there have been no comprehensive efforts to measure the effect of expertise in TGCT in the US. We hypothesized that hospital volume is associated with overall survival in clinical stage III (CSIII) TGCT. **Methods:** Within the National Cancer Data Base [NCDB] we retrospectively identified all patients with CSIII TGCT between 1998 and 2011. Inclusion criteria were CSIII at diagnosis and chemotherapy treatment. Hospital volume was defined as the number of TGCTs diagnosed per hospital per year, and since its distribution was bimodal with an early peak and a second peak of volumes above 60, we categorized by tertiles below 60 (1-5, 6-10, 11-60) and a fourth group of ">60". Association between overall survival and hospital volume categories were assessed by Kaplan-Meier and Cox regression. **Results:** Within the NCDB, of 79119 patients with TGCT, 8205 (10.4%) were diagnosed with CSIII. Median age at diagnosis was 32 years (range 18-84) and median follow-up was 5.7 years (range 0.1-14.9). Therapy was delivered in community, "comprehensive" community and academic hospitals in 10.0%, 47.3% and 40.5%, respectively. PC-RPLND was performed in 1295 (15.8%) patients. Median hospital volume was 8 and ranged from 1 to 115 cases per year. Death occurred in 1225 (24.8%) patients. At 5 years, overall survival was 74.3%, 76.9%, 75.2%, 86.1% for hospital volume categories 1-5, 6-10, 11-60 and >60, respectively. The greatest disparity for risk of death was recorded between groups 1-5 and >60 (HR: 0.85, p=0.03). **Conclusions:** Patients with advanced metastatic testicular cancer treated at high volume hospitals exhibit better overall survival rates compared to their counterparts. These results suggest that broad efforts should be made to develop and improve collaborative care models among institutions in order to disseminate the experience of higher volume centers.

**4520 Poster Highlights Session (Board #12), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**A prospective observational study of metastatic renal cell carcinoma (mRCC) prior to initiation of systemic therapy.** *Presenting Author: Brian I. Rini, Cleveland Clinic, Taussig Cancer Institute, Cleveland, OH*

**Background:** The biology of mRCC includes a subpopulation of patients (pts) with indolent growth. Because of the toxicity and non-curative nature of current systemic therapy, select pts may be better served with initial surveillance. A prospective phase II observation trial was conducted in pts with mRCC prior to initial systemic treatment. **Methods:** Pts with treatment-naïve, asymptomatic, histologically-confirmed mRCC and metastases were enrolled. Local therapy prior to and during the study was permitted. Radiographic assessment was performed at baseline, every 3 months for year 1, every 4 months for year 2, then every 6 months. The primary objective was to characterize time to initiation of systemic treatment. Secondary endpoints included assessment of depression/anxiety using standardized questionnaires (FKSI-DRS and HADS) and peripheral blood immune repertoire (TH1/TH2, MDSC, Tregs). Target accrual of 50 pts provided adequate power for the primary descriptive endpoint and 80% power to detect changes in correlate endpoints based on a two-sided Wilcoxon signed rank test. **Results**: 52 pts were accrued; median age 67 (range, 47-88); 75% male; 94% ECOG 0; 96% clear cell; 8% prior metastasectomy and Heng risk group favorable/intermediate 26%/74%. Baseline tumor burden (per RECIST 1.0) was 3.2cm (0.8-19.6cm). Median time on observation until systemic therapy was started was 14.1 months (95% C.I. 10.6-19.3), with estimated 12 month and 24 month rates of continued surveillance of 58% and 33%, respectively. Median change in tumor burden on study was 0.8cm (0-6.5cm); relative change +34% (0-311%) and median growth rate 0.14 cm/month (0-1.75). 31 pts have come off observation (61% for PD), and 25 pts have received systemic therapy. Pts with baseline tumor burden ≤1.5 cm vs. >1.5 cm had a median observation period of 31.6 months vs. 13.8 months (p=0.06). Neither location nor number of metastatic sites impacted the length of observation. Anxiety/depression were not prevalent at baseline, and scores did not worsen over time. There were no significant changes in immunologic parameters. **Conclusions**: A subset of mRCC pts can be safely observed for a period of time before starting systemic therapy.

**4521 Poster Highlights Session (Board #13), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Outcomes of treatment cessation in select metastatic renal cell carcinoma (mRCC) patients.** *Presenting Author: Kriti Mittal, Cleveland Clinic, Cleveland, OH*

**Background:** Tyrosine kinase inhibitors (TKIs) demonstrate efficacy in mRCC, but may cause significant adverse effects (AEs). We have previously evaluated outcomes in patients (pts) receiving prolonged treatment breaks on TKIs and expand and update this experience herein. **Methods:** mRCC pts on targeted therapy who discontinued treatment for ≥3 months were analyzed retrospectively. Treatment break was defined as a period of drug cessation for reasons other than progressive disease. Pts could receive treatment breaks with multiple lines of therapy (defined sequentially as treatment A, B, C etc.) A number of patients continue on treatment/observation, hence durations were estimated using the Kaplan-Meier method. **Results:** Baseline characteristics (n=112) were: 75% male; median age at diagnosis 56; 95% clear cell. 19% pts had received prior systemic therapy. 48% pts were favorable, 48% intermediate and 4% poor risk by Heng criteria. Table 1 depicts outcomes with sequential lines of therapy. Overall, pts received a median of 2 treatments. Treatment A primarily included sunitinib (55%), sorafenib (13%), or bevacizumab in combination with temsirolimus (10%)/ interferon (9%). Common reasons for breaks in treatment A were toxicity/AEs (57%) & physician choice (26%). 40 (36%) pts remain on treatment break from the first treatment (A). 25 (22%) pts have undergone 2 treatment breaks. 68 (61%) pts restarted treatment (B); 33 (49%) of these were rechallenged with previously used therapy & 35 (51%) received alternative TKIs. Overall, 30 patients have died; median survival is 71.7 months (range 1.3- 93+ months). Achievement of CR prior to the initial treatment break (n=15) was associated with a longer surveillance period (p=.0004). **Conclusions:** A treatment break is feasible in selected pts, especially after achievement of CR with TKIs. This strategy may be associated with acceptable overall disease control and reduced toxicity.

| Treatment | Number of pts starting treatment | Median duration of therapy in months (95% CI) | Number of pts on treatment break | Median duration of break in months (95% CI) |
|---|---|---|---|---|
| A | 112 | 13.5 (11-16.4) | 112 | 16.8 (12.5-26.4) |
| B | 68 | 16.1 ( 11.4-20) | 24 | 9.5 (4.6-10.3) |
| C | 43 | 14.8 ( 12-17.2) | 10 | 7.1 |
| D | 15 | 13.8 (5.7-18.6) | 3 | 15.9 |

**4522 Poster Highlights Session (Board #14), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**A phase II study of pazopanib (P) in patients (Pts) with localized renal cell carcinoma (RCC) to enable partial nephrectomy (PN).** *Presenting Author: Adriana L. Alvarez, Cleveland Clinic, Taussig Cancer Institute, Cleveland, OH*

**Background:** PN is the preferred surgical approach for localized renal masses in order to preserve renal function, but is not always possible due to tumor size/location. VEGF-targeted agents such as a Paz have shown safety and anti-tumor effect in primary RCC tumors, thus allowing for potential conversion to PN in patients who would otherwise require radical nephrectomy (RN). **Methods:** Pts with treatment-naïve, localized clear cell RCC meeting one or more of the following criteria were enrolled on a prospective phase II trial: estimated GFR < 30 mL/min if RN was performed, risk of morbidity > 30% with PN due to tumor anatomy (e.g. proximity to renal vasculature) or Renal Nephrometry Score (RNS) 10-12. Paz 800 mg po daily was given continuously with repeat imaging at 8 and 16 weeks, and PN performed if/when adequate tumor reduction per primary surgeon discretion. The primary endpoint was rate of conversion to PN ($H_o$ 15% vs. $H_a$ 40%; p=0.05; power 90%). **Results:** Twenty-three pts were enrolled; 85% male, median age 64, 70% PS 0, 60% had baseline GFR<60. 90% of pts were able to undergo PN; 2 pts required RN. The median time from the start of Paz to surgery was 10.6 weeks (range, 5.4-18.9). Median baseline tumor size was 7.6 cm (range, 3.7-10.7cm); median RNS was 11 (range, 8-12); 82% were considered highly complex by RNS. 95% of tumors shrank (median decrease 1.8 cm; range 0.2-3.8); median change relative to baseline -26% (range, +6.3% to -40.9%). RECIST PR rate was 32%. RNS decreased in 81% of tumors and complexity group decreased in 43%. The estimated median post-PN change in GFR relative to baseline (ml/minute/1.73 $m^2$ per 2005 MDRD equation) was an 18.0% decrease (range, -46% to +21%). No unexpected surgical complications or unexpected Paz toxicity was observed. **Conclusions:** Neoadjuvant Paz leads to tumor downsizing in clear cell RCC tumors and allows for PN in a subset of patients in whom RN is otherwise required. Clinical trial information: NCT01158521.

**4523 Poster Highlights Session (Board #15), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**High-dose (HD) IL-2 for metastatic renal cell carcinoma (mRCC) in the targeted therapy era: Extension of OS benefits beyond complete response (CR) and partial response (PR).** *Presenting Author: Michael Morse, Duke University Medical Center, Durham, NC*

**Background:** HD IL-2 has been reported to have a overall response rate (ORR) for mRCC of 15% and a median OS of 19 months (Fyfe,1995), however, the studies that led to its regulatory approval are >15 years old and were performed in an era preceding targeted therapies. **Methods:** The PROCLAIM registry (www.proclaimregistry.com), a HD IL-2 observational database currently with over 30 participating sites, consists of a retrospective cohort (treated between 2007 and 2012) informing an ongoing prospective cohort (~ 600 patients). We report on the retrospective mRCC subjects (n=97, 13 sites) with survival status determined as of November 2013 and a median follow-up of 32 months. Sites were encouraged to enroll patients sequentially. Inclusion criteria required that patients have received at least one dose of HD IL-2. **Results:** The ORR was 22% (8% CR and 14% PR). Of 97 subjects, 36 were confirmed deceased and 61 were known to be alive, none were lost to follow-up. The median OS was 51 months, compared to a median OS range of 5-35 months for FDA-approved targeted agents (Harrison, 2013). There was significant clinical benefit in patients with CR, PR, and stable disease (SD), none of which reached median OS compared to 37.9 months in patients with progressive disease (PD). There is a significant advantage in PROCLAIM for those patients treated 1st vs. 2nd line HD IL-2; the median OS was 61.8 months (n=82) vs 15.3 months (n=15), respectively. The clinical benefit of HD IL-2 therapy as front line is consistent with published data (Birkhauser, 2013). No deaths due to IL-2 related toxicity were reported in the retrospective cohort. **Conclusions:** The PROCLAIM registry documents a vastly improved OS for HD IL-2 compared to historical results during a time interval marked by the advent of targeted therapy for advanced RCC. Response to IL-2 (CR or PR) is associated with prolonged survival, however, stable disease as well as front line use also appears to positively impact survival. Issues including patient selection characteristics and treatment sequencing are hypotheses currently being explored in the prospective database.

**4524^ Poster Highlights Session (Board #16), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Long-term survival in unfavorable-risk mRCC patients treated with a combination of autologous immunotherapy (AGS-003) plus sunitinib.** *Presenting Author: Asim Amin, Levine Cancer Institute, Charlotte, NC*

**Background:** Treatment for metastatic renal cell carcinoma (mRCC) has evolved significantly over the last decade due to enhanced understanding of the biology of RCC resulting in availability of number of agents targeting the VEGF axis and mTOR pathway. These treatments however, usually do not elicit durable responses and may have significant toxicities. AGS-003 is an autologous immunotherapy designed to induce an immune response to patient's own tumor. In a phase 2 trial, AGS-003 in combination with sunitinib was studied for safety and efficacy. Updated survival data is presented. **Methods:** In this open label, phase 2 study, subjects with newly diagnosed metastatic clear cell RCC were enrolled. Subjects received sunitinib (4wks on, 2wks off) combined with AGS-003 (every 3wks X 5 doses, then every 12wks) until progression. Subjects were followed for PFS and OS throughout the trial and during a rollover protocol. **Results:** For the twenty-one subjects (11 intermediate risk, 10 poor risk) treated, the median PFS was 11.2 months and the median OS was 30.2 months. The recently achieved median OS for the intermediate risk population (1 to 2 risk factors) was 57.1 months. Accordingly, 52% of all subjects achieved OS ≥ 30 months and 33.3% of subjects were still alive at 48 months after registration. Five of the original 21 (23% of the study population) have exceeded, or are currently nearing the five-year plus survival mark. The absolute change in CD8+CD28+ memory T cells (the proposed MOA for AGS-003) directly and significantly correlated to prolonged OS, PFS, and best tumor response. **Conclusions:** When compared to historical estimates of PFS and OS for unfavorable risk patients (time from diagnosis to treatment of less than one year), the addition of AGS-003 to sunitinib resulted in a 50% increase in median PFS, doubling of expected median OS, more than 50% of patients surviving long-term (OS ≥ 30 months) and 33% of patients surviving for at least 54 months. Updated survival and corresponding CD8+CD28+ memory T cell expansion in long-term survivors will be presented. Currently the combination of AGS-003 plus sunitinib is being compared to sunitinib alone in a large phase III study (ADAPT). Clinical trial information: NCT00678119.

**4525 Poster Highlights Session (Board #17), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**A randomized phase II study of GDC-0980 versus everolimus in metastatic renal cell carcinoma (mRCC) patients (pts) after VEGF-targeted therapy (VEGF-TT).** *Presenting Author: Thomas Powles, St. Bartholomew's Hospital, London, United Kingdom*

**Background:** GDC-0980 (G) is a potent oral dual pan-PI3K and mTOR (TORC1/2) inhibitor that has been evaluated in multiple solid tumors in Phase I and II. Everolimus (E) inhibits TORC1 and is active in mRCC post VEGF-TT. This study is the first to dirctly test if a PI3K/mTOR inhibitor may improve efficacy over a TORC1 inhibitor. **Methods:** Clear cell mRCC pts who progressed on or after VEGF-TT were randomized (1:1) to G (40 mg QD) or E (10 mg QD), stratified by MSKCC score and time to progression on first VEGF-TT ($\leq$ or $>$ 6 months). The primary endpoint was progression-free survival (PFS); secondary endpoints included safety, overall survival (OS), objective response rate (ORR); and pharmacokinetic (PK) and biomarker correlation with safety and efficacy were exploratory. **Results:** Eighty-five pts were randomized (G 42:E 43). After 62 events (G 32:E 30), stratified analysis revealed the median PFS was significantly shorter for G than E (3.7 vs. 6.1 mo: HR 2.04 [95%CI: 1.18-3.54; $p<0.01$]) and did not favor G for any stratification subgroup. Median OS was not significantly different but trended in favor of E (11.9 vs. 14.6 mo: HR 1.73 [95%CI: 0.87-3.43; $p=0.12$]). ORR was 7.1% for G and 11.6% for E. Patients treated with G had greater incidence of Grade 3-4 adverse events (AEs) and were more likely to discontinue treatment because of an AE (G 31%:E 12%). G was associated with substantially more high-grade hyperglycemia (G 40%:E 7%) and rash (G 24%:E 5%). PK analyses of G suggest a relationship between exposure and safety (rash and hyperglycemia), but no clear exposure-efficacy relationship. Retrospective biomarker analyses from archived tissue revealed a relationship between VHL mutation status (by NGS) and outcome with E but not G. High HIF1A protein expression was associated with better outcome in both arms. **Conclusions:** This study was unable to demonstrate that inhibition of PI3K/TORC1/TORC2 with GDC-0980 provides any benefit over inhibition of TORC1 alone with everolimus. This may be due to the high rate of AEs associated with potent pathway inhibition. VHL mutation and HIF1A expression may be predictive of mTOR inhibitor benefit, though future prospective validation is required. Clinical trial information: NCT01442090.

**4526 Poster Highlights Session (Board #18), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**PD-L1 expression in non-clear cell renal cell carcinoma and benign kidney tumors.** *Presenting Author: Andre Poisl Fay, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Programmed death-1 (PD-1) receptor negatively regulates T cell-mediated responses.PD-1 ligand (PD-L1) is aberrantly expressed in clear cell renal cell carcinoma (ccRCC) and is associated with worse prognosis. PD-L1 expression and its association with clinicopathological features/clinical outcome are unknown in non-ccRCC and benign kidney tumors (BKT). **Methods:** Formalin-fixed paraffin embedded (FFPE) specimens were obtained from 124 patients (pts) with chromophobe RCC (CHR), papillary RCC (PAP), translocation Xp11.2 RCC (TrL), collecting duct carcinoma (CDC), oncocytoma (ONC), and angiomyolipoma (AML). PD-L1 expression was evaluated by immunohistochemistry using a mouse monoclonal anti-PD-L1 antibody (405.9A11). The assay was validated using FFPE cell line controls known to be positive or negative for PD-L1 expression by flow cytometry. PD-L1 positivity (PD-L1+) was defined as $\geq$5% tumor cell membrane staining. For immune cells, a combined score based on the extent of infiltrate and percentage of positive cells was used. Baseline characteristics including stage/grade and outcome data [time to recurrence (TTR) and survival (OS)] were also collected. **Results:** Among 124 pts, 17 (13.7%) were considered PD-L1+ in tumor cells: 2/36 (5%) of CHR, 5/50 (10%) of PAP, 4/11 (36%) of TrL, 1/5 (20%) of CDC, 5/15 (33%) of ONC and 0/7 (0%) of AML. In non-ccRCC, PD-L1+ in tumor cells was significantly associated with higher stage ($p=0.025$) and grade ($p=0.03$), as well as lower OS on univariate analysis ($p<0.001$). On the other hand, PD-L1+ by immune cells was observed in 73 (58.8%) pts: 13/36 (36%) of CHR, 30/50 (60%) of PAP, 10/11 (91%) of TrL, 5/5 (100%) of CDC, 8/15 (53%) of ONC and 7/7 (100%) of AML. PD-L1+ in immune cells did not correlate with stage ($p=0.3$) or grade ($p=0.1$). In non-ccRCC, a trend for lower OS was observed in pts with PD-L1+ in immune cells ($p=0.08$). PD-L1+ in tumor cell membrane and immune cells were associated with lower TTR ($p=0.009$ and $p=0.019$, respectively) **Conclusions:** PD-L1 expression is variable in non-ccRCC and BKT and depends on histology. PD-L1+ on tumors cells, but not immune cells was associated with aggressive features. In non-ccRCC, PD-L1+ pts (by either tumor or immune cells) appear to present worse TTR and OS.

**4527 Poster Highlights Session (Board #19), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**CGH array and matching gene expression profiling for identification of distinct molecular variants among type II papillary renal cell carcinomas.** *Presenting Author: Laurence Albiges, Institut Gustave Roussy, Villejuif, France*

**Background:** Type II papillary renal cell carcinoma (pRCC) is a heterogeneous entity with poor prognosis. Limited biological data are available to date. **Methods:** 220 frozen pRCC were collected through French RCC Network, quality controlled for percentage of malignant cells >70% and subsequently RNA and DNA extraction were performed. Gene expression data generated with human whole genome Agilent 8x60K arrays was assessed on 98 pRCC, including, 45 type II pRCC. Copy number alterations were analysed using Agilent Human 2x400K or 4x180 on 37 type II pRCC. **Results:** Using gene expression profiling (GEP), we identified two distinct subgroups of type II pRCC that were associated with distinct pathological features: group A included tumors with higher grade, higher stage and more lymph nodes involvement ($p<0.05$) pRCC than group B harboring more favorable features. CGH array analysis of tumors clustering in GEP groups A vs B identified distinct patterns of copy number alterations (Group A: -1p, -11, +12, -15, Group B: +2, +5, +20). More interestingly, CDKN2A/2B (9p) loss was more likely to be observed in group A tumors 19% vs. 8% in group B tumors, in line with previous report of 9p loss to be associated with a dismal prognosis in pRCC (Klatte 2009). Four cases out of 37 (11%) presented chromothripsis (catastrophic genome rearrangements). This incidence is higher than in other solid tumors reports (<2%). Chromothripsis previously reported in neuroblastoma, melanoma, myeloma and acute myeloid leukaemia has been strongly linked to poor survival and therefore its diagnosis has potential to aid prognosis and stratification in pRCC. **Conclusions:** We report the first cohort of type II pRCC assessed by copy number analysis and matching gene expression profiling in type II pRCC. Gene expression profiling identifies two subgroups among type II pRCC. CDKN2A/2B loss as well as chromothripsis events appear as recurrent mechanism in the biology of type II pRCC.

**4528 Poster Highlights Session (Board #20), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Genotype correlations with blood pressure and efficacy outcomes from the randomized phase III AXIS trial of second-line axitinib versus sorafenib in metastatic renal cell carcinoma.** *Presenting Author: Bernard J. Escudier, Institut Gustave Roussy, Villejuif, France*

**Background:** In the AXIS trial, axitinib significantly increased progression-free survival (PFS) vs sorafenib in patients with previously treated metastatic renal cell carcinoma (mRCC). Final analyses of association between select germline single nucleotide polymorphisms (SNPs) and outcomes in AXIS are reported. **Methods:** DNA samples from blood were genotyped by TaqMan allelic discrimination. Logistic/Cox regression analyses evaluated association between 15 SNPs in 4 genes (*VEGF-A*, *VEGFR1*, *VEGFR2*, *HIF1α*) and blood pressure (BP; grade $\geq$3 hypertension, diastolic BP >90 mmHg or increase $\geq$15 mmHg from baseline) and efficacy (overall survival [OS], independently-assessed objective response rate [ORR] and PFS) endpoints. Kaplan-Meier PFS/OS estimates were compared with 2-sided unstratified log-rank tests. Multivariate analyses assessed SNPs and baseline characteristics as potential predictors of PFS/OS. **Results:** Genotype samples were available for 305/714 (43%) patients: 159 received axitinib, 146 sorafenib. After Bonferroni correction for multiple comparisons, no association was found for SNPs with BP endpoints. In the axitinib arm, *HIF1α* rs11549465 (C/T vs C/C) was associated with shorter PFS (2.8 vs 8.3 mo; HR 1.93; $P_{unadj}=0.006$; $P_{adj}=0.09$) and OS (13.3 vs 22.6 mo; HR 1.88; $P_{unadj}=0.007$; $P_{adj}=0.11$), and *VEGF-A* rs699947 (A/A vs C/C) and rs833061 (C/C vs T/T) with longer OS (27.0 vs 13.4 mo; HR 0.39; $P_{unadj}=0.001$; $P_{adj}=0.015$). In the sorafenib arm, *VEGFR2* rs2071559 (G/G vs A/A) was associated with higher ORR (21% vs 0%; $P_{unadj}=0.005$; $P_{adj}=0.075$), and longer PFS (4.7 vs 2.9 mo; HR 0.49; $P_{unadj}=0.01$; $P_{adj}=0.15$) and OS (26.8 vs 13.8 mo; HR 0.41; $P_{unadj}=0.002$; $P_{adj}=0.03$). In multivariate analyses, no SNP predicted axitinib efficacy; *VEGFR2* rs2071559 predicted PFS ($P=0.0053$) and OS ($P=0.0027$) for sorafenib. Sensitivity/specificity of *VEGFR2*rs2071559 for OS was <80%. **Conclusions:** No SNP predicted axitinib outcomes, whereas *VEGFR2* rs2071559 may have predicted sorafenib efficacy in patients with mRCC. Sensitivity/specificity limitations, however, preclude the use of this SNP for selecting sorafenib in individual patients. Clinical trial information: NCT00678392.

**4529 Poster Highlights Session (Board #21), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Loss of BAP1 and PBRM1 expression in non-clear cell renal cell carcinomas compared to clear cell renal cell carcinomas.** *Presenting Author: Thai Huu Ho, Mayo Clinic Arizona, Scottsdale, AZ*

**Background:** Loss of function mutations in *PBRM1* (41-50%) and *BAP1*(5-15%) are associated with poor outcomes for patients with clear cell renal cell carcinoma (ccRCC) tumors. However, there are no data regarding the prevalence of these mutations in other RCC subtypes (non-ccRCC). We evaluated loss of PBRM1 and BAP1 expression in ccRCC and non-ccRCC tumors using an IHC assay for which negative staining correlates with loss of function mutations. **Methods:** From our Registry database, we identified 311 and 105 patients treated surgically for ccRCC and non-ccRCC. We performed *IHC assays to evaluate PBRM1 and BAP1 protein expression.* We classified tumors as BAP1 or PBRM1 negative when tumor cells showed diffuse absence of nuclear staining. We compared loss of expression of these two proteins between ccRCC and non-ccRCC using Fisher's exact tests. **Results:** Of the total cohort of 416 patients, we successfully stained BAP1 in 406 (97.5%) and PBRM1 in 372 (89.4%). Of those with successful staining, we further excluded samples with focal negative or weak positive expression of BAP1 (n=59) or PBRM1 (n=55). Thus, we were left with 186 ccRCC and 79 non-ccRCC patient samples that had both BAP1 and PBRM1 available for analysis. We observed BAP1 loss of expression in 9% (17/186) of the ccRCC tumors but only 1% (1/79) of the non-ccRCC tumors (p=0.016). Similarly, we noted loss of expression of PBRM1 in 43% (80/186) of the ccRCC tumors but only 4% (3/79) of the non-ccRCC tumors (p=0.0001). Of note, within the non-ccRCC group, we observed 0% (0/61) papillary tumors and 5% (1/18) chromophobe tumors with loss of BAP1. By comparison, 3% (2/61) of papillary tumors and 1/18 (5%) of chromophobe tumors showed loss of PBRM1 expression. **Conclusions:** Our data are the first to suggest that loss of function mutations in *PBRM1* and *BAP1* are less common in non-ccRCC tumors compared to ccRCC. If these findings are independently confirmed, they suggest that while loss of PBRM1 and BAP1 are key events in ccRCC, disruption of other pathways may support tumorigenesis in non-ccRCC subtypes.

| BAP1/PBRM1 | Papillary | Chromophobe | ccRCC |
|---|---|---|---|
| -/- | 0 (0%) | 0 (0%) | 3 (2%) |
| -/+ | 0 (0%) | 1 (5%) | 14 (8%) |
| +/- | 2 (3%) | 1 (5%) | 77 (41%) |
| +/+ | 59 (97%) | 16 (90%) | 92 (49%) |
| | 61 | 18 | 186 |

**4530 Poster Highlights Session (Board #22), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Association of loss of BAP1 expression in cell renal cell carcinomas with PDL1 expression.** *Presenting Author: Richard Wayne Joseph, Mayo Clinic Cancer Center, Jacksonville, FL*

**Background**: A subset (10-20%) of clear cell renal cell carcinoma (ccRCC) tumors evades the immune system through expression of programmed death ligand 1 (PDL1), and these tumors are associated with a more aggressive clinical course. Related to this, loss of PBRM1 or BAP1 expression in ccRCC is also associated with poor outcomes. Herein, we evaluate whether loss of PBRM1 or BAP1 expression is associated with PDL1 expression in ccRCC tumors. **Methods**: From the Mayo Clinic Renal Tumor Registry we identified 1,010 patients undergoing nephrectomy for localized ccRCC from 1990-2004 who had immunohistochemistry (IHC) for PDL1, BAP1, and PBRM1 as part of previous investigations. A pathologist (PK) classified PBRM1 and BAP1 as either positive or negative and excluded those with heterogeneous or weak staining. A separate pathologist (JCC) defined PDL1+ tumors as those with ≥5% on IHC. We examined the association of PDL1 expression with PBRM1 and BAP1 separately and in combination using two-sided p-values from Fisher exact tests. **Results:** Among the 1,010 patients, 126 (12%) were excluded for unclear PBRM1/BAP1 expression leaving a total of 884 (88%) for evaluation. The distribution of each marker is as follows: 87 (10%) BAP1 negative, 458 (52%) PBRM1 negative, and 81 (9%) PDL1 positive (see Table). BAP1-negative tumors were more likely to be PDL1 positive than BAP1-positive tumors (17% vs 8%, p=0.0102)); however, the absolute difference was small (9%). In contrast, PDL1 expression did not differ by PBRM1 status (10% vs 9%, p=0.56). In a combined analysis grouping tumors by both PBRM1 and BAP1 expression, there remained a significant association with PDL1 positivity (p=0.015). **Conclusions**: In this study, BAP1 negative tumors were more likely to be positive for PDL1; however, the majority of BAP1 negative tumors are PDL1 negative. PBRM1 expression was not associated with PDL1 positivity.

| | PDL1- n=803 (91%) | PDL1+ n=81 (9%) | P value |
|---|---|---|---|
| **Univariate** | | | |
| **PBRM1** | | | 0.56 |
| + | 384 (90.1%) | 42 (9.9%) | |
| - | 419 (91.5%) | 39 (8.5%) | |
| **BAP1** | | | 0.0102 |
| + | 731 (91.7%) | 66 (8.3%) | |
| - | 72 (82.8%) | 15 (17.2%) | |
| **Combined PBRM1/BAP1** | | | 0.015 |
| +/+ | 327 (92.1%) | 28 (7.9%) | |
| -/+ | 404 (91.4%) | 38 (8.6%) | |
| +/- | 57 (80.3%) | 14 (19.7%) | |
| -/- | 15 (93.8%) | 1 (6.3%) | |

**4531 Poster Highlights Session (Board #23), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Identification and validation of predictive biomarkers (BM) for everolimus (EVE) in metastatic renal cell carcinoma: Analysis of 442 patients on RECORD-3.** *Presenting Author: Martin Henner Voss, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** RECORD-3 is a phase 2 trial that compared 1st-line EVE then sunitinib (SUT) with first-line SUT then EVE at progression (1:1 randomization). The study did not meet its primary endpoint (median progression free survival (mPFS) non-inferiority) in unselected treatment-naïve mRCC pts. This work investigated BMs predictive of EVE efficacy (PFS in first-line). **Methods:** 121 cancer-related BMs were analyzed by multiplex ELISA on baseline plasma samples collected from 94% of the trial subjects. The subjects were divided into training (327) and validation (115) cohorts. Kaplan-Meier estimates of mPFS for individual BM (low vs high, relative to an optimal cut-point for each BM), hazard ratios (HR) from Cox proportional hazards model and log-rank test p-values for differences in PFS between treatments in BM subgroups were computed. **Results:** Three BM levels were predictive for mPFS with EVE in the training set (table). Similar mPFS between the treatments was seen in the low BM subgroups, while mPFS remained significantly shorter for EVE vs SUT in the high BM subgroups. mPFS for EVE was longer in low than in high BM patients, but independent of the BM levels in SUT treated patients. Some results were supported by the validation set. **Conclusions:** EVE and SUT efficacies were comparable for mRCC patients with low plasma levels of three novel BMs in the first-line setting. The correlation of these BMs with EVE efficacy may be due to their interactions with pathways associated with mTOR inhibitor resistance, such as activation of PI3K and MAPK pathways by RTK-AXL. Clinical trial information: NCT00903175.

| | | EVE | | SUT | | Cox PH | | Log-Rank |
|---|---|---|---|---|---|---|---|---|
| BM | level | mPFS (m) | 95% CI | mPFS (m) | 95% CI | HR (EVE/SUT) | 95% CI | P-value |
| Receptor tyrosine kinase AXL | low | 8.8 | 8.0 - 12.1 | 10.9 | 8.2 - 12.8 | 1.13 | 0.81 - 1.57 | 0.4355 |
| | high | 5.1 | 2.9 - 5.8 | 10.6 | 7.2 - 15.6 | 3.09 | 2.00 - 4.76 | <0.0001 |
| Interferon-inducible T-cell α chemoattractant (ITAC) | low | 13.5 | 8.2 - 18.8 | 10.9 | 7.9 - 15.7 | 0.9 | 0.55 - 1.47 | 0.3783 |
| | high | 5.8 | 5.3 - 8.1 | 10.7 | 8.2 - 12.1 | 2.03 | 1.49 - 2.77 | 0.0009 |
| Kidney injury molecule-1 (KIM-1) | low | 15.5 | 10.5 - 24.0 | 13.4 | 10.7 - 30.8 | 1.05 | 0.62 - 1.77 | 0.3459 |
| | high | 5.4 | 4.4 - 5.8 | 8.3 | 7.6 - 11.1 | 1.93 | 1.42 - 2.60 | 0.0001 |

Intent-to-treat population: mPFS for EVE and SUT: 7.9 m and 10.7 m; HR 1.43 (95% CI 1.15-1.77).

**4532 Poster Highlights Session (Board #24), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Prognostic and predictive tumor-based biomarkers in patients (pts) with advanced renal cell carcinoma (RCC) treated with interferon alpha (IFN) with or without bevacizumab (Bev): Results from CALGB (Alliance) 90206.** *Presenting Author: Harriet M. Kluger, Yale University, New Haven, CT*

**Background:** In CALGB 90206, a phase III trial of IFN +/- Bev, the addition of Bev was associated with an improved progression-free survival (PFS) in RCC pts. Previously, we assessed a panel of soluble cytokines and angiogenic factors and demonstrated that IL-6 and HGF were predictive of overall survival (OS) from Bev. The objective was to evaluate the prognostic importance of tissue expression levels of cytokines and angiogenic factors in pre-treatment specimens from CALGB 90206 pts and to test whether they interacted with the treatment arm in predicting OS and PFS. **Methods:** Tissue microarrays were constructed using 3 cores from pretreatment specimens from 220 patients and stained for VEGFR1-3, VEGF A, B, C and D, HGF, c-Met, IL-6, IL-6R and STAT3 using a method of quantitative immunofluorescence. Vessel density was quantified by area of CD-34 staining. The proportional hazards model was used to test for the prognostic importance of marker levels (prognostic factors) and whether they interacted with the treatment arm (predictive factors) in predicting OS and PFS using prior nephrectomy and Motzer risk groups as stratification factors. No adjustment for multiplicity was performed. **Results:** On multivariable analysis, the onlymarker predictive of PFS independent of treatment was HGF, while IL-6 had an interaction with treatment (p-value for interaction = 0.02). None of the markers tested were predictive or prognostic of OS. **Conclusions:** Expression of HGF in pre-treatment specimens was prognostic for PFS in RCC patients and IL-6 was predictive of PFS in Bev treated patients, consistent with our findings in plasma. If validated, these data suggest that IL-6 may help guide use of anti-VEGF based therapies.

| | Median PFS (months) | HR (95% CI) | p-value |
|---|---|---|---|
| **HGF Expression** | | 1.4 (1.1-1.8) | 0.02 |
| **Low (<= 4.03)** | 7.1 | | |
| **High (> 4.03 )** | 5.7 | | |
| **IL-6 Expression** | | 2.6 (1.2-6.1)* | 0.02* |
| **IFN arm** | 4.1 | 0.4 (0.2-0.8)** | |
| **Low (<= 24.66)** | | | |
| **High (> 24.66)** | 5.4 | | |
| **Bev+IFN arm** | 10.6 | 1.3 (0.7-2.5)** | |
| **Low (≤24.66)** | | | |
| **High (> 24.66)** | 8.0 | | |

*Based on the interaction term; ** Within arm estimates.

**4533 Poster Highlights Session (Board #25), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**VEGF and VEGFRs polymorphisms analysis in advanced renal cell carcinoma tissues: Is heterogeneity ever the answer?** *Presenting Author: Maristella Bianconi, Department of Medical Oncology, Università Politecnica delle Marche, Ancona, Italy*

**Background:** Metastatic renal cell carcinoma (mRCC) ever represented a challenge in patients' treatment, even with the new generation drugs. In fact there is a wide variability in the amount and duration of response among patients. Sunitinib a drug mainly targeting the angiogenic pathway, is commonly used in mRCC treatment. We previously reported how VEGF and VEGFRs SNPs could predict response to treatment with either sunitinib or pazopanib. Tumour heterogeinity and its possible correlation with response is matter of debate in mRCC. The aim of our study is to assess the expression of VEGF and VEGFRs polymorphisms in tumour, metastatic and normal renal tissues. **Methods:** We enrolled 123 patients treated at our Institution. We collected histologic samples of tumour, metastatic and normal renal tissue of 84 patients with mRCC treated with first-line sunitinib. For 61 patients samples of tumour, metastatic and normal renal tissue were available. Histologic samples were tested for VEGF-A, VEGF-C and VEGFR-1,2,3 single nucleotide polymorphisms (SNPs). Polymorphisms were correlated with PFS and OS. We then analysed concordance in SPNs expression among tissues. **Results:** The VEGF A rs833061 resulted significant in PFS (C>T, 17 vs 4 months; p<0.0001) and OS (C>T, 38 vs 10 months; p<0.0001). The VEGF A rs699947 was significant for PFS (A>C, 18 vs 4 months; p=0.0001) and OS (A>C, 37 vs 16 months; p<0.0001). The VEGF A rs2010963 was significant in PFS (G>C, 18 2 months; p=0.0001) and OS (G>C, 36 vs 9 months; p=0.0045). The VEGR3 rs6877011 was significant in PFS (C>G, 12 vs 4 months; p=0.0075) and OS (C>G, 36 vs 17 months; p=0.0001).59 out of 61 patients presented concordance between tumour, metastatic and normal renal tissue (97%). **Conclusions:** Preliminary data fromour analysis show how angiogenic polymorphisms are significantly correlated with either PFS and OS. These polymorphisms genotypes are preserved between tumour, its metastatic sites and the normal renal tissue. Further analyses will be presented at the Meeting.

**4534 General Poster Session (Board #102), Mon, 1:15 PM-5:00 PM**

**Feasibility and activity of two vinflunine (VFL)-based combinations as first-line chemotherapy (CT) in CDDP-unfit patients (pts) with advanced urothelial carcinoma (UC): VFL-gemcitabine (GEM) or VFL-CBDCA in a randomized international phase II trial (JASINT).** *Presenting Author: Maria De Santis, LBI-ACR Vienna and KFJ-Hospital, Vienna, Austria*

**Background:** There is no standard 1st line CT for advanced or metastatic UC in patients (pts) unfit for a CDDP-based regimen. CBDCA-GEM doublet or single agents are frequently used. VFL, a novel EMA approved agent in the post-platinum setting has shown to be safe in pts with renal impairment. The aim of this study is to provide data of the benefit/risk ratio of 2 VFL-based CT regimens in UC. **Methods:** Pts with a creatinine clearance (CrCl) <60mL/min but ≥30, PS 0/1, no prior systemic CT (except neoadjuvant or adjuvant CT if relapse occurred ≥6 months (mo) after last dose) were randomized. Based on the CrCl, <40 or ≥40mL/min, pts received q 21 days (D) VFL 250 or 280mg/m$^2$, plus GEM (Arm A) 750mg/m$^2$ D1&8 escalated to 1000 in cycle 2 (if no toxicity Grade (G) ≥2) or plus CBDCA AUC 4.5 D1 (Arm B). The primary endpoint was the disease control rate (DCR = CR + PR + SD, RECIST 1.1). With H0=41%, H1=63%, $\alpha$ =5% and $\beta$ =20%, 31 evaluable pts/arm were to be included to detect in each arm an improvement of 22% compared to H0. **Results:** 69 pts (34 arm A, 35 arm B) were enrolled 2011-2012: median follow-up 20.4 mo. Median (med) age was 70yrs, PS 0 in 42% and PS 1 in 58%; primary sites: 52% bladder and 46% upper tract; 16% had received prior CT. Pts characteristics were similar in both groups; 71% of pts had multiple comorbidities, cardiac in 23%. Med CrCl was 46mL/min (<40 in 19%). Med number of cycles was 5 [1–17] in arm A and 4 [1–11] in arm B. More haematological G3/4 adverse events (AE) were reported in arm B: neutropenia in 68% (vs 38%) and febrile neutropenia in 14% (vs 3%) of pts. Most common non-haematological G3/4 AE were fatigue (21.7%), infection (7.2%), and constipation (4.3%) without major difference between arms. DCR was similar in both groups: 76.5% (A) and 77.1% (B). ORR was confirmed in 44.1% vs 28.6%, med PFS was 5.9 vs 6.1 mo and med OS 13.9 vs 12.8 mo in arms A and B, respectively. **Conclusions:** This study confirms that both VFL doublets are feasible and can be administered for ≥4 cycles. The DCR was similar in both arms but haematological toxicity was more pronounced with VFL-CBDCA. Med OS warrants further study with VFL-GEM. Clinical trial information: NCT01599013.

**4535 General Poster Session (Board #103), Mon, 1:15 PM-5:00 PM**

**Stathmin-1 as a potential therapeutic target in urinary bladder cancer.** *Presenting Author: Ulrika Segersten, Department of Surgical Sciences, Uppsala University Hospital, Uppsala, Sweden*

**Background:** The oncoprotein-18/stathmin 1 (STMN1), involved in cell cycle progression and cell migration, has been reported to be expressed in several types of cancer, and is associated with clinical outcome in e.g. breast and liver cancer. The aims in this study were to investigate the clinical significance of STMN1 and to examine if STMN1 might be a possible therapeutic target in urinary bladder cancer. **Methods:** Immunohistochemical analyses of STMN1 protein expression were performed in three urinary bladder cancer cohorts; cohort I (115 Ta-, 115 T1-, 112 T2-4-tumors), a validation cohort II (236 T2-T4 tumors) based on randomized controlled trials and a metastatic primary tumor/matched metastasis-material (90 patients). In the urinary bladder cancer cell line, T24, the effect of STMN1 on cell proliferation and migration was evaluated by inhibiting the cellular expression of STMN1 using STMN1-siRNA. **Results:** Patients with T1- or muscle-invasive disease exhibiting high expressionof STMN1 had shorter overall survival (OS) and disease specific survival (DSS). In multivariate analysis, adjusting for stage, age and gender, the results were for T2-T4 patients: OS (HR=1.77 95% CI 1.02-3.07; p=0.04) and DSS (HR=2.04 95% CI 1.13-3.68; p=0.02); for T1-4 patients: DSS (HR=1.83 95% CI 1.09-3.08; p=0.02). The higher risk of cancer death within 2 years for T2-T4 patients with high STMN1-expressing tumors was validated in cohort II (HR= 1.76 95% CI 1.04 -2.99; p=0.03). In the metastatic bladder cancer material, 69% of the patients with one metastasis and 75% of the patients with several matched metastases were STMN1-positive in both the primary tumor and matched metastases. Moreover, the ability of the urinary bladder cancer cell line to grow or migrate was significantly reduced, (p<0.01 respectively p<0.0001) when transfecting the cells with a siRNA targeting STMN1. **Conclusions:** Our results suggest that STMN1 protein-expression has a potential both as a prognostic marker and a novel treatment target in urinary bladder cancer.

**4536 General Poster Session (Board #104), Mon, 1:15 PM-5:00 PM**

**A patient-derived xenograft (PDX) platform to optimize omics-driven precision medicine in bladder cancer.** *Presenting Author: Chong-xian Pan, Division of Hematology and Oncology, UC Davis Comprehensive Cancer Center, Sacramento, CA*

**Background:** Almost all cancers harbor multiple genetic alterations as determined by omics technologies, but most of these alterations are not driver ones critical for tumorigenesis. Hence, the efficacy of targeted therapy matching those alterations is still disappointing in most patients. We developed PDXs that share essentially the same genetic background as the parental cancers, and use this platform to optimize omics-drive precision medicine. **Methods:** PDXs were developed by direct implantation of fresh clinical cancer specimens in immunocompromised NSG mice (Jackson Laboratory, Sacramento, CA). Whole exome, transcriptome and microRNA sequencing was performed, followed by computational biological analysis to identify druggable genetic alterations that were further validated with immunofluorescence (IF) and immunohistochemical (IHC) staining. Efficacy tests together with mechanistic analysis were performed in NSG mice carrying PDXs. **Results:** So far, 21 PDXs have been established with an engraftment rate of 41 % (13/42) for invasive bladder cancer. The fidelity of PDXs was confirmed with cell morphology, tissue microarray IHC/IF staining and comparison of mutations in parental cancers and PDXs. Exome sequencing showed that 2 of the first 8 PDXs harbored PIK3CA mutations at the highly conserved helical and kinase domains. Transcriptome sequencing and IHC/IF staining revealed overexpression of several tyrosine kinase receptors. Of the first 8 PDXs, 5 had HER2/Neu overexpression (3+ by IHC), 5 fibroblast growth factor receptor 3 (FGFR3), and 4 EphB4 overexpression. Compared to the progression-free survival (PFS) of 9.5 days in the control arm, matched therapy with an FGFR3 inhibitor BGJ398 prolonged PFS to 18.5 days (p=2.61 X $10^{-6}$) in PDXs overexpressing FGFR3. Based on the miRNA profiling, a miRNA expression signature was identified that highly correlated with clinical response to chemotherapy (p=0.02) and accurately predicted response for defined responders (24/25 patients) or non-responders (11/11 patients). **Conclusions:** PDXs can potentially be used for efficacy assessment and mechanistic studies that can guide the design of precision cancer medicine.

**4537 General Poster Session (Board #105), Mon, 1:15 PM-5:00 PM**

**Delivery of peri-operative chemotherapy for muscle-invasive bladder cancer (MIBC) in routine clinical practice: Does regimen and timing matter?** *Presenting Author: Christopher M. Booth, Division of Cancer Care & Epidemiology, Cancer Research Institute, Queen's University, Kingston, ON, Canada*

**Background:** Few studies have documented regimens used and timing of peri-operative chemotherapy for MIBC in routine practice. In metastatic bladder cancer cisplatin has superior efficacy to carboplatin. Time to initiation of adjuvant chemotherapy (TTAC) from surgery is known to be associated with survival in other solid tumors. Here we describe regimens used and TTAC in the general population of Ontario, Canada. **Methods:** Treatment and physician billing records were linked to the Ontario Cancer Registry to describe use of neoadjuvant (NACT) and adjuvant (ACT) chemotherapy among all patients with MIBC treated with cystectomy in Ontario 1994-2008. Time to initiation of ACT (TTAC) was measured from cystectomy. Multivariate Cox regression was used to identify factors associated with overall (OS) and cancer-specific survival (CSS). **Results:** Of 2944 patients undergoing cystectomy, 4% (129/2944) and 19% (571/2944) were treated with NACT and ACT respectively. Five-year OS was 25% (95%CI 17-34%) for NACT, 29% (95%CI 25-33%) for ACT cases. Among patients with identifiable drug regimens, cisplatin was used in 82% (253/308) and carboplatin in 14% (43/308). The most common regimens were gemcitabine-cisplatin (54%, 166/308) and MVAC (21%, 66/308). Mean TTAC was 10 weeks; 23% of patients had TTAC >12 weeks. Advanced age (70+ years OR 3.86, 95%CI 1.25-11.9) and lower socioeconomic status (poorest quintile OR 2.38, 95%CI 1.13-5.02) were more likely to have TTAC > 12 weeks. Patients with node positive disease were less likely to have TTAC >12 compared to node negative (OR 0.58, 95%CI 0.34-0.99). TTAC greater than 12 weeks was associated with inferior OS (HR 1.28, 95%CI 1.00-1.62) and CSS (HR 1.30, 95%CI 1.00-1.69). In adjusted analyses, OS and CSS were lower among patients treated with carboplatin compared to those treated with cisplatin; OS HR 2.14 (95%CI 1.40-3.29) and CSS HR 2.06 (95% CI 1.26-3.37). **Conclusions:** Most patients with MIBC in the general population receive cisplatin and this may be associated with superior outcomes to carboplatin. Initiation of ACT beyond 12 weeks is associated with inferior survival. Patients should start ACT as soon as they are medically fit to do so.

**4538 General Poster Session (Board #106), Mon, 1:15 PM-5:00 PM**

**Next-generation sequencing to identify molecular alterations in DNA repair and chromatin maintenance genes associated with pathologic complete response (pT0) to neoadjuvant accelerated methotrexate, vinblastine, doxorubicin, and cisplatin (AMVAC) in muscle-invasive bladder cancer (MIBC).** *Presenting Author: Elizabeth R. Plimack, Fox Chase Cancer Center, Philadelphia, PA*

Background: Neoadjuvant cisplatin based chemotherapy prior to cystectomy is standard of care for MIBC, with 30-40% expected to achieve a pT0. Biomarkers predictive of pT0 are lacking. Methods: 36 MIBC pts treated on study with 3 cycles of neoadjuvant AMVAC were included. 14/36 were pT0. DNA from pre-treatment tumor tissue underwent sequencing of 287 cancer related genes and was analyzed for presence of base substitutions, indels, copy number alterations, and selected re-arrangements. The mean number of variants and variant status for each gene were correlated with pT0 using two-sample t-test and Fisher's exact tests. Variant data were used to create a classification tree to discriminate pts with and without pT0. Missense mutations were predicted to be deleterious/neutral using a support vector machine trained with sequence and protein structural features. Results: 747 alterations in 216 genes were detected. Pts with pT0 had more alterations (mean 25, range 11-39) than those with residual tumor (mean 18, range 8-32), p=0.01. All 13 pts with ≥ 1 variant in *ATM*, *RB1*, or *FANCC* achieved pT0 (positive predictive value=100%), while only 1/23 without a variant in 1 of these 3 genes achieved pT0 (negative predictive value=96%). This decision rule has a specificity of 100% and sensitivity of 93% for pT0. Permutation studies show the probability of this rule resulting in ≥ 97% accuracy by chance is ≤ 0.0001. Alterations in *ATM* and *RB1* remained independently associated with pT0 after correction for multiple testing. All but 1 of the alterations detected in *ATM*, *RB1* and *FANCC* were predicted to be deleterious. Conclusions: Alterations in ≥1 of *ATM*, *RB1* and *FANCC* predict pT0 to neoadjuvant AMVAC with high sensitivity and specificity. We hypothesize that defects in these genes, which are important for maintenance of chromatin structure and DNA repair, confer sensitivity to DNA damaging chemotherapy and that the accumulation of alterations seen among pts with pT0 reflect this phenotype. Independent validation of these findings is underway. Clinical trial information: NCT01031420.

**4539 General Poster Session (Board #107), Mon, 1:15 PM-5:00 PM**

**Assessing tumor response using CT density-volume trajectory in metastatic bladder cancer.** *Presenting Author: Les Folio, Radiology and Imaging Sciences, National Institutes of Health, Bethesda, MD*

**Background:** Automation advances in PACS provide efficient volumetric measurement capability not utilized by existing tumor criteria. We developed a combined density and volume assessment termed Automated Density and Volume Application (ADaVA) to quantify change in viable versus necrotic tumor volumes responding to anti-angiogenic therapy. Volume is not assessed in the Response Evaluation Criteria In Solid Tumors (RECIST) or other criteria such as MASS (Morphology, Attenuation, Size and Structure) and Choi. We compared overall survival (OS) predictive ability in ADaVA with existing and evolving criteria in metastatic bladder cancer. **Methods:** We assessed 141 lesions using RECIST, MASS, Choi, lesion volumes, and ADaVA at baseline and serial follow-up Contrast Enhanced CT exams (n=55) in 17 patients with metastatic bladder cancer treated with cabozantinib, a tyrosine kinase inhibitor. A semi-automated PACS tool (Carestream Health; Rochester, NY) segmented volumes for density thresholds representing viable (50-180 HU) or necrotic tissue (0-50 HU). RECIST response equivalents (partial response (PR), stable disease (SD) and progressive disease (PD)) were used. For each criterion, Kaplan-Meier curves and two-tailed log-rank test compared OS based on early response determination (PR+SD vs. PD); a Cox proportional hazards model assessed PR at any follow-up exam as a time-varying covariate for OS. **Results:** There was a statistical association between response determinations and OS (with binary tumor response) in total and low density-volume change in ADaVA (two-tailed, p=0.019); compared to other criteria that showed weak or no association. Low-density ADaVA change had the closest trend towards association (p=0.087; Hazard ratio=0.16; 95% CI on HR: 0.02 to 1.30) with time to developing PR. **Conclusions:** Our pilot study suggests that ADaVA incorporating lesion density and volume may predict OS as early as the first follow-up CT, potentially outperforming existing criteria. Combined density-volume criteria accurately reflect tumor burden and may predict outcomes earlier, improving therapeutic efficacy. Further study is warranted. Clinical trial information: 9236.

**4540 General Poster Session (Board #108), Mon, 1:15 PM-5:00 PM**

**High neutrophil to lymphocyte ratio persistent during first-line chemotherapy to predict clinical outcome in patients with advanced urothelial cancer.** *Presenting Author: Ugo De Giorgi, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) - IRCCS, Meldola, Italy*

**Background:** Increased neutrophil to lymphocyte ratio (NLR), an index of systemic inflammation, is associated with poor outcome for various types of cancers. We aimed to assess the role on outcome prediction of NLR at baseline and persistent during first-line chemotherapy in patients with advanced urothelial cancer (UC). **Methods:** We retrospectively reviewed 292 patients with unresectable or metastatic UC treated with first-line chemotherapy between January 2003 and December 2012. The cut-off values of NLR (>3 vs ≤3) were evaluated at pre-therapy and at day 1 of the second and third cycle (follow-up NLR). After univariate analysis, a multivariate analysis was carried out by Cox regression model and included the following variables: Eastern Cooperative Oncology Group (ECOG) performance status (≥2 vs 0-1), visceral disease (present vs absent), hemoglobin (<12 g/dL vs ≥12 g/dL), pre-therapy NLR (>3 vs ≤3) and follow-up NLR (>3 vs ≤3). **Results:** The median follow-up was 40.2 months (range, 0.5 to 100.4). The median progression-free survival (PFS) was 5.8 months (95% confidence interval (CI) 5.0-6.6) and the median overall survival (OS) was 10.9 months (95% CI 9.6-12.4). Patients with pre-therapy and follow-up NLR > 3 had a median PFS of 3.2 months and a median OS of 5.7 months. In multivariate analysis, visceral metastases, pre-therapy hemoglobin and follow-up NLR were significant predictors of PFS (HR 1.75, $p = 0.0001$; HR 1.57, $p = 0.0015$; HR 2.77, $p < 0.0001$, respectively), and of OS (HR 1.60, $p = 0.0023$; HR 1.59, $p = 0.0024$; HR 2.89, $p < 0.0001$, respectively); whereas pre-therapy NLR remained as predictor of OS only (HR 1.53, $p = 0.0101$). **Conclusions:** An increased NLR persistent during first-line chemotherapy is an independent predictive factor for patients with advanced UC.

**4541^ General Poster Session (Board #109), Mon, 1:15 PM-5:00 PM**

**Preliminary product parameter and safety results from NeuACT, a phase 2 randomized, open-label trial of DN24-02 in patients with surgically resected HER2+ urothelial cancer at high risk for recurrence.** *Presenting Author: Dean F. Bajorin, Memorial Sloan-Kettering Cancer Center, New York, NY*

**Background:** DN24-02 is an investigational HER2-targeted autologous cellular immunotherapy (ACI) based on the same manufacturing platform as sipuleucel-T, an ACI approved by the FDA and EMA for certain patients (pts) with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. DN24-02 consists of antigen presenting cells (APC) cultured with BA7072, a recombinant HER2-derived antigen (HER500) linked to GM-CSF. NeuACT (N10-1; NCT01353222) compares the efficacy and safety of adjuvant DN24-02 to surveillance in HER2+ urothelial cancer (UC) pts at high risk of relapse after resection. Preliminary product potency, immune response and safety data are reported. **Methods:** Pts randomized to DN24-02 received 3 infusions at 2 week intervals. Primary endpoint is overall survival. Secondary objectives include disease-free survival, antigen-specific immune response, product potency (measured by APC activation) and safety. **Results:** As of November 2013, 38 pts completed DN24-02 infusions and were assessed for product potency. APC activation was observed for each infusion and the profile was indicative of a prime boost effect, with a greater magnitude at infusions 2 (median 15.26; range: 6.42–23.97) and 3 (14.69; 7.38–30.86) than 1 (6.73; 3.47–14.34). T-cell associated cytokines were greater at infusions 2 and 3 than 1. Following treatment, significant increases were observed in peripheral immune responses ($p<0.01$), and were comparable in pts with and without neoadjuvant chemotherapy. Adverse events (AEs) occurring in >15% of 48 pts receiving ≥1 leukapheresis were fatigue (41.7%), chills (37.5), nausea (25.0), pyrexia (18.8) and headache (16.7). Three pts had treatment-related grade ≥3 AEs or SAEs. No clinically significant changes were reported in left ventricular ejection fraction. **Conclusions:** This preliminary analysis suggests a pattern of DN24-02 APC activation and T-cell cytokines consistent with immunological prime-boost similar to that of sipuleucel-T. DN24-02 appears well-tolerated in UC pts, and the most common AEs are similar to those reported with sipuleucel-T. Clinical trial information: NCT01353222.

**4542 General Poster Session (Board #110), Mon, 1:15 PM-5:00 PM**

**External validation of nomogram to predict progression-free survival at 6 months (PFS6) in patients receiving salvage therapy for advanced urothelial carcinoma (UC).** *Presenting Author: Guru Sonpavde, The University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL*

**Background:** A nomogram incorporating baseline prognostic factors has been reported to facilitate the evaluation of activity of salvage therapy for advanced UC (Pond GR, BJUI 2013). We performed an external validation in a phase III trial dataset. **Methods:** Data were obtained for patients randomized to vinflunine in the phase III trial comparing best supportive care +/- vinflunine. Progression-free survival at 6 months (PFS6) as well as the 4 prognostic factors: hemoglobin (Hb), performance status (PS), liver metastasis (LM) and time from prior chemotherapy (TFPC) were analyzed. Patients were grouped based on nomogram score and risk groups. Bootstrap analysis was performed and 95% bias-corrected and accelerated [BCa] CI were calculated. **Results:** Of 253 patients, 5 had missing TFPC and were excluded; thus, 248 were evaluable (Table). The number of nomogram points as a continuous variable was associated with PFS6 (odds ratio [OR]=1.10, 95% confidence interval [CI] = 1.05 to 1.15 / 10 point increase, c-index=0.680, $p<0.001$). Risk group was also significantly associated with PFS6 (OR=0.51, 95% CI=0.37 to 0.70 / increase in risk group, c-index=0.674, $p<0.001$). 95% BCa CI were calculated for the c-index (0.602 to 0.747) and for the estimated odds ratio (0.37 to 0.70). **Conclusions:** This external validation confirms the utility of the previously reported nomogram to predict PFS6 with salvage therapy in advanced UC. The nomogram is a useful tool to estimate the required minimal efficacy of agents in phase II trials to justify further investigation.

| | | N (%) | N (%) with PFS ≥6 months | p-value |
|---|---|---|---|---|
| **All patients** | | 248 | 63 (25.4) | |
| **PS** | 0 | 72 | 26 (36.1) | 0.016‡ |
| | ≥1 | 176 (71.0%) | 37 (21.0) | |
| **LM** | No | 177 | 56 (31.6) | <0.001‡ |
| | Yes | 71 (28.6%) | 7 (9.9) | |
| **Hb** | ≥10 g/dL | 212 | 58 (27.4) | 0.10‡ |
| | <10 g/dL | 36 (14.5%) | 5 (7.9) | |
| **TFPC** | ≥6 months | 74 | 26 (35.1) | 0.026‡ |
| | <6 months | 174 (70.2%) | 37 (21.3) | |
| **Risk factors** | 0 | 25 (10.1) | 12 (48.0) | <0.001† |
| | 1 | 66 (26.6) | 23 (34.9) | |
| | 2 | 86 (34.7) | 21 (24.4) | |
| | 3 | 65 (26.2) | 7 (10.8) | |
| | 4 | 6 (2.4) | 0 (0.0) | |
| **Nomogram estimated risk** | >30% | 49 (19.8%) | 23 (46.9) | <0.001† |
| | 20-29.9% | 75 (30.2%) | 21 (28.0) | |
| | 10-19.9% | 76 (30.7%) | 15 (19.7) | |
| | 5-9.9% | 43 (17.3%) | 4 (9.3) | |
| | <5% | 5 (2.0%) | 0 (0.0) | |

† Cochran-Armitage test for trend. ‡ Fisher's exact test.

**4543 General Poster Session (Board #111), Mon, 1:15 PM-5:00 PM**

**Trans Tasman Radiation Oncology Group (TROG) 02.03 phase III trial: Concurrent weekly cisplatin and radiation therapy in localized muscle-invasive bladder cancer—Compliance, toxicity, QOL, and overall results.** *Presenting Author: Nirdosh Kumar Gogna, Princess Alexandra Hospital - Mater Radiation Oncology Centre, Brisbane, Australia*

**Background:** This phase III trial investigated the benefits and toxicities of a combination of weekly cisplatin and radiation therapy (Arm A) compared with radiation therapy (RT) alone (Arm B)in the definitive treatment of muscle-invasive bladder cancer (MIBC). **Methods:** Adult patients with localized Stage T2-T4a, bladder cancer of predominant transitional cell carcinoma histology with no contraindications to the use of pelvic radiation therapy or cisplatin chemotherapy were eligible. Othet exclusion criteria included extensive or multifocal carcinoma in situ and a contracted bladder. An initial maximal transurethral resection of the bladder tumour (TURBT) preceded randomisation. The primary outcome was local failure at 3 years. The secondary endpoints included complete response rate at3 months, overall and disease free survival, acute and late toxicity and QoL. The QoL of patients receiving organ preserving treatments for MIBC had not been previously investigated in a randomised Phase III setting. Intitial accrual target was set at 150 patients over 4 years. Slow accrual lead to early closure with Thirty eight patients were being randomised to arm A and 30 patients to arm B. **Results:** Compliance with RT in both arms was excellent. About 15% of patients in the chemoradiation arm required a significant reduction in cisplatin dose delivery mainly because of declining renal function. Acute and late toxicity was similar in the two arms, but in the short to medium term chemoradiation did affect QoL. Trends towards better local control, distant disease free and overall survival were noted in the chemoradiation arm. **Conclusions:** Overall weekly cisplatin and radiation therapy in MIBC are reasonably well tolerated. Treatment however in the short to medium term does affect Qol. Notwithstanding this negative impact, recovery does follow in the longer term. This is yet another study which suggests that chemoradiation does offer the prospect of improving local control and overall survival compared to radiation therapy alone. Clinical trial information: No NCT00330499.

**4544 General Poster Session (Board #112), Mon, 1:15 PM-5:00 PM**

**Updated analysis of circulating tumor cells (CTCs) in patients with urothelial cancer (UC) undergoing systemic treatment: Implications across the clinical stages.** *Presenting Author: Andrea Necchi, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

**Background:** CTCs from patients (pts) at different clinical stages were analyzed by a never explored experimental approach based on a combination of two techniques. Provision of this information may contribute to optimize tailored therapies. **Methods:** 3 cohorts of have been analyzed: pts with muscle-invasive bladder cancer receiving neoadjuvant (NA) sorafenib + chemotherapy (CT) (NCT01222676), and metastatic pts receiving first-line MVAC (M1), and second-line (M2) anti-TGF$\beta$ receptor ALK1 PF-03446962 in a phase 2 trial (NCT01620970). 5 ml of whole blood were filtered by ScreenCell Cyto devices and CTC status was assessed with centralized scoring by referral pathologists. Additional 5 ml of whole blood were processed by immunomagnetic beads (AdnaTestSelect® kit) and the expression level of a panel of markers (including *EPCAM* and *MUC1*) was studied using RT-multiplex PCR. The objective was the association with clinical endpoints (pathologic/clinical response, and relapse). **Results:** From 07/2012 to 1/2014, 65 pts (20 NA, 31 M1, and 14 M2) were enrolled. Rates of baseline CTC+ were: 92, 75, 91%, and 31, 50, 64% with the 2 techniques, respectively. NA setting: all pts had a stepwise reduction of CTC count/5 ml blood by ScreenCell (median baseline of 14 [0-40] to 0 [0-9] – end of treatment). Increase in circulating EPCAM±MUC1 levels by CTC was seen in accordance with the 3 disease progressions (PD). M1 setting: While there was a discrepancy between CTC signals and partial/complete response (PR/CR), a trend towards an increase in CTC levels was observed in 7/9 evaluable relapsers. Pts who relapsed had a median of 43 CTC/5 ml (IQR: 17-51.5) at the end of CT, while all the others had levels <13. EPCAM profile was not concordant in all cases (median 1.01 vs 1 ng/ul). Interestingly, an increase in both CTC signals anticipated relapse in 5/9 evaluable responders (CR+PR). M2 setting: an increase in CTC was documented by both methods in each case, in accordance with PD. **Conclusions:** This combined technique was endowed with promising utility to anticipate the detection of clinical relapse. Refining molecular characterization might help designing informed clinical trials.

**4545 General Poster Session (Board #113), Mon, 1:15 PM-5:00 PM**

**Engrailed-2 (EN2) protein expression and prognosis in bladder cancer following radical cystectomy (RC).** *Presenting Author: Simon J. Crabb, University of Southampton, Southampton, United Kingdom*

**Background:** Dysregulation of various developmental genes is associated with urological malignancies. In particular, HOXB13 overexpression is associated with aggressive invasive bladder cancer. Engrailed-2 (EN2), a member of the HOX gene family, was recently shown to be expressed and secreted by non-muscle invasive bladder cancer (NMIBC) leading to its development as a potential urinary diagnostic marker. However, the role of EN2 as a prognostic marker in muscle invasive advanced bladder cancer is unknown. **Methods:** We assessed EN2 protein expression in a tissue microarray of consecutive bladder cancer RC samples from a UK center. EN2 expression was prospectively dichotomised as positive (3+ nuclear and cytoplasmic staining) or negative. Univariate analyses of known prognostic factors and EN2 for survival outcomes from date of RC were by the Kaplan Meier method and log rank test. Statistically significant variables were then assessed by multivariate Cox regression. p values $<$ 0.05 were considered statistically significant. **Results:** 226 samples were eligible for inclusion (median age 72, range 33-87; 76.1% male, 90.3% pure/predominant transitional cell carcinoma). EN2 expression status was positive in 39 (17%) cases and negative in 160 (71%). No scoring was possible (mostly for missing cores) in 27 (12%) cases. Overall survival was reduced in patients with positive vs. negative EN2 staining (median survival 2.23 vs. 5.23 years, p=0.007) which was maintained in multivariate analysis (hazard ratio 1.61, 95% CI 1.05-2.48, p=0.03). Bladder cancer specific and relapse free survival were also reduced in EN2 positive cases in both univariate and multivariate analyses (multivariate analysis hazard ratios 2.00, 95% CI 1.21-3.30, p=0.007 and 2.17, 95% CI 1.35-3.49, p=0.001 respectively). Pathological complete response (pCR) rate following RC was inversely related to EN2 status (1 of 39 if EN2 positive vs. 23 of 160 if negative, $\chi 2=4.12$, df=1, p=0.04). **Conclusions:** EN2 protein expression is an independent poor prognostic factor following RC for bladder cancer and correlates with a reduced pCR rate. External validation is ongoing. If validated then EN2 expression might assist patient stratification strategies.

**4546 General Poster Session (Board #114), Mon, 1:15 PM-5:00 PM**

**Bladder cancer risk: Use of PLCO and NLST to identify a suitable screening cohort.** *Presenting Author: Laura-Maria Krabbe, University Hospital of Muenster, Muenster, Germany*

**Background:** Bladder cancer (BC) screening is not accepted in part due to low overall incidence. We utilized the PLCO and NLST to identify optimal high-risk populations most likely benefit from screening. **Methods:** Data were extracted from PLCO and NLST to stratify risk of BC by overall population, gender, race, age at inclusion and smoking status. Incidence rates between groups were compared using chi-square test. **Results:** BC was identified in 1430/154,898 in PLCO and 439/53,173 in NLST. BCs were grades III/IV in 36.8% and 41.3%, respectively. Incidence rates were significantly higher in men than women (PLCO: 1.4 vs. 0.31/1000 person-years, NLST: 1.84 vs. 0.6/1000 person-years, both p$<$0.0001). In proportional hazards models, male sex, higher age, duration and intensity of smoking were associated with higher risk of BC (all p$<$0.0001). In men $>$70 with smoking exposure of 30 pack years (PY) and more, incidence rates were as high as 11.92 (PLCO) and 5.23 (NLST) (per 1000 person-years). In current high intensity smokers ($\geq$50 PY) the gender disparity in incidence persists in both trials (0.78 vs. 2.99 per 1000 person-years in PLCO and 1.12 vs. 2.65 per 1000 person years in NLST). **Conclusions:** Men over 60 years with a smoking history of $>$30 PY generate incidence rates over 2/1000 person-years, which could serve as an excellent population for screening trials. Gender differences in BC incidence cannot be readily explained by differences in exposure to tobacco, since in PLCO and NLST the gender disparity persisted regardless of smoking intensity.

**4547 General Poster Session (Board #115), Mon, 1:15 PM-5:00 PM**

**Immunohistochemistry (IHC) to enhance the prognostic allocation of locally advanced and metastatic urothelial cancer (UC) undergoing first-line chemotherapy (CT).** *Presenting Author: Patrizia Giannatempo, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

**Background:** Knowledge of the expression of molecular drivers and potentially druggable targets may enhance prognostic classification of metastatic UC. We aimed at assessing the expression of multiple key molecular biomarkers (BMK) by IHC and their potential to enhance prognostic allocation of patients (pts) with UC. **Methods:** We analyzed formalin-fixed paraffin embedded tumor from pts with UC undergoing first-line CT with MVAC for locally-advanced unresectable (LA, T3-4$\pm$N+) and metastatic (M) disease between the years 2000 and 2013. The expression of the following panel of BMKs by IHC were evaluated using conventional protocols: ERCC1, EGFR, HER2, VEGFR-3, PDGFR$\alpha$, p53, p63. Expression levels were dichotomized as positive (2+,3+) or negative ($\leq$1+). Fisher exact test was used to evaluate the association with response and setting (LA vs M). Cox regression multivariate (MVA) models evaluated the association with PFS and OS of each biomarker, adjusted for recognized prognostic variables (setting [LA vs M], Bajorin score [0 vs 1-2], primary site). **Results:** Since 06/2009, tissues of 88 pts (27 LA, 61 M) underwent IHC. Samples were from primary tumor (N=67) or metastases (N=21). Rates of positive IHC/number evaluable were as follows: ERCC1: 30/66 (45%); HER2: 24/52 (46%); EGFR: 31/54 (57%); VEGFR-3: 50/66 (76%); PDGFR$\alpha$: 10/63 (16%); p53: 25/56 (45%); p63: 46/53 (87%). HER2 trended for a significant association with higher stage (p=0.079). Median follow up was 41 months (IQR, 15-64). On MVA, significant results were obtained for VEGFR-3 and PDGFR$\alpha$, in addition to Bajorin score (Table). The c-index was 0.68 for both PFS and OS. **Conclusions:** VEGFR-3 and PDGFR$\alpha$ expression appears to confer a divergent prognostic impact in pts receiving first-line cisplatin-based CT for advanced UC. These data warrant external validation and underline the difficulties in defining the role of angiogenesis as a molecular driver and therapeutic target.

| | PFS | | | OS | | |
|---|---|---|---|---|---|---|
| **Variable** | **HR** | **95% CI** | **p** | **HR** | **95% CI** | **p** |
| **VEFGR-3 Pos vs Neg** | 0.45 | 0.21-1.01 | 0.054 | 0.36 | 0.15-0.85 | 0.019 |
| **PDGFR$\alpha$ Pos vs Neg** | 3.32 | 1.28-8.58 | 0.013 | 2.66 | 0.96-7.42 | 0.060 |
| **Bajorin score 1-2 vs 0** | 4.24 | 1.94-9.26 | $<$0.001 | 4.49 | 1.91-10.56 | $<$0.001 |

**4548 General Poster Session (Board #116), Mon, 1:15 PM-5:00 PM**

**Changes in conditional survival (CS) in de novo metastatic urothelial carcinoma (mUC): A Surveillance, Epidemiology, and End Results (SEER) database analysis.** *Presenting Author: Kara DeWalt, City of Hope Comprehensive Cancer Center, Duarte, CA*

**Background:** No agents have been approved by the US FDA for the 2$^{nd}$-line treatment of mUC. Still, many US patients receive treatment in this setting, calling upon phase II datasets emerging over the past decade for payor justification. While the cumulative disease-specific survival (DSS) for mUC may not change on account of this practice, assessment of CS may allow greater focus on patients who receive post-1$^{st}$-line therapies. **Methods:** The SEER database was queried to compare the DSS and CS of de novo mUC patients diagnosed from 1994-2000 (T1) and 2001-2009 (T2). The year 2000 was chosen as a cutoff due to multiple phase II datasets for 2$^{nd}$-line regimens published subsequent to this date. DSS in subgroups divided by time period were summarized using the Kaplan-Meier method and compared using the log-rank test. The chi-square test was used to compare the CS of subgroups divided time period at annual intervals up to 5 years. Multivariate analysis (MVA) was performed to determine the relationship between DSS and clinicopathologic/treatment-related variables. **Results:** Outcomes were assessed for a total of 4,465 pts, with 1,155 diagnosed during T1 and 3,310 diagnosed during T2. Mean age of the overall cohort was 70, and the majority of patients had poorly differentiated or undifferentiated tumors. For the overall cohort, 1-year DSS for T1 and T2 were 23% and 25% (P=NS). At landmark analyses at 1 yr, 2 yrs and 3 yrs following diagnosis, 1-yr CS in groups diagnosed during T1 and T2 were 46% and 39%, 71% and 68%, and 76% and 78%, respectively (P=NS for each comparison). On MVA, time period of diagnosis (T1 vs T2) was not a significant predictor of DSS. Instead, older age ($>$65) and undifferentiated histology were predictive of poorer DSS, while use of radiation or surgery were associated with improved DSS. **Conclusions:** Multiple published phase II studies emerging over the past decade have been used to justify use of post-1$^{st}$-line therapies for mUC to payors. Our assessment of CS should better account for the impact of these therapies as compared to cumulative DSS. The lack of improvement CS calls into question the impact post-1$^{st}$-line therapies have had on the natural history of mUC.

**4549 General Poster Session (Board #117), Mon, 1:15 PM-5:00 PM**

**Long-term results and prognostic factors for survival following adjuvant chemotherapy (AC) for muscle-invasive urothelial bladder cancer (UC): A French retrospective multicenter cohort.** *Presenting Author: Damien Pouessel, Department of Medical Oncolgy, Hopital Saint-Louis - APHP, Paris, France*

**Background:** Role of AC in patients (pts) with UC undergoing radical cystectomy (RC) is debated. **Methods:** We retrospectively analyzed survival of 226 consecutive pts treated with RC and AC for UC with muscle-invasion or lymph node (LN) involvement in 6 French academic hospitals between 2000 and 2009. Non-urothelial cases were excluded. Multivariate Cox proportional hazards regression adjusted for center was used to estimate adjusted hazard ratios with 95% confidence interval. **Results:** Median age was 62.4 [range: 35-82], 189 (84%) were male. ECOG performance status was 0-1 in 211 pts (93.3%). Stage were p<T2 (n=15), pT2 (n=31), or pT≥3 (n=180), pN0 (n=37), pN1 (n=54), pN≥2 (n=114) or pNx (n=21), M0. Mixed UC were 43 (19%). Median number of resected LN was 11.5 [1-36]; density (LND) 25% [3.1-100]. Median time between RC and AC was 61.5 days [18-162]. Gemcitabine-cisplatin (GC), gemcitabine-carboplatin (GCb), and methotrexate-vinblastine-doxorubicine-cisplatin (MVAC) regimen were delivered in 71.2%, 21.7% and 5.3% of pts. Median number of cycles was 4 [1-6]. Thirteen pts (5.7%) with LN metastases (LN+) received adjuvant pelvic radiotherapy (ART) after AC. Median follow-up was 4.2 years [0.38-11.0], 135 (59.7%) pts have relapsed, 99 (73.3%) received at least one chemotherapy regimen for metastasis. Also 133 pts (59.2%) died, most death (90.1%) were related to recurrence. Median overall survival (OS) and disease-free survival were 3.4 and 1.03 years. Five-year OS and cancer-related survival (CRS) rates were 40.7% and 42.6% respectively. In multivariate analysis, pT≥3 stage (HR: 2.31, 95%CI 1.27-4.19, p=0.006), < 4 cycles (1.99, 1.15-3.45, p=0.01), and LND > 50% (2.34, 1.23-4.46, p=0.01) were adverse prognostic factors for CRS. ART (0.33, 0.10-1.11, p=0.07) tend to provide survival benefit. **Conclusions:** In this large contemporary retrospective study reporting real-life survivals in pts receiving AC after RC with survival results consistent with published data, LND < 50% and ART in LN+ pts predict a more favorable prognosis after AC. Further studies are warranted to reveal the exact impact of ART in this subset of pts.

**4550 General Poster Session (Board #118), Mon, 1:15 PM-5:00 PM**

**Pathologic down-staging following standard (SD) MVAC (methotrexate-vinblastine-doxorubicine-cisplatin) or dose-dense MVAC (DD) neoadjuvant chemotherapy (NC) for muscle-invasive urothelial bladder cancer (UC): A retrospective multicenter cohort of the French Genitourinary Tumor Group (GETUG/AFU).** *Presenting Author: Damien Pouessel, Department of Medical Oncolgy, Hopital Saint-Louis - APHP, Paris, France*

**Background:** The benefit of NC on survival in UC has been shown with SD and is most evident in patients (pts) who achieve a pathological complete response (ypT0). In the last decade, physicians used SD or DD. **Methods:** We conducted a retrospective cohort study in 246 pts who received SD or DD for NC before a planned RC for cT2-T4, cN0 or cN+, M0 UC at 16 French centers from 2004 to 2012. The primary outcome was stage ypT0 at RC. Other PDS end points were no residual muscle-invasion (< ypT2), stage < ypT3, and nodal status. Toxicities, disease-free survival (DFS) and overall survival (OS) were also evaluated. **Results:** A total of 246 pts (182 cN0 and 64 cN+) were identified, 208 (84.5%) were male, 56 and 190 were treated with SD and DD, respectively. Median age was 62 [range: 56.3-67.4]. The median time from start of NC to RC was 101 days [80-122]. RC has been realized in 214 pts (87.0%), 48 (85.7%) and 166 (87.6%) after SD and DD respectively. In 17 unoperated pts, concomitant chemoradiotherapy was performed, 8 (14.28%) and 9 (4.7%) after SD and DD respectively. Mean follow−up from RC was 15 months [7-28.3]. Stage ypT0 were found in 18 (40%) and 58 (36.4%) pts after SD and DD respectively (p= 0.73). PDS were reported in 27 (61%) and 81 (55%) pts after SD and DD respectively (p=0.49). The following adverse events were observed with SD and DD respectively: grade 4 neutropenia (25% and 11%), grade 3/4 anemia (63% and 36%), grade 4 thrombopenia (0% and 4%), febrile neutropenia (9% and 7%), and grade 2 peripheral neuropathy (0% and 4%). Median DFS following RC was not reached (NR) and 50.9 months (95%CI 24.2-NR, p= 0.37) after SD and DD respectively, 31 (55.3%) and 103 (54.2%) pts were still disease-free. The median OS was NR in SD versus 55 months in DD (39.3-NR, p=0.85). **Conclusions:** The proportion of pts whose primary tumor were downstaged was not different according to the two regimen. Toxicity was confirmed to be higher in SD than in DD. The GETUG/AFU has launched a randomized trial assessing the DD and gemcitabine-cisplatin regimens in the perioperative setting.

**4551 General Poster Session (Board #119), Mon, 1:15 PM-5:00 PM**

**Met signaling in urothelial carcinoma of the bladder.** *Presenting Author: Donald P Bottaro, Urologic Oncology Branch, National Cancer Institute, Bethesda, MD*

**Background:** Mounting evidence of hepatocyte growth factor (HGF)/Met signaling in urothelial carcinoma (UC) suggests that pathway inhibition could have therapeutic benefit in some patients. The effects of two Met inhibitors, cabozantinib (which also targets VEGFR2), and crizotinib (which also targets ALK), on Met-driven UC cell growth, invasion and tumorigenicity were analyzed in biochemical, cell-based and animal models. **Methods:** The effects of cabozantinib or crizotinib on HGF signaling were assessed in 9 human UC-derived cell lines: RT4, TCC-SUP, T24M2, T24M3, J82, SW780, UMUC3, UMUC5, and 5637. Biochemical assays included total Met protein, phospho-Met (pMet), pAkt, total Akt, pErk and total Erk analysis. Cultured cell assays of invasion, proliferation and anchorage independent growth were performed in all 9 lines. The growth rates of SW780 xenografts in SCID and human HGF knock-in SCID (hHGF/SCID) mice treated daily with cabozantinib or vehicle alone, as well as tumor levels of Met and pMet, were determined. **Results:** Met content was low in RT4 and higher in T24M2, T24M3, TCC-SUP, J82, SW780 UMUC3, UMUC5, and 5637 cells. Basal pMet content in quiescent cells was universally low and significantly enhanced by added HGF, an effect that was reversed by treatment with cabozantinib or crizotinib. HGF-driven increases in pAkt/Akt and pErK/ErK in all 9 cell lines were also reversed by cabozantinib or crizotinib treatment, as were HGF-enhanced cell invasion, proliferation and anchorage independent growth. SW780 xenograft growth rate in hHGF/SCID mice was significantly higher than in SCID mice and significantly inhibited by cabozantinib treatment, as was tumor pMet content. **Conclusions:** Cultured UC cell Met content was higher in cell lines derived from higher stage disease. HGF stimulated the activation of Met and known effectors, and enhanced invasion, growth rate and anchorage-independent growth; treatment with cabozantinib or crizotinib effectively reversed these HGF-driven effects. Cabozantinib also significantly inhibited HGF-driven tumor xenograft growth and Met activation in SCID and, more dramatically, in hHGF/SCID mice. These preclinical studies support further investigation of Met inhibitors for the treatment of UC in human clinical trials.

**4552 General Poster Session (Board #120), Mon, 1:15 PM-5:00 PM**

**PD-L1 expression in mononuclear cells and not in tumor cells, correlated with prognosis in metastatic urothelial carcinoma.** *Presenting Author: Stephanie A. Mullane, Bladder Cancer Center, Dana Farber Cancer Institute/ Brigham and Women's Cancer Center, Boston, MA*

**Background:** Programmed death-1 (PD-1) receptor negatively regulates T cell-mediated responses.PD-1 ligand (PD-L1) is expressed in several malignancies and is associated with higher grade, 9p24 loss and worse clinical outcome. Its role as potential predictive biomarker for immunotherapy is of clinical relevance. The prognostic impact of PD-L1 expression in tumor cells versus its expression in mononuclear (MNC) infiltrates in urothelial carcinoma (UC) is unknown. **Methods:** Formalin-fixed paraffin embedded (FFPE) tumor samples from 160 clinically annotated UC patients were retrieved. PD-L1 expression was evaluated by immunohistochemistry using a mouse monoclonal anti-PD-L1 antibody (405.9A11). The assay was validated using FFPE cell line controls known to be positive or negative for PD-L1 expression by flow cytometry. PD-L1 tumor positivity (PD-L1+) was defined as ≥5% tumor cell membrane staining. For PD-L1 expression in MNC, a score based on the extent of infiltrate and percentage of positive cells was used. Fisher's exact test was used to assess the associations with clinical variables (smoking history, prior BCG treatment and stage at diagnosis) and 9p24 copy number variation (CNV). Log rank test was used to assess the association of PD-L1 expression with overall survival (OS). **Results:** Among 160 UC patients, PD-L1+ expression was seen in 32 (20%) of tumors cell membrane and in 58 (37%) of MNC. Smoking history did not correlate with expression of PD-L1 in tumor cells or in MNC. PD-L1+ in MNC was non significantly higher in stage III/IV versus stage I/II tumors at diagnosis (41.8% versus 30%; p=0.56). In the subgroup of patients that developed metastatic disease (89 patients), MNC PD-L1+ was significantly associated with a longer OS (p=0.04). In patients that developed metastatic disease, PD-L1+ was seen in 14% of tumor cells and did not correlate with OS (p=0.45). Correlation with prior BCG exposure and CNV of 9p24 will be presented. **Conclusions:** PD-L1 is widely expressed in tumor cell membrane and MNC in UC. PD-L1+ in MNC is significantly associated with survival in those patients that subsequently develop metastatic disease.

**4553 General Poster Session (Board #121), Mon, 1:15 PM-5:00 PM**

**Identification of potentially targetable kinases by concurrent high-throughput functional kinomics and RNA-sequencing (seq) of muscle-invasive bladder cancer (MIBC).** *Presenting Author: Christopher Douglas Willey, The University of Alabama at Birmingham, Birmingham, AL*

**Background:** Interrogation of kinases in tumor and matched normal tissue by concurrent kinomic activity profiling and RNA-seq might identify the most relevant kinases and inform the development of agents for MIBC. We report the first such analysis followed by supportive analysis of the TCGA (The Cancer Genome Atlas). **Methods:** We performed kinomic profiling and RNA-seq of frozen tumor samples and matched adjacent normal bladder from 6 pts with MIBC. Kinomic profiling was performed using the PamStation 12 high-content phosphopeptide substrate microarray system (PamGene International). Protein tyrosine and serine/threonine kinome PamChips were used to measure global kinase activity by detecting phosphorylation of peptide substrates through FITC-labeled antibodies. Upstream kinase prediction was determined by a scoring algorithm derived from the phosphonet database. RNA-seq libraries were prepared using standard techniques and were sequenced on the Illumina HiSeq2000 platform. RNA-seq of kinases from 59 pts with MIBC and complete pathologic staging information were compared with 16 normal bladder controls from TCGA. Pathway analysis was conducted for kinases with gene expression changes concordant between the TCGA dataset and the 6 UAB pts. **Results:** Kinomic activity profiling identified increased tumor (vs. matched normal) kinase activity corresponding to BRK, FAK, PYK2, ZAP70 and CTK target peptides. Interestingly, kinase gene expression showed no concordance with activity. Among 529 kinase genes, 124 genes were significantly altered in tumor v. matched normal, of which 28 overlapped with the TCGA dataset. The top 5 up-regulated tumor kinases from both sets were CIT, CDK4, PRKD2, IKBKE, and EPHB2. Pathway analysis revealed significant involvement of post-translational modification and survival signaling. **Conclusions:** Comprehensive kinase analyses of MIBC using kinomic activity profiling and RNA-seq identified multiple potential therapeutic targets. Preclinical validation of agents targeting these kinases and pathways is warranted and will facilitate integration of kinomic and transcriptomic data.

**4554 General Poster Session (Board #122), Mon, 1:15 PM-5:00 PM**

**Screening for carcinoma in situ (CIS) testis and occurrence of metachronous germ cell cancer (mGCC).** *Presenting Author: Maria Gry Gundgaard, Survivorship, Danish Cancer Society, Copenhagen, Denmark*

**Background:** CIS is present in the contralateral testicle in 5-6% of untreated patients with unilateral germ cell cancer (GCC). A Danish screening program for contralateral CIS was initiated in order to prevent mGCC. **Methods:** In total, 4,180 GCC patients diagnosed from 1984 through 2007 were offered a contralateral single-site biopsy in relation to orchiectomy (intention to screen, ITS). A non-screened group included 450 patients. Recommended treatment for CIS was radiotherapy (RT) in doses of 14 to 20 Gy, also in chemotherapy treated (CT) patients. CIS-negative (CISneg) patients who developed mGCC had the biopsy revised according to today's standard including immunohistochemical staining. Data was merged with national administrative registries, and information on second GCC and vital status was obtained for all patients up to December 2012. **Results:** Median observation time was 14.1 years (range 0.1-28.9). Contralateral CIS was found in 193 patients (4.6%). Seven CIS-positive (CISpos) patients developed mGCC (n=3 after 14 Gy and n=4 after CT without local RT). Out of 3,987 CISneg patients, 55 developed mGCC. Revision of 46 biopsies available showed CISpos in 17 and confirmed CISneg biopsies in 29 patients. Older age at diagnosis and treatment with CT were significantly correlated with decreased risk of mGCC (HR 0.93 per year, p<0.0001 and HR 0.34, p=0.006, respectively). **Conclusions:** The risk of mGCC in a screened population was significantly lower than in a non-screened group after re-evaluation of false-negative biopsies. Further efforts should concentrate on the improvement of screening to eliminate false-negative biopsies and on the definition of risk factors to avoid taking biopsies in low-risk groups.

**Cumulative incidence of mGCC (% [95% CI]).**

| Time point years | ITS, n=4,180 | ITS with CISpos patients removed, n=3,970 | Nonscreened group, n=450 |
|---|---|---|---|
| **15** | 1.7 (1.3-2.2)* | 1.2 (0.8-1.6)** | 2.8 (1.2-4.3) |
| **20** | 2.1 (1.5-2.7)* | 1.3 (0.9-1.7)** | 3.3 (1.6-5.0) |

*p=0.12, **p=0.003; compared to non-screened group.

**4555 General Poster Session (Board #123), Mon, 1:15 PM-5:00 PM**

**Renal impairment and late toxicity in germ-cell cancer (GCC) survivors.** *Presenting Author: Jakob Lauritsen, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark*

**Background:** Treatment with bleomycin-etoposide-cisplatin (BEP) decreases renal glomerular filtration rate (GFR) and confers a risk of later cardiovascular disease (CVD) and death. We investigated the influence of BEP on renal function and looked at associations between renal toxicity and late effects in a large cohort of GCC survivors. **Methods:** Patients were identified in the Danish DaTeCa database, housing GCC patients diagnosed 1984-2007. All patients (N=1,046) received BEP with measurements of GFR (51Cr-EDTA clearance) before and after treatment. GFR was repeatedly measured at 1, 3, and 5 years of follow-up. Late toxicity was identified by merging with national registers. Influence of covariates on renal toxicity was evaluated by a linear mixed model approach. Risk factors for late toxicity were estimated by a landmark analysis adjusting for covariates and the cohort was compared to the background population with standardized hospitalization/mortality rates (SHR/SMR). **Results:** After treatment, GFR decreased (ΔGFR) with median 13 ml/min/1.73m2. ΔGFR was inversely associated to GFR pre-treatment (P<0.0001) and associated to number of cycles (P<0.0001). Patients who received 3 or 4 cycles of BEP had significant rebound of renal function during follow-up, whereas patients treated with 5 cycles or more stayed reduced. Compared to the background population all patients, irrespective of renal function, had an increased risk of CVD and death. The risk of CVD and death depended significantly on chronic kidney disease (CKD) stage before treatment but not after treatment (Table). ΔGFR had no influence on risk of late toxicity (CVD: HR 1.08, P=0.34; Death: HR: 0.98, P=0.71). **Conclusions:** BEP decreases renal function, but the changes in GFR are partly reversible and have no impact on late effects or death.

| | | Before treatment | | After treatment | | SHR/SMR |
|---|---|---|---|---|---|---|
| **Outcome** | **CKD** | **P** | **HR (CI)** | **P** | **HR (CI)** | **(CI)** |
| **Death** | I | 0.25 | 1.00 | 0.93 | 1.00 | 1.81 (1.24-2.56) |
| | II | 0.03 | 1.41 (0.78-2.53) | 0.24 | 1.02 (0.61-1.73) | 2.06 (1.46-2.83) |
| | III | | 2.60 (1.10-6.16) | | 1.69 (0.71-4.05) | 3.43 (1.48-6.75) |
| | Total | | | | | 2.03 (1.60-2.53) |
| **CVD** | I | 0.74 | 1.00 | 0.32 | 1.00 | 1.96 (1.64-2.28) |
| | II | 0.19 | 1.11 (0.62-1.98) | 0.47 | 0.80 (0.51-1.25) | 1.16 (0.93-1.42) |
| | III | | 2.00 (0.70-5.68) | | 1.40 (0.56-3.51) | 2.03 (1.22-3.18) |
| | Total | | | | | 1.57 (1.39-1.78) |

**4556 General Poster Session (Board #124), Mon, 1:15 PM-5:00 PM**

**A contemporary population-based study of testicular sex cord stromal tumors: Presentation, treatment patterns, and predictors of outcome.** *Presenting Author: Lindsay M Yuh, University of California at Davis, Sacramento, CA*

**Background:** Testicular sex cord stromal tumors (SCST) - consisting of Leydig and Sertoli cell subtypes - are a rare adult malignancy. Contemporary clinical data are gathered only from anecdotal case reports or small case series. Therefore, few evidence-based guidelines have been developed regarding the optimal management and surveillance of such tumors. In order to define SCST demographics and patient outcomes and to identify prognostic features, we analyzed the California Cancer Registry, a large statewide database. **Methods:** All male patients over the age of 18 diagnosed with SCST in California between 1988 and 2010 were included. Baseline demographic variables included age, race, histology, tumor stage, primary treatment, and socioeconomic status. Primary outcome measures were cause-specific survival (CSS) and overall survival (OS). Bivariate and multivariate Cox proportional hazards models were employed to identify predictors of CSS and OS. **Results:** Of 19,792 patients with testicular tumors, a total of67 patients with SCST were identified, representing 0.3% of the total population. Of these patients, 45 (67%) had Leydig cell and 19 (28%) had Sertoli cell tumors. Median age at presentation was 40 years and the vast majority of patients (84%) presented with localized disease. Following orchiectomy, 9 patients (15%) underwent RPLND, whereas 54 patients (80%) had no further treatment. With a median follow-up time of 75 months, 2-year OS and CSS was 91% and 95% for those presenting with stage I disease. For those presenting with stage II disease, 2-year OS and CSS was 30%. Significant predictors of worse OS on multivariable analysis included age >60 (HR 5.64, p<0.01) and metastatic disease (HR 8.56, p<0.01). Presentation with metastatic disease was the only variable associated with worse CSS (HR 13.36, p<0.01). Histology was not found to be a significant predictor of either CSS or OS. **Conclusions:** We present the largest reported series to date for this rare tumor and provide contemporary epidemiologic and treatment data. The primary driver of prognosis in patients with SCST is disease stage, emphasizing the importance of early detection and intervention.

**4557 General Poster Session (Board #125), Mon, 1:15 PM-5:00 PM**

**A retrospective analysis of patients with poor-risk germ cell tumor (PRGCT) treated at Indiana University from 1990 to 2011.** *Presenting Author: Nabil Adra, Indiana University, Indianapolis, IN*

**Background:** Based on the International Germ Cell Cancer Collaborative Group (IGCCCG), PRGCT represents 14% of germ cell tumors with a 5-year survival of only 48% and 5-year PFS of 41%. PRGCT is defined by primary mediastinal non-seminomatous germ cell tumor (PMNSGCT), non-pulmonary visceral metastasis (NPVM), AFP $>$ 10,000 or hCG $>$ 50,000. This analysis attempts to identify subsets of patients with more or less favorable outcomes among the poor risk groups. **Methods:** Retrospective analysis of all patients with testicular cancer seen at Indiana University from 1990-2011. 411 patients with PRGCT identified of whom 211 received initial therapy at Indiana University. Median follow-up time was 35.3 months. We analyzed the following variables: primary site testis/retroperitoneal T/RP (169) vs. PMNSGCT (42), no NPVM (109) vs. NPVM (102), PMNSGCT with no metastasis (18) vs. PMNSGCT with distant metastasis (24), and single criterion (128) vs. multiple criteria (83) for PRGCT. **Results:** Mean age 29, mean AFP 9,449, mean hCG 169,087. 20% had PMNSGCT, 48% NPVM. Patients with NPVM had significantly worse PFS. Patients with PMNSGCT had significantly worse OS compared to patients with other primary sites. Multiple different criteria for poor risk disease carried significantly worse impact on PFS when compared to having a single criterion for poor risk disease. Patients with PMNSGCT with distant metastasis had worse PFS. **Conclusions:** Our results for patients with PRGCT treated at Indiana University from 1990-2011 are superior to the IGCCCG patients treated from 1975-1990. Patients with PRGCT treated after 1990 had better outcome compared to 1975-1990 with a 5-year survival of 74% and PFS of 54%. Our data indicate that patients with NPVM, PMNSGCT, more than one criteria for poor risk disease, or PMNSGCT with distant metastasis have a worse outcome compared to other PRGCT subgroups.

| | 5-yr PFS | 5-yr OS | P value |
|---|---|---|---|
| **All patients** | 54% | 74% | |
| **No NPVM vs NPVM** | 60% vs 49% | 78% vs 71% | PFS 0.06; OS 0.2 |
| **PMNSGCT vs T/RP** | 46% vs 56% | 57% vs 78% | PFS 0.69; OS 0.002 |
| **Single criterion vs multiple criteria for poor-risk disease** | 60% vs 45% | 78% vs 69% | PFS 0.03; OS 0.12 |
| **PMNSGCT vs PMNSGCT + metastasis** | 69% vs 36% | 78% vs 45% | PFS 0.06; OS 0.16 |

**4558 General Poster Session (Board #126), Mon, 1:15 PM-5:00 PM**

**Evolving patterns of care in the management of stage I non-seminomatous germ cell tumors: Data from the California Cancer Registry.** *Presenting Author: Stanley A Yap, University of California, Davis, Sacramento, CA*

**Background:** Standard options for the management of stage I non-seminomatous germ cell tumors (NSGCT) following radical orchiectomy include active surveillance, retroperitoneal lymph node dissection (RPLND), or adjuvant systemic chemotherapy. However, few studies have assessed population-level practice patterns and how these have evolved over time. Here, we assess the shifting practice patterns across a 20 year timespan in the management of stage I NSGCTs. **Methods:** Using the California Cancer Registry, we reviewed all patients diagnosed with stage I NSGCT in California between 1988 and 2010. We determined whether primary treatment consisted of RPLND, chemotherapy, or surveillance, and their overall rates across the years. Other analyzed variables included patient age, socioeconomic status, race, year of diagnosis, and region. Predictors of treatment selection were assessed using logistic regression analysis. **Results:** A total of3,961 patients with stage I NSGCT were identified. The most common primary treatment was surveillance (48%), followed by RPLND (26%) and chemotherapy (24%). Significant changes in the rate of various treatment strategies were noted across the study period ($p<0.01$). Rates of surveillance increased from 35% in 1988 to 61% in 2010, while rates of chemotherapy remained relatively stable. However, rates of RPLND decreased from 44% in 1988 to 10% in 2010. Significant predictors of undergoing surveillance on multivariable logistic regression included diagnosis after 2006 (OR 1.52, CI 1.25-1.84) and age at diagnosis $>$60 years old (OR 1.63, CI 1.19-5.82). With a median follow-up of 96 months, 5-year overall survival (OS) rate among those undergoing RPLND, chemotherapy, or surveillance was 98%, 92%, and 97%, respectively. **Conclusions:** Treatment patterns in the management of stage I NSGCT have shifted with an increased utilization of surveillance and a concurrent decrease in the use of RPLND. Treatment patterns have evolved over the past 2 decades, where active surveillance is now the dominant strategy, potentially reflecting changes in perception of the oncologic safety and morbidity profile of such an approach.

**4559 General Poster Session (Board #127), Mon, 1:15 PM-5:00 PM**

**Bone metastases in germ cell tumors: Results from an international data base.** *Presenting Author: Christoph Oing, Department of Oncology, Hematology and BMT with Section of Pneumology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

**Background:** Bone metastases (BM) are rare in germ cell tumor (GCT) patients (pts). Systematic data on risk factors, treatment and outcome are largely lacking. **Methods:** An international data base including 272 GCT pts with BM (140 at primary diagnosis, 132 with first BM occurrence at relapse) diagnosed between 1983 - 2013 from 23 centers was retrospectively analyzed. **Results:** BM at primary diagnosis mostly affected spine (71%) and pelvis (24%), 40% had a single and 60% multiple lesions. Pts had a primary gonadal / retroperitoneal / mediastinal GCT in 68% / 16% / 16% and seminoma / nonseminoma in 25% / 74%. Primary treatment was standard dose chemotherapy in 90% (SD-CTX) and dose intensified CTX in 10% (DI-CTX). Secondary resection (SR) / radiotherapy (RTX) of BM was performed in 10 pts (7%) / 20 pts (14%). Histology was necrosis / mature teratoma / vital tumor in 6 / 2 / 1 pts. 45% of pts relapsed, 79% again with BM. Median FU was 21 months (mos). Calculated median PFS and OS were 31 mos (range, 0-225) and 98 mos ($^{95\%}$CI, 14–182). No survival benefit was achieved by DI-CTX (PFS p=.29; OS p=.96) or SR of BMs (PFS p=.25; OS p=.99). 132 pts developed BM at relapse: Mostly in spine (67%) and pelvis (24%). 47% had a single, 53% multiple lesions. Median time from initial GCT diagnosis to detection of BM was 20 mos ($^{95\%}$CI, 16-24). Salvage treatment was SD-CTX / DI-CTX in 86% / 14%. SR / RTX of BM were performed in 14% / 42%. Histology was necrosis / mature teratoma / vital tumor in 1 / 2 / 14 pts. Overall, 52% of pts progressed during salvage CTX. After a median FU of 45 mos (range, 2-335), median OS was 13 mos ($^{95\%}$CI, 8 – 17). PFS and OS seem to be improved by DI-CTX (2yr-PFS 37% vs 14%, p=.006; 2yr-OS 47% vs 25%, p=.008) and / or SR of residual bone lesions (2yr-PFS 37% vs 14%, p=.016; 2yr-OS 74% vs 20%, p<.001). Additional RTX of BM did not impact survival in the salvage setting (PFS p=.73; OS p=.15). No other characteristics (tumor markers, non-bone metastases) were associated with the occurrence of BM in both cohorts. **Conclusions:** Pts with BM at primary diagnosis will achieve long-term survival (median OS 98 mos), but pts relapsing with BM have a dismal prognosis (median OS 13 mos). In patients relapsing with BM intensification of salvage therapy and resection of residual bone lesions may improve survival.

**4560 General Poster Session (Board #128), Mon, 1:15 PM-5:00 PM**

**Salvage chemotherapy for relapsed germ cell tumors: A phase II trial of gemcitabine, paclitaxel, ifosfamide, and cisplatin (Gem-TIP).** *Presenting Author: Matthew James Wheater, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom*

**Background:** Cure is possible for patients with relapsed germ cell tumours using further intensive cisplatin based combination chemotherapy. The Medical Research Council TIP trial reported a complete response (CR) rate of 19%, 1 year progression free survival (PFS) of 38% and overall survival (OS) 65% (Br J Cancer 2005;93:178). The previously reported phase I Gem-TIP trial demonstrated the feasibility of delivering full dose gemcitabine (Gem) in combination with TIP (J Clin Oncol 27, 2009 [suppl; abstr e16031]). We now report efficacy and safety data on an expanded cohort of patients treated within a phase II trial. **Methods:** Patients with germ cell cancers at first relapse following cisplatin based chemotherapy received a maximum of 4 cycles of Gem-TIP (Gem 1200mg/m$^2$ d1, paclitaxel 175mg/m$^2$ d1, ifosfamide 1g/m$^2$ d2-6, cisplatin 20mg/m$^2$d2-6) with pegfilgrastim 6mg d7 of a planned 21 day cycle. Subsequent cycles were started on adequate haematological recovery with no planned dose reductions. **Results:** 20 patients were treated, 19 male, 1 female, median age 32 years (range 20-61). Histology 6 seminoma, 14 non-seminoma. 6 patients had poor prognostic features using the Memorial criteria. The mean relative dose intensity (RDI) for TIP for patients treated with Gem-TIP was paclitaxel 95%, ifosfamide 91% and cisplatin 94% compared with 92%, 92% and 94% respectively in the MRC TIP trial. Response was CR 9 patients (45%), CR surgery 1 (5%), PR marker negative 6 (30%), incomplete response 3 (15%), 1 unevaluable. 1 year PFS was 57.9% (95% CI 33.2-76.3%), 1 year overall survival 84.2% (95% CI 58.7%-94.6%). Of the 16 patients with a favourable response this was sustained for 11 (69%) with a median overall follow up of 29 months. Toxicity was manageable and predominantly haematological. Grade 3/4 neutropaenia 60%, thrombocytopaenia 75% febrile neutropaenia 15%. There were no toxic deaths. **Conclusions:** The addition of gemcitabine to TIP chemotherapy is a feasible chemotherapy combination with no detrimental impact on RDI of TIP drugs and acceptable toxicity. Response rate and duration are improved on those reported in the MRC TIP trial and warrant further evaluation in a larger study. Clinical trial information: 37453564.

**4561 General Poster Session (Board #129), Mon, 1:15 PM-5:00 PM**

**Etoposide, methotrexate, and dactinomycin alternating with cyclophosphamide and vincristine (EMA/CO) for males with HCG-expressing, chemorefractory germ cell tumors (GCT): Long-term efficacy and safety outcomes.** *Presenting Author: Daniele Raggi, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

**Background:** Patients (pts) with GCT who fail to be cured following multiple chemotherapy (CT) courses (including high-dose CT) have an extremely poor prognosis. EMA/CO regimen has shown efficacy in high-risk gestational trophoblastic tumors. Since 1992 we introduced this regimen for human chorionic gonadotropin (HCG)-producing refractory GCT. **Methods:** We retrieved data of adult male pts who received methotrexate (MTX) 100 mg/m$^2$ followed by MTX 200 mg/m$^2$ over 12h d1, etoposide 100 mg/m$^2$ and dactinomycin 0.5 mg mg/m$^2$ d1-2, folinic acid 15 mg orally every 6h d2-3, followed by cyclophosphamide 600 mg/m$^2$ plus vincristine 1 mg/m$^2$ d8, every 21 days. Treatment was continued until marker normalization. Pts had a HCG+ GCT and had failed at least 2 CT regimens. Multivariable analysis (MVA) was undertaken to analyze candidate prognostic factors. ITT analysis was applied. **Results:** From 02/92 to 05/13, 41 pts were treated in 3$^{rd}$ (20, 49%) or >3$^{rd}$ line (21, 51%). 36 (88%) had a mixed GCT, 2 a pure seminoma and 3 a clinical diagnosis. 7 (17%) had an extragonadal primary, 17 (41%) had liver, bone, or brain (LBB) metastases, and 21 (51%) HCG>1000 IU/l. 16 (39%) had received HDCT. 33 pts (80.5%) had a response with marker reduction, including 5 complete (12.2%) and 7 (17.1%) partial responses (PR) with HCG normalization. After a median follow up of 98 months (IQR: 80-183), 6 pts did not relapsed and 6 were alive. Median progression-free survival was 3 months (95%CI, 2-4) and median overall survival was 8 months (95%CI, 6-10). On MVA, the line of treatment (>3$^{rd}$ vs 3$^{rd}$) was the only significant predictor of both PFS (HR: 2.50, 95%CI, 1.20-5.24, p=0.015) and OS (HR: 3.17, 95%CI: 1.46-6.89, p=0.004). Overall 16 pts (39%) had G3-4 hematologic and 1 pt mucositis and gastrointestinal toxicity each. No discontinuations for toxicity occurred. 1 toxic death (cerebral hemorrhage) occurred. **Conclusions:** EMA/CO is an active regimen with acceptable toxicity and could be considered an option for the subset of HCG+ chemoresistant GCT having failed multiple lines, including pts who are not candidate to salvage HDCT.

**4562 General Poster Session (Board #130), Mon, 1:15 PM-5:00 PM**

**Validation of a prognostic classification system for mediastinal nonseminomatous germ-cell tumors (MGCT).** *Presenting Author: Lance C. Pagliaro, Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** The anterior mediastinum is the most common location for extra-gonadal germ-cell tumors. MGCT has poor prognosis (International Germ Cell Consensus Classification); overall survival (OS) is 45–50% with standard treatment. Based on a prior study (Urol Oncol 2012, 30:879-85) we hypothesized that men with MGCT have favorable (Fav), intermediate (Int) or very poor (VP) prognosis when grouped by number of risk factors (RF). **Methods:** To validate the RF scoring system, we applied it to a prospectively collected subset of 66 men with MGCT who were registered on the GETUG-13 phase III trial (ASCO 2013, abstr #LBA4500). Patients (pts) were registered 11/2003–5/2012 and received bleomycin/etoposide/cisplatin (BEP) in the first cycle. Pts with unfavorable marker decline in cycle 1 were randomized to BEP (N=28) or an intensified regimen (paclitaxel-BEP-oxaliplatin x2 cycles and cisplatin/ifosfamide/bleomycin x2 cycles; N=29); the other 9 pts remained on BEP. One point was assigned for each of 3 RF at diagnosis: hCG ≥ 1,000 mg/ml, histology other than yolk sac tumor, and extra-mediastinal dissemination. Pts were then scored as Fav (0 RF), Int (1 RF), or VP (2–3 RF). We performed Kaplan-Meier analysis of OS and progression-free survival (PFS) for these groups and prognostic analyses (univariate and multivariate) for each RF. **Results:** Median age was 28 (18–65). Biopsy results were available for 30 pts (45%) and 36 (55%) had been diagnosed clinically. 27 pts died; 34 progressed and/or died. Median OS and PFS were not reached in the Fav (N=26) and Int groups (N=24). By contrast, the VP group (N=16) had median OS and PFS of 13 months and 4 months, respectively (log-rank P=.03; P<.001). Hazard ratios (HR) for RF are shown in the table. **Conclusions:** RF score predicted OS and PFS in this validation cohort of men with MGCT. Histology alone was not a strong RF, but the data were incomplete because a biopsy was not always clinically indicated.

| | | HR (95% CI) | | | |
|---|---|---|---|---|---|
| | | Univariate | | Multivariate | |
| RF | N (%) | OS | PFS | OS | PFS |
| Metastasis | 26 (39) | 2.3* (1.1–4.9) | 2.8* (1.4–5.6) | 2.1 (0.9–4.5) | 2.5* (1.2–5.2) |
| hCG ≥ 1,000 | 12 (18) | 2.5* (1.1–6.1) | 3.3* (1.5–7.1) | 2.1 (0.9–5.2) | 2.7* (1.2–6.0) |
| Non-yolk sac | 21 (32) | 1.4 (0.6–3.1) | 1.2 (0.6–2.4) | 1.5 (0.7–3.3) | 1.2 (0.6–2.4) |

*P<.05

**4563 General Poster Session (Board #131), Mon, 1:15 PM-5:00 PM**

**Chemotherapy compared to surgery: Quality-of-life analysis of the German prospective multicenter trial in clinical stage I NSGCT (AUO AH 01/94).** *Presenting Author: Peter Albers, Department of Urology, Heinrich-Heine-University, Düsseldorf, Duesseldorf, Germany*

**Background:** Although the superiority of one course of BEP over RPLND and surveillance in terms of recurrence rate has been shown, studies providing validated prospective quality of life (QoL) data in patients (pts) with NSGCT I treated with only one cycle of BEP are lacking. Therefore, the objective of the present trial was to examine long-term QoL issues in pts with clinical stage I NSGCT randomized after orchiectomy to either RPLND or one cycle of PEB chemotherapy. **Methods:** Results of the EORTC QLQ C30 plus additional scales questionnaire (QLQ C30+) were reviewed in 382 pts included in a prospective trial, which have been randomly assigned to receive either RPLND (n=191) or one course of BEP (n=191) after orchidectomy [AH 01/94, JCO 2008]. Pts with completed QLQ C30 and available data on treatment response were eligible for analysis. Pts with recurrences or 2$^{nd}$ malignancies were excluded. Treatment related changes of QoL in the no-event population were evaluated for the first 5 years after the end of treatment. A difference of >= 17% on the global item about "strain by treatment and/or tumor" was considered a clinically relevant difference between both treatment arms. Statistical comparisons between groups were performed using the Mann–Whitney U-test for nonparametric unpaired data. **Results:** The hazard ratio to experience a tumour recurrence with surgery as opposed to chemotherapy was 7.937 (95% CI, 1.808 to 34.48), i.e. 15 versus 2 recurrences. QoL results of pts with no event after the 1$^{st}$year were available from 138 pts with BEP and 126 pts with RPLND. For year 5, still 83 BEP pts had QoL assessments compared to 72 pts in the RPLND group. No significant differences between treatment groups in any of the QoL domains occurred during 5 years, not even at the time of treatment. Neither physical, nor emotional or global domains revealed any difference between the two approaches. As expected, hair loss reflected the side effects of chemotherapy during years 1 and 2, but recovered fully thereafter. **Conclusions:** This large randomized trial was not able to detect significant short- or long-term differences in QoL scores between RPLND and PEB. Clinical trial information: Number 141 / AH 01/94.

**4564 General Poster Session (Board #132), Mon, 1:15 PM-5:00 PM**

**Fatigue in relation to treatment and gonadal function in a population-based sample of 796 testicular cancer survivors 12 and 19 years after treatment.** *Presenting Author: Mette Sprauten, OUS, The Norwegian Radium Hospital, Oslo, Norway*

**Background:** Chronic fatigue (CF) is more prevalent in Testicular Cancer Survivors (TCSs) 12 years after treatment than in the general population (16% versus 10%). CF-related symptoms of emotional, physical and/or cognitive tiredness may be associated with poor gonadal function (low testosterone (T) and/or high Luteinizing Hormone (LH)). In this longitudinal study we assessed the prevalence of CF median 12 (12y) and 19 years (19y) after treatment in relation to applied treatment, age and levels of T and LH. **Methods:** T and LH levels were retrieved from 796 TCSs who completed fatigue questionnaires median 12y and 19y after treatment and categorized according to quartile thresholds of healthy controls for decadal age groups. Treatment was categorized as surgery (S, n=162), radiotherapy (RT, n=339) or chemotherapy (CT, n= 295). CF was defined according to previously published cut-off levels. Associations between CF and hormone levels, age and treatment were assessed with logistic regression. **Results:** CF increased overall significantly from 16% at 12y to 27% at 19y. A total of 67% of those reporting CF at 12y had persistent CF at 19y. The proportion of TCSs with T and/or LH within the poorest quartile increased from 72% at 12y to 81% at 19y. There were no significant associations between CF and T, LH, age or treatment 12 years after therapy. 19y after treatment, CF was significantly associated with the lowest quartile of T (compared to the highest quartile, referent) and previous RT (compared with S, referent) (Odds Ratio 1.9 95%CI: 1.0- 3.5 and 1.7; 95%CI: 1.0- 2.6, respectively). **Conclusions:** The increase of CF from 12 to 19 years after treatment was remarkable and disturbing. A significant association between CF and RT and the lowest T quartile emerged first almost 20 years after treatment. The increasing proportion of TCSs with CF and decreasing T levels underline the importance of continued long-term assessments of TCSs. T substitution may be considered many years after treatment of TCSs in order to treat CF.

**4565 General Poster Session (Board #133), Mon, 1:15 PM-5:00 PM**

**Survival of good-risk germ cell tumor patients following post-chemotherapy retroperitoneal lymph node dissection: The effect of bleomycin during induction chemotherapy.** *Presenting Author: K. Clint Cary, Indiana University School of Medicine, Department of Urology, Indianapolis, IN*

**Background:** Patients presenting with metastatic International Germ Cell Cancer Collaborative Group (IGCCCG) good risk testicular cancer may receive either 4 cycles of etoposide and cisplatin (EP) or 3 cycles of bleomycin, etoposide, and cisplatin (BEP). Those with residual retroperitoneal masses following either of these induction chemotherapy regimens will require a post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND). We sought to examine differences in survival following PC-RPLND between patients receiving EPx4 compared to BEPx3. **Methods:** The Indiana University Testis Cancer database was queried to identify IGCCCG good risk PC-RPLND patients who received either EPx4 or BEPx3 induction chemotherapy. The primary outcome was overall survival (OS). Kaplan-Meier plots were generated for the EPx4 and BEPx3 groups and compared using the log-rank test. Survival time was calculated from the date of surgery until date of death or the last date the social security death index was accessed. **Results:** A total of 226 patients met inclusion criteria between 1985 and 2011. Induction chemotherapy consisted of EPx4 in 47 (21%) patients and BEPx3 in 179 (79%). Most patients (78%) received their chemotherapy at outside institutions and were subsequently referred for PC-RPLND. Of the 12 patients who received adjuvant chemotherapy following PC-RPLND, 8 (66%) had received induction EPx4 while 4 (33%) had received BEPx3 (Fisher's exact $p=0.001$). Median follow-up was 126 months (IQR: 65-228) during which 16 deaths occurred. The 10-year OS for the EPx4 and BEPx3 groups were 87% and 98%, respectively (log-rank $p<0.01$). Of the 29 patients with active cancer in the PC-RPLND specimen, the 10-year OS for EPx4 was 50% compared to 83% in the BEPx3 group (log-rank $p=0.03$). **Conclusions:** Good risk testicular cancer patients who received BEPx3 may have a modest improvement in survival compared to those who received EPx4 as induction chemotherapy in this retrospective analysis. The overall burden of treatment may be higher with EPx4 as those patients also received more adjuvant chemotherapy compared to those who received induction BEPx3.

**4566 General Poster Session (Board #134), Mon, 1:15 PM-5:00 PM**

**A two-part phase 2 randomized study of dalantercept and axitinib versus placebo plus axitinib in advanced renal cell carcinoma: Results from the part 1 dose escalation cohorts.** *Presenting Author: Michael B. Atkins, Georgetown University Lombardi Comprehensive Cancer Center, Washington, DC*

**Background:** The activity of agents that target the vascular endothelial growth factor (VEGF) pathway in metastatic renal cell cancer (mRCC) may be enhanced in combination with agents that inhibit non-VEGF angiogenesis pathways and may lead to improved outcomes for pts. Activin receptor-like kinase 1 (ALK1) is a type I receptor of the TGF$\beta$ superfamily that is expressed on endothelial cells and is involved in blood vessel maturation. Dalantercept (Dal) is an ALK1 receptor-fusion protein that inhibits signaling through ALK1 and has demonstrated additive efficacy with a VEGF receptor (VEGFR) TKI in RCC models. **Methods:** Part 1 of this randomized 2-part phase 2 study assessed the safety and tolerability of Dal plus axitinib, a VEGFR TKI in pts. with mRCC who had up to 3 prior lines of therapy and determined the recommended phase 2 dose (RP2D). Cohorts of 3-6 pts. each received Dal (0.6, 0.9, or 1.2 mg/kg) SC Q3W and axitinib 5 mg PO BID. An expansion cohort at the RP2D will enroll an additional 10-20 pts. Eligibility criteria include 1 prior VEGFR TKI, $\leq 3$ prior tx., and ECOG $\leq 1$. **Results:** 13 pts. were enrolled in the three cohorts (n= 4, 4, 5) and there were no DLTs within 28 days of the first dose. Of the 13 pts., 46% had $\geq 2$ prior tx and 15% had 2 prior anti-VEGF tx. Common Dal-related AEs were grade 1-2 diarrhea, fatigue, anemia, arthralgia, creatinine rise, constipation, nausea, dysphonia, headache, muscle spasms. There have been no Dal associated SAEs. AEs associated with axitinib did not occur with higher than expected frequency or severity. 3 of 12 (25%) evaluable patients (2 at 0.6 mg/kg and 1 at 0.9 mg/kg) 2 of whom had three prior tx, achieved partial responses and were on study for $\geq 10$ cycles (7.5 mo). 6 of 11 (55%) evaluable pts. completed $\geq 6$ cycles (4.5 mo). Enrollment in the expansion cohort at 1.2mg/kg Dal is ongoing. **Conclusions:** In this pretreated mRCC population, the combination of Dal and axitinib is well tolerated and associated with clinical activity including disease control in the majority of pts.These data support 1.2 mg/kg as the RP2D of Dal in the randomized double-blind part 2 of this study in which pts. will be randomized to Dal + axitinib vs. placebo + axitinib. Clinical trial information: NCT01727336.

**4567 General Poster Session (Board #135), Mon, 1:15 PM-5:00 PM**

**Subgroup analyses of a randomized sequential open-label study (SWITCH) to evaluate efficacy and safety of sorafenib (SO)/sunitinib (SU) versus SU/SO in the treatment of metastatic renal cell cancer (mRCC).** *Presenting Author: Peter J. Goebell, AURONTE (Urologische Klinik und Klinik fuer Haematologie und Onkologie (Med5); Universitaetsklinikum Erlangen), Erlangen, Germany*

**Background:** Results of the sequential randomized phase III SWITCH study comparing SO/SU and SU/SO have been reported previously (ASCO GU 2014, abstract 393) showing no significant difference in the primary endpoint total PFS (T-PFS, Hazard Ratio [HR] 1.01) nor the secondary endpoints overall survival (OS, HR 1.0) and 1st-line PFS (HR 1.19). We here report results of SWITCH study subgroup analyses per endpoints T-PFS, OS, and 1st-line PFS. **Methods:** Pts with mRCC unsuitable for cytokines without prior systemic therapy, ECOG PS 0/1, MSKCC score low or intermediate, and $\geq 1$ measurable lesion were randomized to receive open-label SO/SU (arm A) or SU/SO (arm B) in standard dosage. Retrospective subgroup analyses according to age, sex, MSKCC score, and ECOG PS were performed to identify any subgroup that profits more from one sequence or the other by comparing both groups using Cox proportional hazard regression model and log-rank testing. **Results:** A total of 365 pts were enrolled: 182 arm A, 183 arm B.At time of final T-PFS analysis 220 events had occurred (A, n=117 [64%]; B, n=103 [56%]). The Table shows the subgroup analyses comparing group A vs group B including HR and p value of tests for difference. **Conclusions:** There was no significant difference in T-PFS, OS, and 1st-line PFS in the evaluated subgroups between the two sequential treatments apart from OS per age group in which different results have been found. Both drugs provided overall benefit regardless of sequence and subgroup. However, the analyses were exploratory and hypothesis-generating as they were retrospective and the significance analysis was not corrected for multiple testing. Clinical trial information: NCT00732914.

| Subgroup | T-PFS HR (p value) | OS HR (p value) | PFS in 1st-line HR (p value) |
|---|---|---|---|
| **Age < 65 yrs** | 1.17 (0.37) | 1.57 (0.04) | 1.25 (0.18) |
| **Age ≥ 65 yrs** | 0.84 (0.40) | 0.60 (0.04) | 1.10 (0.63) |
| **Male** | 1.04 (0.80) | 0.99 (0.94) | 1.27 (0.09) |
| **Female** | 0.86 (0.59) | 1.08 (0.81) | 0.96 (0.86) |
| **ECOG PS 0** | 1.02 (0.91) | 1.05 (0.82) | 1.33 (0.08) |
| **ECOG PS 1** | 1.04 (0.84) | 0.97 (0.90) | 1.08 (0.14) |
| **MSKCC low** | 0.98 (0.91) | 1.24 (0.48) | 1.30 (0.20) |
| **MSKCC intermediate** | 1.01 (0.95) | 0.83 (0.34) | 1.14 (0.44) |

**4568 General Poster Session (Board #136), Mon, 1:15 PM-5:00 PM**

**Overcoming mTOR resistance: Results of a phase I study of the mTOR inhibitor ridaforolimus and the HDAC inhibitor vorinostat.** *Presenting Author: Matthew R. Zibelman, Fox Chase Cancer Center, Philadelphia, PA*

**Background:** Elevation of pAKT levels has been shown to result from mTOR inhibition. We hypothesized that the HDAC inhibitor vorinostat (Vori) would abrogate ridaforolimus (Rida) resistance due to down-regulation of pAKT when used in combination in patients with renal cell carcinoma (RCC). **Methods:** The primary objective was to determine the maximum tolerated dose (MTD) for RCC patients (pts), thus while all solid tumors were allowed, prior cytotoxic chemotherapy was limited to 1 regimen. There was no limit to the number of prior targeted or immunotherapies. ECOG PS 0-1 and adequate organ and marrow function were required. A modified 3+3 dose escalation design tested 2 dose levels concurrently by escalating each drug in separate cohorts. Rida was dosed days 1-5 and Vori days 1-3, weekly. **Results:** 15 pts (10 clear cell RCC, 3 papillary RCC, 1 esophageal, 1 carcinoid) were treated at 1 of 3 dose levels: 1) Rida 20mg QD + Vori 100mg BID, 2) Rida 20 mg QD + Vori 200 mg BID, 3) Rida 40 mg QD + Vori 100 mg BID. Inability to complete 80% of doses during cycle 1 due to thrombocytopenia resulted in dose limiting toxicities (DLTs) in 2/6 pts at dose level 2. There were no other DLTs and no grade 4-5 toxicities. Related grade 3 toxicities were: hyperglycemia (1), anemia (2), fatigue (1), and mucositis (1). Grade 2 pneumonitis was seen in 2 pts. The MTD was Rida 20mg QD + Vori 100mg BID, however all 7 pts who received >2 cycles required dose reduction to Rida 10-20 mg QD + Vori 100 mg QD, 6 due to thrombocytopenia. Thus the recommended phase II dose (RP2D) to allow for chronic dosing is Rida 20mg QD + Vori 100mg QD. Stable disease for 19, 21, 46+ and 74+ weeks, respectively, was maintained in 4 pts with RCC. Of these, 3 had progressed on prior mTOR therapy, including 2 pts with papillary RCC and ongoing disease control at the time of data cutoff. **Conclusions:** Rida 20mg QD + Vori 100 mg QD is the RP2D for this combination. Prolonged, ongoing disease control was seen in 2 papillary RCC pts, both of whom had progressed on a prior mTOR inhibitor. Further study of combined mTOR and HDAC inhibition in RCC, with tumor sampling to assess for pharmacodynamics and proof of concept, is warranted to further define the toxicity, efficacy and mechanism of this combination. Clinical trial information: NCT01169532.

**4569 General Poster Session (Board #137), Mon, 1:15 PM-5:00 PM**

**Dovitinib in first-line metastatic renal cell carcinoma and correlation of efficacy with tumor gene status: A phase II clinical trial.** *Presenting Author: Reuben James Broom, Auckland City Hospital, Auckland, New Zealand*

**Background:** Dovitinib is an anti-VEGFR tyrosine kinase inhibitor which also inhibits FGFR-1,-2,-3 and PDGFR$\beta$. We studied its activity as 1st-line therapy in patients with metastatic clear-cell renal cell carcinoma (mCCRCC) and correlated genes related to its action mechanism with clinical outcomes. **Methods:** The 31 treatment naïve patients with mCCRCC enrolled in this single-arm, single-site, phase II study received dovitinib at 500mg 5 days on/2 days off until progression. An optional post-treatment biopsy was offered to study resistance mechanisms. The primary endpoint was progression free survival (PFS) using RECIST 1.1. Secondary endpoints included response rate and efficacy by gene status (FISH and DNA sequence). **Results:** Accrual occurred over 15 months from March 2012. Median patient age was 64 and 72% were male. ECOG performance status was 0 in 45% and 1 in 55%. Heng prognostic group was favorable risk in 38%, intermediate risk in 52% and poor risk in 10%. 38% had bone metastases. 4 patients stopped treatment due to toxicity and 1 patient withdrew. Median PFS was 6.2 months (inter quartile range: 3.3 to 8.2). Of 28 evaluable patients, best response was: PR (29%), SD (53%) and PD (18%). All-cause grade 3/4 adverse events (AE's) occurring in $\geq$5% of patients were: fatigue (16%), abdominal pain (13%), pancreatitis (10%), gout (7%), diarrhea (7%), bone pain (7%), hypercalcemia (7%), elevated lipase (7%) and pulmonary embolism (7%). Pre-treatment metastatic and primary tumor tissue was available from 93% and 54% of patients respectively. 6 patients donated post-progression tissue. Gene status (FISH) for FGFR-1,-2,-3, PDGF$\beta$ and PDGFR$\beta$ was available for 20 primary and 17 metastatic specimens. FGFR-1 showed a trend towards positive correlation between gene gain/amplification and response (Spearman's rho = 0.32, p = 0.17). FGFR-2, FGFR-3, PDGFR$\beta$ and PDGF$\beta$ showed no statistically significant associations. **Conclusions:** Dovitinib has activity in the first line setting of mCCRCC with a tolerable safety profile at the given dosing schedule. A non-significant correlation of this activity with FGFR-1 gene gain/amplification was seen and further study with a larger sample size is warranted. Clinical trial information: ACTRN12612000140853.

**4570 General Poster Session (Board #138), Mon, 1:15 PM-5:00 PM**

**A phase II study of bevacizumab (Bev) and temsirolimus (Tem) in VEGF-refractory metastatic renal cell carcinoma (mRCC).** *Presenting Author: Kathleen Margaret Mahoney, Beth Israel Deaconess Medical Center, Boston, MA*

**Background:** Inhibiting VEGF and mTOR pathways are standard treatment approaches for patients (pts) with mRCC. Combinations of these agents have potential to improve efficacy. Here we report the activity and safety of the Bev and Tem combination in pts with clear cell (cc) and non-clear cell (ncc) mRCC who had failed prior VEGF blockade. **Methods:** In this phase II investigator-initiated multicenter study pts received Bev (10 mg/kg) IV q2 weeks and Tem (25 mg) IV weekly until progression of disease (PD) or unacceptable toxicity. The primary endpoint was progression free survival (PFS). Secondary endpoints included overall response rate (ORR), median overall survival (OS), toxicity, and correlative studies. The design provided 88% power (10% alpha) to prove a progression free rate of 50% at 2 months. **Results:** Forty-one pts were enrolled and 40 were treated; 31 (77.5%) had good/intermediate risk per the IMDC criteria (Heng JCO 2009) and 13 (32.5%) had ncc histology. Thirteen (32.5%) had primary VEGF-refractory disease, in which best response on prior VEGF-targeted therapy was PD. Median prior therapies was 1 (75% sunitinib). Median PFS was 5.8 months. Median OS was 13.1 months as of 10/2013. There were no CR. Confirmed PR occurred in 7 pts (17.5%). Median PFS and ORR were 7.8 months and 15% (2/13) in pts with primary VEGF-refractory disease and 7.6 months and 7.6% (1/13) in pts with nccRCC. All grade and grade 3/4 toxicities, at least possibly attributable to Bev and Tem, were seen in 62% and 49%, respectively. Dose reduction occurred in 77.5% of pts and 27.5% were taken off study because of toxicity. Most frequent toxicities include fatigue, dyslipidemia, and proteinuria. The most serious toxicity included deep vein thrombosis (1), esophageal fistula (1), bowel perforation (1), cerebrovascular accident (1) and ventricular arrhythmia/cardiac arrest (1). **Conclusions:** Combining Bev and Tem in a VEGF-refractory mRCC population was possible with dose reductions, and resulted in longer than expected PFS in pts with primary VEGF-refractory disease and non clear cell histology, both 2 unmet needs in RCC. We are currently in the process of assaying pretreatment tumor samples for predictive biomarkers. Clinical trial information: NCT00782275.

**4571 General Poster Session (Board #139), Mon, 1:15 PM-5:00 PM**

**Characterization of the mTOR autophosphorylation site, S2481, as a novel biomarker in renal cell carcinoma (RCC).** *Presenting Author: Lauren Christine Harshman, Dana-Farber Cancer Institute, Boston, MA*

**Background:** mTOR inhibitors have clinical utility in VEGF-refractory RCC and may be useful in non-clear cell disease. In general, mTOR inhibition is inferior to targeting VEGF in the treatment-naïve setting. However, some patients clearly demonstrate mTOR-dependent disease. It is critical that new biomarkers are identified to optimize patient selection for mTOR-targeting therapeutics. One such potential marker, the mTOR autophosphorylation site, S2481, is a direct readout of mTOR activation. The objective of this pilot study was to analyze the levels of phospho-S2481 in different RCC subtypes. **Methods:** Utilizing standard immunohistochemistry methods, archived, formalin-fixed paraffin-embedded primary tumor samples from an existing tissue microarray of patients with clear cell (cc, n=203), chromophobe (n=21) and papillary RCC (n=38) were stained for the presence of phospho-S2481. Samples from transitional cell carcinoma cases (n=38) were included as a control. Mean scores from the four cancer subtypes were calculated, and the Kruskal-Wallis test was applied to demonstrate the statistical relevance of the mean scores. Covariates such as stage, grade, age, and tumor size were analyzed by logistic regression. **Results:** ccRCC patients were most likely to have high levels of phospho-S2481 staining (mean=2.08), while the TCC controls had the lowest amount (mean=1.11), with papillary and chromophobe falling in between (mean=1.41 and 1.38 respectively). The mean score difference among the four cancer subtypes was highly significant (Chi-square statistic: 54.51, p $<$.0001). Tumor size and cancer subtype were highly correlated with the score (p$<$.01). Comparison of the odds ratios for the three RCC subtypes demonstrated that ccRCC cases were three times more likely to have high levels of phospho-S2481 and four times more likely than papillary RCC (p$<$.05). **Conclusions:** Phospho-S2481 may have the ability to classify RCC patients of different subtypes. Exploration of phospho-S2481's ability to predict patient response to mTOR inhibitors is under way.

**4572 General Poster Session (Board #140), Mon, 1:15 PM-5:00 PM**

**Comprehensive functional kinase profiling to classify clear cell (cc)-renal cell carcinoma (RCC).** *Presenting Author: Amitkumar N. Mehta, The University of Alabama at Birmingham, Birmigham, AL*

**Background:** Comprehensive high throughput functional kinase activity in localized cc-RCC tumors may assist in devising a classification system and help identify therapeutic targets. **Methods:** Kinomic profiling of fresh frozen cc-RCC tumor lysates was performed using the PamStation12(PamGene Intl). The protein tyrosine kinome (PTK) and serine/threonine kinome (STK) PamChips were used to measure global kinase activity. Advanced network modeling of altered phospho-peptides was performed using MetaCore (Thompson Reuters) while upstream kinase prediction scoring was based off of phosphonet (www.phosphonet.ca). Patients with localized tumors with minimum clinical follow-up of 18 months (mo) were studied to perform a supervised analysis of kinomics guided by objective tumor recurrence. Unsupervised cluster analyses were performed to classify tumors based on kinomics. **Results:** Tumor was available from 41 pts with localized tumors undergoing surgery and a minimum follow-up of 18 mo. The median age was 61 and baseline pathologic stage was 1, 2, 3 and 4 in 19, 1, 20 and 1 patients, respectively. Unsupervised clustering analyses showed 3 major kinomic groups A, B, C. Potential driver kinases implicated include PFTAIRE (PFTK1), PKG1 and SRC, which were identified in groups A, B, and C, respectively. Network modeling of these kinase groupings identified many Process Mappings including, but not limited to Inflammation pathways (A), translation initiation (B) and immune response and cell adhesion pathways(C).Five of the 9 patients who progressed were classified as Group C, 1 progressor was in Group B, and 3 were in Group A. Supervised analysis showed decreased CDK1, RSK1-4, ERK1-2, PKG2 and AKT2 kinase activity in those who progressed. Twelve tumors exhibited increased PIM1 and MAPKAPK3, and decreased JNK2 and CDK1 compared to normal. **Conclusions:** Comprehensive kinase profiling of cc-RCC tumors from patients with localized disease was used to classify tumors based on an unsupervised clustering, which appeared to confer differential long-term outcomes while supervised analysis also identified potential pathways related to outcome. Significant heterogeneity of kinases was found with no single dominant kinase.

**4573 General Poster Session (Board #141), Mon, 1:15 PM-5:00 PM**

**Pre-existing hypertension is an independent prognostic factor in metastatic renal cell carcinoma (mRCC) patients treated with sunitinib (SU).** *Presenting Author: Lisa Derosa, Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France*

**Background:** Hypertension (HTN), one of the most frequent side effects of VEGF inhibitors, has been related with outcome in mRCC. We aimed to investigate the prognostic value of history of pre-existing HTN (HTN-PRE) and pre-existing medications with angiotensin system inhibitors (ASI-PRE). **Methods:** mRCC patients (pts) treated with SU as first line therapy at Gustave Roussy from April 2004 to January 2014 with available data about HTN-PRE and pre-existing concomitant medications were included. Overall survival (OS) and progression free-survival (PFS) were compared with the log rank test and hazard ratios (HR) and 95% confidence interval (CI) estimated through a multivariable Cox model adjusted on age, gender, histology and IMDC prognostic groups. **Results:** 213 pts with a 44 (95%CI=31-60) months median follow-up received SU as first line treatment. Most pts were male (78%), 59 years median age (28-86), had clear-cell histology (87%) and intermediate IMDC risk (61%). 84 pts (39%) had HTN-PRE including 54 (64%) receiving ASI-PRE. Pts with HTN-PRE received ASI-PRE more often than pts without (64% vs 6%, p<0.001). The total number of deaths and PFS events was 59% and 85%. Pts with HTN-PRE had a longer OS (median: 32 vs 23 months, p=0.03) and longer PFS (median: 12 vs 9 months, p<0.02) with respectively HR of 0.59 [0.39-0.89], p=0.01 for OS and HR of 0.66 [0.48-0.91], p=0.01 for PFS. In HTN-PRE subgroup, pts with ASI-PRE had a better OS but similar PFS than pts without ASI-PRE with HR of 0.45 [0.23-0.89], p=0.02 and HR of 0.72 [0.41-1.26], p=0.24, respectively. **Conclusions:** HTN-PRE is an independent prognostic factor in pts with mRCC treated with SU. The mechanism of action of ASI in SU treated pts deserves further evaluation.

**4574 General Poster Session (Board #142), Mon, 1:15 PM-5:00 PM**

**Association of CpG island methylator phenotype with clear-cell renal cell carcinoma aggressiveness.** *Presenting Author: Gabriel Malouf, Department of Medical Oncology, Groupe Hospitalier Pitié-Salpêtrière, University Pierre and Marie Curie (Paris VI), Institut Universitaire de cancérologie, AP-HP, Paris, France*

**Background:** The key roles of epigenetic dysregulation of chromatin remodeling genes in clear-cell renal cell carcinoma (ccRCC) have been recently discovered through exome-sequencing which showed frequent mutations of PBRM1, SETD2 and UTX genes. However, the contribution and the prognosis impact of DNA methylation aberrations in ccRCC remain limited. **Methods:** We herein analyzed DNA methylation of 298 primary ccRCC samples, fully annotated for clinico-pathological features and profiled by the cancer genome atlas (TCGA) project using infinium 450K arrays. Furthermore, we established DNA methylation subtypes based on distinct signatures, and correlated them with clinico-pathological tumor features and copy-number alterations. **Results:** Unsupervised hierarchical clustering based on DNA methylation of promoters located in CpG islands (CGI) revealed three clusters of ccRCC. Cluster C1 (n=65) displays a CpG island methylator phenotype (CIMP+), while cluster C2 (n=53) and C3 (n=153) correspond to CIMP-low and CIMP negative subgroups, respectively. Tumors belonging to CIMP+ subgroup were more aggressive with higher pathological Fuhrman grade (p<0.00001), higher TNM stage (p<0.0001) and poorest overall survival (p=5.4e-9). After adjusting for classical clinico-pathological prognostic factors using multivariate analysis, CIMP+ was not found to be independently associated with poor overall survival, suggesting that aberration DNA methylation might be acquired during tumor progression. Integration of DNA methylation with copy-number changes identified frequent gain of chr8q24.22 (p=0.0007) in CIMP+ subgroup, as well as losses of 9p23 (p=5.7E-09) and 9p21.3 (p=4.6E-07) regions. GSEA analysis reveals that promoters that gain DNA methylation in CIMP+ tumors were enriched for polycomb targets, and this was consistent with EZH2 increase (Fold change=1.5; p=0.05). **Conclusions:** Our study defines a novel genetically distinct CIMP subgroup in ccRCC associated with ccRCC aggressiveness and patient outcome. Furthermore, it provides evidence about the involvement of polycomb deregulation in ccRCC progression.

**4575 General Poster Session (Board #143), Mon, 1:15 PM-5:00 PM**

**105 cases of renal tumors in patients age 15 to 35: A specific entity? Experience of the Gustave Roussy Institute.** *Presenting Author: Charles Dariane, Gustave Roussy Institute, Villejuif, France*

**Background:** To describe the specific features of malignant renal tumors occurring in young adults. **Methods:** Medical charts of all 15-35 yo pts diagnosed with a primary renal malignant tumor from1990 to date and treated at Gustave Roussy were retrieved. **Results:** Overall, 105 pts were analyzed with a median follow up of 21.1 months (IQR 5.53-47.2). First pathological entity was Renal Cell Carcinoma (RCC) (n= 89) and second one was nephroblastoma (n=9). Median age at diagnosis was 28.7(24-32) : 31.1 (27.8-33.6) for RCC and 23.6 (22.2-25.8) for nephroblastoma. Only 24% pts underwent a tumor biopsy as first procedure while others had nephrectomy or tumorectomy front line. Among nephroblastoma, only 2 had first biopsy and received neo-adjuvant chemotherapy. Four had synchronous metastasis, 3 remained localized and received adjuvant chemotherapy and 2 developed peritoneal immediate recurrence after surgery requiring additional chemotherapy and radiation therapy. Regarding ccRCC (37pts), 87% of pts presented with symptoms; 76% presented metastasis at diagnosis or during follow up. Prognosis groups of mRCC (83pts), according to IMDC, were good/intermediate and poor in 44/34/5 respectively. One out of 9 pts with nephroblastoma has died. **Conclusions:** We report a large cohort of 15-35 yo patients with malignant renal tumors, highlighting (i) the issue of highly aggressive RCC disease in young adults and (ii) the challenge of differential diagnosis of nephroblastoma. Interestingly, nephroblastoma were diagnosed in pts aged up to 31 and diagnosis procedure did not comply with required pediatric guidelines. This report suggests the need of standardized guidelines in young adult renal tumors management.

| Age | [15-20] | [20-25] | [25-30] | [30-35] |
|---|---|---|---|---|
| **1/ Histology** | | | | |
| **Nb of pts** Total =105 | 13 | 19 | 28 | 45 |
| **RCC** 89 | 10 | 11 | 25 | 43 |
| **- ccRCC** 37 | 2 | 4 | 10 | 21 |
| **- translocation** 20 | 3 | 3 | 9 | 5 |
| **- pRCC** 17 | 2 | 1 | 2 | 12 |
| **- other RCC** 15 | 3 | 3 | 4 | 5 |
| **Nephroblastoma** 9 | 1 | 4 | 2 | 2 |
| **Miscellaneous** 7 | 2 | 4 | 1 | 0 |
| **2/Survival mRCC (n=83)** OS (mos) | PFS first-line (mos) | | | |
| **ccRCC** 21.5 (4.6-44.4) | 3.2 (1.8-7) | | | |
| **translocation** 11.1 (5.4-23.4) | 3.6 (2.6-6.5) | | | |
| **pRCC** 19.1 (11-50.6) | 2.9 (2.3-9.2) | | | |

**4576 General Poster Session (Board #144), Mon, 1:15 PM-5:00 PM**

**The impact of body mass index (BMI) on treatment outcome of targeted therapy in metastatic renal cell carcinoma (mRCC): Results from the International Metastatic Renal Cell Cancer Database Consortium.** *Presenting Author: Laurence Albiges, Dana-Farber Cancer Center Institute, Boston, MA*

**Background:** Obesity increases risk for RCC, yet recent report suggest that tumors developing in an obesogenic environment may be more indolent. We investigated the effect of BMI on treatment outcome in patients (pts) treated with targeted therapy (TT) for mRCC. **Methods:** Baseline characteristics and outcomes on 1975 pts from 19 centers of the IMDC were analyzed to study the impact of BMI on survival and treatment outcome of first and second line TT. Toxicity profile in relation to BMI was also assessed. **Results:** Median follow-up was 21.1 months. Median time to treatment failure on first-line TT was 7.2 months and median overall survival (mOS) was 21.5 months [95%CI: 20.1-23.3]. At therapy initiation, 785(40%) pts were considered underweight or normal weight (BMI<25 kg/m$^2$), 663(33.5%) overweight (BMI 25-<30 kg/m$^2$) and 527 (26.5%) obese (BMI≥30 kg/m$^2$). Overweight/obese pts had a longer mOS (25.6 vs. 17.1 months) than underweight/normal weight pts (p<0.0001). After adjusting for the IMDC prognostic risk factors, the mOS difference persisted in favor of the overweight/obese pts group (HR=0.84, (95%CI: 0.73-0.95), p=0.008). In addition, pts with higher BMI indices (overweight/obese) had improved time on therapy in both first-line (8.1 vs. 5.7 months, p<0.0001) and second-line (4.2 vs. 3.0 months, p=0.0006), and the difference remained after adjustment for the IMDC prognostic risk factors (p<0.01). Estimates of the cumulative incidence of treatment failure because of toxicity did not differ between the underweight/normal and overweight/obese groups (p=0.936), but the cumulative incidence of treatment failure because of progression/death favored the overweight/obese group after adjustment for the IMDC risk groups (p<0.002). **Conclusions:** We found that being overweight or obese is independently associated with an improved outcome in mRCC pts treated with TT. Increased toxicity was ruled out as a potential bias for treatment discontinuation or dose reduction in normal/underweight pts. Biological investigation in tissues collected from the IMDC cohort is in process to better characterize the obesity paradox in mRCC.

**4577 General Poster Session (Board #145), Mon, 1:15 PM-5:00 PM**

**Correlation of stable disease (SD) as best response with survival outcomes in patients (pts) with clear cell (cc) metastatic renal cell carcinoma (mRCC) treated with high-dose interleukin-2 (HD IL-2).** *Presenting Author: Joseph Merriman, University of Utah Huntsman Cancer Institute, Salt Lake City, UT*

**Background:** HD IL-2 is a standard of care for selected pts with mRCC. Generally objective responses (OR), i.e. complete response (CR) + partial response (PR), of 16-20% are discussed with pts, and not SD. Recent data suggest that cancer immunotherapy may improve survival without inducing OR. Thus, HD IL-2 may provide survival benefit to an additional group of pts not experiencing OR, but only SD as the best response. **Methods:** All sequential cc mRCC pts treated with HD IL-2 at the University of Utah (1988-2012) were included. Two practitioners independently assessed responses. Best responses were correlated with survival outcomes using Kaplan-Meier analysis. **Results:** A total of 176 pts (79% male; median age 55 yrs, range 13-76) were included and belonged to the following MSKCC risk categories: 51 (29%) good, 115 (65%) intermediate, and 10 (6%) poor. A CR was identified in 16 (9%), PR in 11 (6%), SD in 52 (30%), progressive disease (PD) in 68 (39%), and not evaluable for response (NE) in 29 (16%) pts. Median overall survival (OS) by risk category for the favorable, intermediate and poor groups was 47.6 ($p=0.0005$ vs intermediate), 18.0 ($p<0.0001$ vs poor), and 5.4 ($p<0.0001$ vs favorable) months (mo), respectively. Table shows correlation of best response with survival outcomes. **Conclusions:** A clinical benefit of HD IL-2 wasachieved in nearly half of all cc mRCC pts. SD was associated with clinically relevant survival outcomes. There was no statistical difference in outcomes between pts achieving a PR or SD. SD is an important response criterion for treatment with HD IL-2, and may be discussed with pts.

**Correlation of best responses with survival outcomes in mRCC pts treated with HD IL-2 .**

| | PFS, mos | OS, mos |
|---|---|---|
| **Overall** | 5.6 | 19.9 |
| **CR vs PR** | 113.8 vs 14.8 (HR 0.34, CI 0.12-0.95) | 182.0 vs 37.8 (HR 0.23, CI 0.06-0.74) |
| **CR vs SD** | 113.8 vs 11.0 (HR 0.22, CI 0.09-0.47) | 182.0 vs 29.2 (HR 0.16, CI 0.04-0.41) |
| **SD vs (PD and NE)** | 11.0 vs 2.6 (HR 0.40, CI 0.28-0.58) | 29.2 vs 9.7 (HR 0.42, CI 0.28-0.61) |
| **OR vs (SD, PD and NE)** | 40.3 vs 4.3 (HR 0.27, CI 0.15-0.44) | 83.5 vs 16.3 (HR 0.24, CI 0.13-0.42) |
| **PR vs SD** | 14.8 vs 11.0 (HR 0.64, CI 0.28-1.31) | 37.8 vs 29.2 (HR 0.68, CI 0.29-1.41) |

**4578 General Poster Session (Board #146), Mon, 1:15 PM-5:00 PM**

**Comparison of stem cell signaling pathways in long-term responders (LR) versus primary refractory (PR) patients with metastatic clear-cell renal cell carcinoma (ccRCC) under sunitinib (SU) treatment (SULONG study).** *Presenting Author: Javier Puente, Hospital Clinico Universitario San Carlos, Madrid, Spain*

**Background:** Deregulation of stem cell signaling pathways, such as Notch and Sonic Hedgehog (SHH) seems necessary for tumor initiation, maintenance and progression. Preclinical evidence supports that they may play an oncogenic or tumor suppressor role depending on the tumor type. **Methods:** Retrospective, observational and multicenter study of patients (pts) treated with SU under clinical practice aimed to compare clinical and molecular characteristics in two groups of pts: Metastatic ccRCC pts who achieved progression free survival ≥ 22 months (LR), and pts who showed progressive disease at first radiological evaluation (PR). Tumour expression of different Notch (Jagged-1, Notch-1, nuclear N1ICD) and SHH (SFU-SHH suppressor and GLI-1) signalling components was evaluated by immunohistochemistry and correlated with treatment outcome. This study was approved by the Regulatory Authorities. **Results:** From a total of 123 pts, 97 were identified as LR and 26 as PR. Pts with higher Fuhrman grade, metastasis at diagnosis, shorter time from primary to metastatic diagnosis, no nephrectomy and brain, lung and hepatic metastasis were significantly higher in the PR cohort. So far, 47 tumor samples have been analyzed, 36 of LR and 15 of PR. Expression of Jagged-1 ($p<0.001$) and SFU ($p<0.001$) was significantly correlated with PR; as well as the join expression of Jagged-1/Notch-1+ and Jagged-1/N1ICD+ ($p<0.001$) confirming the activation of the pathway in this group. Jagged-1 expression was also significantly correlated to Furhman G4 ($p<0.05$) in the PR group, metastasis at diagnosis ($p<0.001$) in LR and poor risk group by Heng's criteria ($p<0.05$) in the overall population. The ongoing molecular analysis of the remaining tumour samples and their correlation with PFS and OS in the LR group is warranted to confirm their predictive value under SU treatment. **Conclusions:** These preliminary results suggest that Notch signaling activation predicts poor outcome in metastatic ccRCC. By contrast, SHH seems to be activated in the LR group suggesting an opposite role for both pathways in this tumor.

**4579 General Poster Session (Board #147), Mon, 1:15 PM-5:00 PM**

**Molecular subtypes of clear cell renal cell carcinoma: Impact of diabetes mellitus, metformin, and immunotherapy on patient outcomes.** *Presenting Author: Scott Mattox Haake, Medical Oncology Fellowship, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

**Background:** A 34-gene subtype classifier was previously developed to define clear cell renal cell carcinoma (ccRCC) tumors as either clear cell A (ccA) or B (ccB). The objective of this study was to investigate clinical factors and immunotherapies in the context of these subtypes. **Methods:** In this retrospective analysis, the Total Cancer Care (TCC) database at Moffitt Cancer Center was queried and 255 patients with ccRCC were identified with primary tumor gene expression analyses. The TCC database and medical record were queried to define patient characteristics, treatments, and outcomes. **Results:** The classifier identified tumors as ccA (206) and ccB (49). Prognostic outcomes including overall survival (OS) in all patients ($p<0.01$), stage IV patients ($p=0.01$), and recurrence free survival ($p<0.01$) were confirmed. The superior prognostic group, ccA, had higher BMI (29.7 vs. 27.8 kg/m$^2$, $p=0.03$). There was a trend towards a higher rate of DM2 in ccA patients (26% vs. 12%, $p=0.058$). Thus, we analyzed the impact of metformin on survival in ccA patients. The nondiabetic ccA patients had a similar outcome to diabetic ccA patients treated with metformin but diabetic ccA patients not treated with metformin had decreased survival ($p=0.02$). For the 37 stage IV patients treated with cytoreductive nephrectomy (CRN), ccA patients demonstrated superior OS (median survival 39 vs. 15 months, $p=0.02$) and remained significant in multivariate analysis that included age, gender, nuclear grade, and tumor size. Among 12 patients treated with interleukin-2 (IL2), the six ccA patients had a nonsignificant ($p=0.12$) better outcome. **Conclusions:** The ccA patients have a higher BMI and a trend towards higher frequency of DM2. When compared to nondiabetic ccA patients, ccA diabetic patients have decreased survival that is improved in those treated with metformin. The ccB patients have a worse prognosis and decreased survival when treated with CRN or IL2. Overall, ccA and ccB patients represent distinct populations that may have differential responses to therapies.

**4580 General Poster Session (Board #148), Mon, 1:15 PM-5:00 PM**

**Association of hand-foot syndrome (HFS), treatment dose reductions (TDRs), and outcomes in patients (pts) with metastatic renal cell carcinoma (mRCC) treated with vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (TKIs).** *Presenting Author: Erin B. Bailey, University of Utah Huntsman Cancer Institute, Salt Lake City, UT*

**Background:** HFS is a common toxicity of VEGF TKIs, often requiring TDRs. Correlation between HFS, in the context of TDRs, with survival outcomes has not been reported in mRCC. **Methods:** From a single-institutional database (2004-2013), incidence of HFS and TDRs (for any reason) in mRCC pts receiving VEGF TKIs were recorded and correlated with survival outcomes. Univariate and multivariate analyses were performed using Kaplan-Meier method and COX Proportional Hazard model. **Results:** Of 123 pts (median age 60 yrs, males 71%), the majority had clear cell histology (71.5%) and were in the MSKCC (71%) and Heng (55%) intermediate-risk groups. Pts received the following TKIs: sunitinib (77.2%), sorafenib (14.6%), pazopanib (7.3%), and axitinib (0.8%). HFS (G1 20.3%, G2 8.9%, G3 9.8%) occurred in 39% of pts. The most common reasons for TDRs were mucositis (38.8%), HFS (29.9%), and fatigue (17.9%). The median progression free survival (PFS) and overall survival (OS) were significantly longer in pts with HFS (Table). The median OS was improved in those who had TDRs for HFS as compared with those who had TDRs for other reasons (Table). Two multivariate analyses were conducted. The first included age, sex, HFS, TSH > 10 mIU/L while on VEGF TKI, and risk criteria. HFS remained significant for improvements in PFS and OS (PFS: HR 0.38, CI 0.19-0.76, $p=0.0060$; OS: HR 0.37, CI 0.15-0.83, $p=0.0157$). In the second multivariate analysis, development of HFS was substituted for TDRs for HFS and it was not an independent predictor of survival (PFS: HR 0.58, CI 0.25-1.23, $p=0.1601$; OS: HR 0.46, CI 0.16-1.14, $p=0.0981$). **Conclusions:** HFS in mRCC pts treated with VEGF TKIs predicts improved survival despite TDRs. Thus, VEGF TKI dose reductions for the management of HFS are not expected to negatively impact survival outcomes.

**Outcomes with HFS and TDRs.**

| | n | PFS, months | OS, months |
|---|---|---|---|
| **HFS vs no HFS** | 123 | 14.1 vs 6 (HR 0.51, CI 0.32-0.79, p=0.0021) | 42.8 vs 10.8 (HR 0.39, CI 0.23-0.63, p<0.0001) |
| **TDRs for HFS vs TDRs for other reasons** | 67 | 21.9 vs 8.5 (HR 0.55, CI 0.28-1.02, p=0.0582) | 45.1 vs 13.9 (HR 0.37, CI 0.16-0.76, p=0.0061) |

**4581 General Poster Session (Board #149), Mon, 1:15 PM-5:00 PM**

**Q-TWiST analysis of patients with metastatic renal cell carcinoma (mRCC) randomized to pazopanib (PAZ) or sunitinib (SUN).** *Presenting Author: Jennifer L Beaumont, Northwestern University Feinberg School of Medicine, Chicago, IL*

**Background:** In a phase 3, randomized, open-label trial (NCT00720941), PAZ demonstrated non-inferiority for progression-free survival vs SUN in mRCC patients with no prior therapy (NEJM 2013; 369: 722). Overall treatment differences were evaluated in a post-hoc analysis using the quality-adjusted time without symptoms of progression or toxicity of treatment (Q-TWiST). **Methods:** Each patient's overall survival (OS) was partitioned into 3 health states: grade 3 or 4 toxicity (TOX), time without symptoms of progression or toxicity (TWiST), and time after progression or relapse (REL). The time spent in each state was then weighted by a health-state utility associated with that state and summed to calculate the Q-TWiST. A threshold utility analysis was used, applying utilities across the range of 0 (similar to death) to 1 (perfect health). **Results:** A total of 1,110 patients were enrolled (557 PAZ, 553 SUN). The mean number of days spent with TOX was 31 days (95% CI: 13, 49) higher for SUN compared to PAZ. In the threshold utility analysis the difference in Q-TWiST ranged from 3 days (utility TOX=1, REL=0) to 38 days (TOX=0, REL=1), always in favor of PAZ across all analyses. Differences were statistically significant in roughly half of the utility combinations examined, typically when the utility for TOX was ≤ the utility weight for REL. A subset of these results are in the Table. For instance, when TOX is weighted at 0.75 relative to TWiST and REL is weighted somewhat worse than TOX at 0.50, the Q-TWiST difference between arms is 13 days (95% CI: –7, 32), in favor of PAZ. **Conclusions:** Patients randomized to PAZ had slightly longer Q-TWiST compared to SUN patients, primarily due to a reduced length of time spent with grade 3/4 toxicities. This difference (3 to 38 days, depending on utility combination) is less than 10% of OS (median: 28 months).

| Utility weights | | | PAZ vs SUN Q-TWiST difference, days (95% CI) |
|---|---|---|---|
| TOX | TWiST | REL | |
| **0.25** | 1 | 0.25 | 27 (2, 52) |
| **0.5** | 1 | 0.25 | 19 (–5, 43) |
| **0.75** | 1 | 0.25 | 12 (–12, 36) |
| **0.25** | 1 | 0.5 | 28 (7, 49) |
| **0.5** | 1 | 0.5 | 20 (1, 40) |
| **0.75** | 1 | 0.5 | 13 (–7, 32) |
| **0.25** | 1 | 0.75 | 29 (10, 48) |
| **0.5** | 1 | 0.75 | 21 (4, 39) |
| **0.75** | 1 | 0.75 | 14 (–3, 30) |

**4582 General Poster Session (Board #150), Mon, 1:15 PM-5:00 PM**

**Osteopontin (OPN), TIMP-1, and interleukin (IL)-6 as prognostic (prog) for overall survival (OS) and independent from clinical criteria in patients (pts) with metastatic renal cell carcinoma (mRCC).** *Presenting Author: Amado J. Zurita, MD Anderson Cancer Center, Houston, TX*

**Background:** No biomarker has been incorporated into clinically based prog algorithms for mRCC. In previous work in pts with ECOG PS ≤1 treated in a randomized placebo-controlled phase III trial of pazopanib (paz, veg105192), we identified for progression-free survival (PFS), IL-6 as predictive (pred) of paz benefit (Tran, Lancet 2012) and OPN and IL-6 as prog, independent of established criteria (Zurita, ESMO 2012). Here, we evaluate cytokines and angiogenic factors (CAFs) relative to clinical prog variables (varbs) for OS. **Methods:** Seven baseline plasma CAFs (IL-6, IL-8, OPN, VEGF, HGF, TIMP1, E-Selectin) were measured (Searchlight, Aushon), and 10 prognosis varbs (ECOG PS, time from diagnosis to treatment [TDT], hemoglobin, calcium, neutrophils, platelets, LDH, sum of the longest diameters [SLD], bone metastasis (meta), and number of meta sites) were correlated with OS ($n$=343: n=225 paz/n=118 placebo [plb]; $n$=310 including TDT: n=202 paz/n=108 plb) using uni- and multivariable Cox (multiCox) proportional hazard and stepwise models (stm) based on the randomization assignment. **Results:** Median OS for all pts was 22.7 months (mo) (95% CI 20.2-25.5), 22.9 mo (95% CI 20.2-25.4) for those treated with paz and 20.9 mo (95% CI 15.6-28.8) for plb. Neutrophilia (NEUT), anemia, high LDH, PS 1 ($v$0) and SLD (plus TDT instead of LDH in $n$=310) were significantly associated with poor prognosis in multiCox regression and stm that only considered clinical criteria (and treatment as a variable). When the 7 CAFs were incorporated into the stm, OPN, TIMP-1 and IL-6 were identified as independently prog [Table, $n$=343, minus IL-6 and treatment in $n$=310]. **Conclusions:** Circulating OPN, TIMP-1 and IL-6 are prog for OS independent of established clinical criteria in mRCC pts with good PS. These CAFs should be incorporated into prog and pred models for validation in mRCC trials.

| Variable ($n$=343) | HR | P value |
|---|---|---|
| **TRT (paz v plb)** | 0.7 | 0.032 |
| **IL6** | 1.6 | 0.016 |
| **TIMP1** | 1.5 | 0.007 |
| **OPN** | 1.5 | 0.007 |
| **SLD** | 1.2 | 0.001 |
| **NEUT** | 1.7 | 0.001 |
| **LDH** | 1.7 | 0.014 |
| **PS** | 1.4 | 0.032 |

Abbreviations: HR, hazard ratio.

**4583 General Poster Session (Board #151), Mon, 1:15 PM-5:00 PM**

**The effect of *SETD2* mutation (mts) on histone 3 lysine 36 tri-methylation (H3K36me3) and correlation with clinical outcome in patients (pts) with metastatic clear cell renal cell carcinoma (ccRCC) enrolled in COMPARZ.** *Presenting Author: Thai Huu Ho, Mayo Clinic Arizona, Scottsdale, AZ*

**Background:** Systematic sequencing studies of ccRCC identified loss of function mts in histone modifying enzymes such as *SETD2 (15%)*. *A*ll *SETD2* mts identified in pts disrupt expression of the SET domain, a conserved motif responsible for H3K36 tri-methyltransferase activity. In this study, we hypothesized that *SETD2*mts are associated with decreased H3K36me3 in ccRCC and we also investigate this association in relation with clinical outcome. **Methods:** Tumor samples were collected from consented subjects enrolled in a phase III trial of pazopanib vs. sunitinib (Motzer, NEJM 2013). Immunohistochemistry (IHC) for H3K36me3 was optimized with corresponding isotype controls. The Aperio platform was used to scan the slides for analysis of nuclear H3K36me3 levels using the CellMap image algorithm by Flagship Biosciences on 46 subjects with known *SETD2* gene status by next generation sequencing. H3K36me3 signal was scored according to an H-score. **Results:** IHC shows a decrease in H3K36me3 staining in the tumor cells of SETD2 mutant (insertion/Deletion/Stop) while adjacent matched uninvolved kidney tissue retains H3K36me3 expression. Some SETD2 wild-type tumors also had decreased H3K36me3 staining, while the majority of these tumors displayed relatively robust, uniform staining for H3K36me3. Using an H-score cutoff of H≤29 (n=24) or >29 (n=22), we also observed significant differences in overall survival between patients with higher and lower H3K36me3 staining regardless of SETD2 mutation status (P=0.0454, Log-Rank). **Conclusions:** Loss of function *SETD2* mts are associated with decreased H3K36me3 IHC. Loss of H3K36me3 staining in SETD2 wild-type RCC may reflect tumor heterogeneity or other post-translational mechanisms that promote dysregulation of SETD2 methyltransferase activity. Future studies will also examine the correlation of H3K36me3 with treatment response to contemporary therapy.

**4584 General Poster Session (Board #152), Mon, 1:15 PM-5:00 PM**

**Impact of angiotensin system inhibitors (ASI) on outcome in sunitinib (SU)-treated patients for metastatic renal cell carcinoma (mRCC): Gustave Roussy experience.** *Presenting Author: Lisa Derosa, Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France*

**Background:** ASIs are widely used for hypertension (HTN) and proteinuria. Limited data for their anti-angiogenic effect exists in combinations with targeted therapy. We aimed to evaluate the role of ASI on outcome in mRCC. **Methods:** Patients (pts) treated with SU as first line at Gustave Roussy from 04/04 to 11/13 with available data about the use of ASI before, or during treatment (defined as during first month) were included. Overall survival (OS) and progression free-survival (PFS) were compared with log-rank test and hazard ratios (HR) and 95% confidence interval (CI) through a multivariable Cox model adjusted on age, gender, histology, IMDC risk groups and history of HTN. **Results:** N=213 pts with a 44 month median follow-up received SU as first line. Median age was 59, most pts were male (78%), with clear-cell histology (86%), intermediate IMDC risk group (61%). N=102 (48%) pts were ASI-users either before SU (n=61, 29%) or during SU (n= 41, 19%). ASI use was associated with improved OS and PFS when compared to ASI nonuser pts. Among ASI users, OS and PFS were not significantly different. **Conclusions:** Use of ASI in mRCC pts receiving SU significantly improves outcome (PFS and OS). There is no difference between pts who receive ASI before starting SU or those who received ASI within one month of SU.

**ASI users compared to nonusers.**

| | OS median (months) | PFS median (months) |
|---|---|---|
| **ASI nonusers (n=109)** | 18 [12, 23] | 7 [5, 8] |
| **ASI users (n=102)** | 44 [30, 55] | 15 [12, 17] |
| **Log rank test** | p<0.0001 | p<0.0001 |
| **HR user / non user [95%CI]** | 0.32 [0.21, 0.49] | 0.45 [0.32, 0.63] |
| **ASI users (n=102)** | | |
| **ASI users during SU only (n=41)** | 51 [38, 92] | 15 [10, 20] |
| **ASI users before SU (n=61)** | 37 [27,55] | 15 [11, 17] |
| **Log rank test** | p=0.30 | p=0.41 |
| **HR user / non user [95%CI]** | 0.91 [0.39, 2.11] | 1.12 [0.62, 2.02] |

**4585 General Poster Session (Board #153), Mon, 1:15 PM-5:00 PM**

**PD-L1 expression in primary clear cell renal cell carcinomas (ccRCCs) and their metastases.** *Presenting Author: Marcella Callea, Brigham and Women's Hospital, Boston, MA*

**Background:** Clinical trials evaluating anti-PD-1 and anti-PD-L1 antibodies (Abs) in ccRCC have shown tumor responses in a subset of patients. Tumor PD-L1 expression increases the likelihood of benefit with anti-PD-1 Ab, but fails to identify all responders. One explanation for these results is that predictive biomarkers are usually evaluated in the primary tumors, which may not accurately reflect expression in the metastases (mets) that are targeted by therapy. In this study, we compared PD-L1 expression in a series of ccRCCs and their mets. **Methods:** Paraffin tissue blocks from 33 primary ccRCCs and corresponding lymph node or distant mets (excisional biopsies) were retrieved. Multiple areas of the primary tumors (e.g. areas of predominant and highest Fuhrman nuclear grade (FNG)) were selected for analysis. Slides were immunostained with a validated mouse monoclonal anti-PD-L1 Ab (405.9A11). Membranous expression in tumor cells was quantified using an H-score. A case was considered positive when any tumor cell positivity was detected. For expression in intratumoral immune cells, a combined score based on the extent of inflammatory infiltrate and percentage of positive cells was used. **Results:** PD-L1 expression in tumor cells of primary tumors and their mets is summarized in Table 1. The pattern of PD-L1 staining was highly heterogeneous in the primary tumors and was restricted to areas of highest FNG. The staining was more homogeneous in the mets. In 12/33 (36%) cases with positive primary tumors and/or mets, PD-L1 expression in tumor cells tended to be higher in the mets (median average H-score=4.5) compared to the primary tumors (median average H-score=1.3) (p=0.13). No significant difference was found in PD-L1 expression in immune cells between primary tumors and their mets (p>0.5). **Conclusions:** Discordant expression of PD-L1 between the primary tumor and their mets was detected in 5/33 (15%) of cases suggesting that accurate assessment of predictive biomarkers for PD-1 blockade in ccRCC may require analysis of multiple areas of primary tumors and/or mets. Analysis of a larger patient cohort is ongoing to confirm these findings.

| | | Metastases | | Total |
|---|---|---|---|---|
| | | PD-L1- | PD-L1+ | |
| **Primary tumors** | PD-L1- | 21 | 2 | 23 |
| | PD-L1+ | 3 | 7 | 10 |
| **Total** | | 24 | 9 | 33 |

**4586 General Poster Session (Board #154), Mon, 1:15 PM-5:00 PM**

**Molecular characterization of renal medullary carcinoma (RMC).** *Presenting Author: Jianjun Gao, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** RMC is a rare and highly aggressive malignancy that affects primarily young individuals with sickle cell trait. RMC usually presents at advanced stages and is universally fatal with a median survival of <12 months despite chemotherapy and targeted therapy. Molecular insights of RMC are needed for identification of potential therapeutic targets. **Methods:** We performed whole-exome sequencing using the Illumina platform on RMC tumor tissues from 11 patients for somatic mutational analysis. We also performed Affymetrix microarray and Ingenuity pathway analyses to identify genes that are differentially expressed. In addition, reverse phase protein arrays (RPPA) were carried out to identify differentially expressed proteins. Molecular changes were compared and correlated at DNA, RNA, and protein levels to identify genes and signaling pathways that may play important roles in RMC pathogenesis and serve as potential therapeutic targets in RMC. **Results:** Exome sequencing identified 981 genes that were mutated in 1 tumor; 87 genes mutated in 2 tumors; 10 genes mutated in 3 tumors; 1 gene mutated in 4 tumors; 4 genes mutated in 5 tumors; and 1 gene mutated in 6 tumors. Microarray analysis indicated mRNA expression levels of a total of 2166 genes were changed ≥ 2 fold with p-value <0.05 in RMC tumors. RPPA data showed that protein expression levels of a total of 60 genes were changed ≥1.4 fold with p<0.05. Further correlation analyses demonstrated genes involved in signaling pathways such as PI3 kinase (PIK3C2G), cell cycle control (CDC25D and CDC73), and histone synthesis (HIST2H3D) are significantly changed at DNA, mRNA, and protein levels. **Conclusions:** Our data suggest that genes in at least 3 signaling pathways may be important for RMC pathogenesis and may have therapeutic relevance for future targeting.

**4587 General Poster Session (Board #155), Mon, 1:15 PM-5:00 PM**

**Impact of perioperative chemotherapy on survival in patients with advanced primary urethral cancer: Results of the international collaboration on primary urethral carcinoma.** *Presenting Author: Georgios Gakis, Department of Urology, University of Tuebingen, Tuebingen, Germany*

**Background:** The present analysis aims to investigate the prognostic benefit of perioperative chemotherapy in patients undergoing surgery for primary urethral carcinoma. **Methods:** A total of 124 patients (86 men, 38 women) who were diagnosed with primary urethral carcinoma in ten tertiary international academic centers between 1993 and 2012, underwent surgery for primary treatment. Platinum-based neoadjuvant and adjuvant chemotherapy was administered in 18 (15%) and 21 (17%) patients, respectively. Kaplan-Meier analysis with log-rank testing was used to investigate the impact of perioperative chemotherapy on progression-free (PFS) and overall survival (OS). The median follow-up was 20 months (mean: 32 months; IQR: 4-48). **Results:** Median age at surgery was 67 years (IQR: 53-74). Receipt of neoadjuvant chemotherapy was associated with clinically node-positive tumor stage (cN+; p=0.009). Conversely, delivery of adjuvant chemotherapy was associated with locally advanced primary tumors (≥cT3; p=0.003). No further significant associations were found between perioperative chemotherapy and age, gender, tumor location (proximal vs. distal), underlying histology, tumor grade and use of palliative therapy. The 3-year PFS/3-year OS for patients with cN+-stage disease who underwent neoadjuvant chemotherapy was 40%/100%, compared to 0%/29% for no neoadjuvant chemotherapy (p=0.043 and p=0.034, respectively). By contrast, the 3-year PFS/3-year OS for patients with ≥cT3-stage disease who received adjuvant chemotherapy was 23%/46%, versus 20%/53% for no adjuvant chemotherapy (p=0.44 and p=0.20, respectively). The 3-year OS for patients with ≥cT3 and/or cN+ stage disease who received neoadjuvant chemotherapy was 100%, compared to 20% for adjuvant chemotherapy (p=0.031). **Conclusions:** In this series, patients who received neoadjuvant platinum-based chemotherapy for locally advanced primary urethral carcinoma exhibited improved survival compared to those who underwent immediate surgery and adjuvant chemotherapy.

**4588 General Poster Session (Board #156), Mon, 1:15 PM-5:00 PM**

**Phase II study of dovitinib in first line metastatic or (non resectable primary) adrenocortical carcinoma (ACC): SOGUG study 2011-03.** *Presenting Author: Jesús García-Donas, Centro Integral Oncológico Clara Campal, Madrid, Spain*

**Background:** Dovitinib is a novel targeted therapy that inhibits the fibroblast growth factor receptor (FGFR). Preclinical studies have pointed to a major role of this pathway in adrenocortical carcinoma (ACC) thus we aimed to test its clinical activity in this tumor. **Methods:** A phase II proof of concept trial was designed. Based on a two-stage Gehan model 15 patients needed to be included to show a treatment efficacy of at least 15% (probability of Type I error $\alpha = 0.05$, power $[1 - \beta] = 0.8$). Main inclusion criteria was advanced non-resectable ACC, histologically confirmed, with no prior therapy other than mitotane. Primary endpoint was response rate (RR) by RECIST 1.1 centrally assessed. Dovitinib was administered at 500mg daily dose 5 days on 2 days off for 6 months. Continuation of therapy was permitted at physician criteria. A translational substudy looking for biomarkers of efficacy was also scheduled. **Results:** From January 2012 to August 2012, 17 patients (5 male and 12 female) were included. Median age was 53 years (range 26–72); ECOG was 0–1 in 15 patients, 2 in one patient and N/A in one patient. Grade 3–4 adverse events deemed as related to the drug were: rash (6%), asthenia (12%), diarrhea (6%), GGT elevation (18%), nausea (6%),hypertriglyceridemia (6%), hypertension (6%), hyperkalemia (6%). No toxic death was reported. After a median follow-up of 5.2 months (range 2.27–21) one partial response has been observed. Median PFS was 1.8 months (95%CI [1.35–2.25]), however clinical benefit has been achieved in 30% of patients with long lasting stable disease (>6 months) in 23%. One patient remains on dovitinib 21 months after initiating therapy. We sequenced 409 tumor suppressor genes and oncogenes frequently mutated in cancer (Ion AmpliSeq Comprehensive Cancer Panel) in 9 FFPE tumor samples. Putative variants are currently being validated by Sanger sequencing and will presented at the meeting. **Conclusions:** Though primary endpoint was not reached, dovitinib showed activity in a subpopulation of ACC patients. The ongoing molecular identification of such subpopulation will be key in order to prompt further investigation. Clinical trial information: NCT01514526.

**TPS4589 General Poster Session (Board #157A), Mon, 1:15 PM-5:00 PM**

**Pazopanib versus paclitaxel in relapsed urothelial tumors: A randomized phase II study investigating pazopanib versus weekly paclitaxel in relapsed or progressive transitional cell carcinoma of the urothelium (PLUTO).** *Presenting Author: Robert J. Jones, University of Glasgow, Glasgow, United Kingdom*

**Background:** Urothelial cancer (UC) is a chemosensitive disease. There is a clear role for first line, platinum-based chemotherapy in advanced disease, response rates being around 40-50%. However, responses are usually brief and the role of subsequent therapy remains unclear. There are currently no approved second line therapies in North America, although vinflunine is approved in some countries. Nevertheless, a variety of second line therapies are widely used on the basis of modest response rates observed in small, non-randomized phase II trials. In the UK, the most commonly used second line therapy is paclitaxel. Two non-randomized phase II trials with the vascular endothelial growth factor (VEGF) receptor targeted tyrosine kinase inhibitor pazopanib suggest clinical activity in this setting. **Methods:** 140 patients with progressive advanced UC who have failed a single prior line of chemotherapy which must have contained platinum will be randomized to receive either pazopanib 800mg once daily until progression or paclitaxel 80mg/m$^2$ days 1, 8, 15 of a 28 day cycle for up to 24 weeks. The primary endpoint of the study is overall survival. Secondary endpoints include progression free survival, response rate, safety and tolerability. Archival tissue, blood and urine samples will be collected prospectively from patients, in order to explore molecular and genomic predictors of benefit for both drugs. The trial is designed to detect a 50% improvement in overall survival (paclitaxel 8 months; pazopanib 12 months) with power 90% and 1-sided significance level of 20%. If positive, a randomized phase III trial will be required to confirm efficacy of pazopanib in this population. On 1 Feb 2014, 70 patients had been recruited. Clinical trial information: 73030316.

**TPS4590 General Poster Session (Board #157B), Mon, 1:15 PM-5:00 PM**

**A randomized, prospective, phase II study to determine the efficacy of BCG given in combination with panvac versus BCG alone in adults with high grade non-muscle invasive bladder cancer who failed at least one induction course of BCG.** *Presenting Author: Sam Joseph Brancato, National Institutes of Health, Bethesda, MD*

**Background:** High grade non-muscle invasive bladder cancer (NMIBC) has a 70% recurrence rate and rate of 15-30% progression. The standard of care is an induction course of bacillus Calmette-Guerin (BCG). A second induction course can be used in patients who fail the initial course, however only 35% of patients will experience a 12 month disease free survival. For those patients failing a second induction course, radical cystectomy is the gold standard treatment, although the morbidity rate is high. Therefore there is an unmet need for localized treatment for patients who fail an initial induction course of BCG. Recently, a pox viral vector-based vaccine, PANVAC, has been shown to induce a CD4 and CD8 antigen-specific immune response against the tumor-associated antigens, carcinoembryonic antigen (CEA) and mucin-1 (MUC-1). This vaccine also contains transgenes for three human T cell co-stimulatory molecules that can potentially augment an immune response. We hypothesize that the combined administration of BCG and PANVAC may augment the BCG-induced cytotoxic T lymphocyte response against bladder cancer cells expressing MUC-1 and/or CEA and potentially reverse BCG failure. MUC-1 is overexpressed in 93% and CEA is over-expressed in 76% of high grade bladder tumors and therefore PANVAC may enhance BCG response. **Methods:** This is a randomized, prospective Phase II study in subjects with NMIBC who have failed at least one induction course of intravesical BCG. Patients will be randomized to one of the following arms: BCG + PANVAC or BCG alone. All subjects will receive intravesical BCG as per usual standard of care once weekly for a total of 6 weeks. The combination arm will receive the pox viral vaccines (rV-PANVAC and rFPANVAC) that contain the transgenes for CEA and MUC-1 as well as 3 human T-cell costimulatory molecules. We will test the hypothesis that subjects in the BCG + PANVAC arm have a better disease-free survival at 12 months than subjects in the BCG alone arm. Secondary endpoints include disease progression, treatment-related toxicities, and immunologic correlates. Clinical trial information: NCT02015104.

**TPS4591 General Poster Session (Board #158A), Mon, 1:15 PM-5:00 PM**

**A randomized trial comparing two different retention periods of intravesical pirarubicin instillation for intermediate risk non-muscule-invasive bladder cancer after transurethral resection.** *Presenting Author: Yoshiaki Kawano, Department of Urology, Kumamoto University Faculty of Life Sciences, Kumamoto, Japan*

**Background:** Anthracyclines are recommended reagents for one immediate intravesical instillation after transurethral resection (TUR) and additional adjuvant instillation in intermediate risk non-muscule invasive bladder cancer (NMIBC) to reduce the risk of recurrence. Pirarubicin (THP), an anthracycline analogue, is widely used reagent for intravesical instillation chemotherapy. Several studies have showed that THP can rapidly penetrate tumor tissue after intravesical instillation. Therefore long instillation time (e.g. 120 min) may not be required for its prophylactic effect against recurrence since it may reduce the risk of adverse events such as cystitis and hematuria without compromising its efficacy. However, there is no high level evidence regarding optimized intravesical THP instillation time in terms of both toxicity and efficacy. **Methods:** This randomized, prospective, open-label trial intends to enroll 160 pts with primary non-muscle invasive bladder cancer (NMIBC) with intermediate risk based on EORTC criteria. All pts receive initial THP instillation within 24 hr after TUR-Bt followed by weekly repetitive THP instillation for a total of 9 treatments. Pts are randomized into two groups with different intravesical THP retention times, (a) 30 min versus (b) 120 min. Eligibility criteria include pts with pathological diagnosis of urotherial carcinoma, with complete tumor resection by TUR-Bt, and with ECOG-PS 0-2. Exclusion criteria include pts who had previously treated with therapeutic BCG intravesical instillation or prophylactic maintenance intravesical instillation of anti-cancer drug, with coexisting cancer, and with history or coexistence of upper urinary tract urothelial cancer. Follow-up period is 3 years. Primary endpoint is change from baseline in quality of life (assessed by SF36, OABSS and I-PSS), which will be evaluated every 3 months until 2 years after TUR, then half-yearly for another year. Secondary endpoint is recurrence-free survival rates at 1, 2 and 3 years, and safety. Currently 82 pts have enrolled. Clinical trial information: UMIN000006861.

**TPS4592 General Poster Session (Board #158B), Mon, 1:15 PM-5:00 PM**

**Development of a phase 2 study of the aurora kinase-A inhibitor alisertib (MLN8237) in pretreated patients (pts) with urothelial cancer (UC).** *Presenting Author: Andrea Necchi, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

**Background:** Progress in developing new effective therapies in advanced and relapsing urothelial cancer has been stagnant in the last few decades and a paradigm shift is desperately needed. Aurora kinase-A overexpression has been previously described in bladder cancer and spindle checkpoint dysregulation is a common feature of human UC. Alisertib (Millennium Inc.) is an orally available, selective small molecule inhibitor of Aurora A kinase. Single agent and combination treatment of MLN8237 with either paclitaxel (TXL) or gemcitabine synergistically reduced UC cell viability compared with either drug alone. Hence, sequential application of MLN8237 and TXL warrants clinical investigation. Phase 1 trials of both single agent and the combination with TXL defined the recommended doses for phase 2 trials. **Methods:** A multistep approach will be adopted for this Phase 2 trial. A single-group run-in phase will be conducted first with Alisertib 50 mg orally BID for 7 days, followed by 14d rest until disease progression. In case of activity, a confirmatory randomized (1:1) trial of weekly TXL plus either Alisertib or Placebo will follow, incorporating efficacy and futility boundaries for early stopping. In a single-blind design, TXL will be given on days 1,8,15 q4wks at the dose of 60 mg/m2 with alisertib and 80 mg/m2 with placebo. Alisertib dose will be 40 mg BID days 1-3, 8-10 and 15-17, q4wks. In the single-arm phase, primary endpoint (EP) will be RECIST 1.1 response-rate. 20 pts will be accrued, $\geq$3 responses will be required (10% type I and 20% type II error costraints). An accrual of 110 pts is foreseen in the randomized phase. Primary EP: progression-free survival (PFS), assuming an improvement in PFS from a median of 2.5 months ($H_0$) to a median of 4.5 months ($H_1$) (44% hazard rate reduction, 10% drop out rate). Eligibility will include diagnosis of metastatic UC and failure of 1-2 CT regimens (single-arm) or 1 prior CT only (randomized phase). A relapse within 6 months of a peri-operative CT will be counted as 1 line. Computed tomography and PET will be done every 2 cycles (2 months). Additional pharmacodynamic and translational analyses are planned on pre- post- blood and tissue samples. Clinical trial information: 2014-000557-36.

**TPS4593^ General Poster Session (Board #159A), Mon, 1:15 PM-5:00 PM**

**The Borealis-2 clinical trial: A randomized phase 2 study of OGX-427 (apatorsen) plus docetaxel versus docetaxel alone in relapsed/refractory metastatic urothelial cancer.** *Presenting Author: Toni K. Choueiri, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Heat shock protein 27 (Hsp27) is over-expressed in many cancers including bladder, lung, prostate, and breast. Increased Hsp27 has been associated with inhibition of chemotherapy-induced apoptosis, increased tumor cytoprotection, and development of treatment resistance. OGX-427 (Apatorsen) is an antisense oligonucleotide designed to bind Hsp27 mRNA, inhibiting production of the Hsp27 protein. Inhibition of Hsp27 has been shown to increase apoptosis, inhibit tumor growth, and sensitize tumor cells to chemotherapy in a variety of malignancies, including urothelial cancer. Results of preclinical and phase 1 studies suggest that addition of apatorsen to chemotherapy is well tolerated and may improve treatment efficacy. Borealis-2 is a randomized, multicenter, phase 2 study of apatorsen in combination with docetaxel (DOC) vs. DOC alone in locally advanced/metastatic bladder cancer patients who received at least one line of prior platinum-based therapy. The primary objective is to evaluate overall survival. Secondary objectives include comparisons of safety and tolerability, disease response, and serum levels of Hsp27 and other pathway-related proteins. Associations between clinical outcomes, levels of Hsp27 and other proteins, and circulating tumor cells will be evaluated. **Methods:** Patients (N=200) are randomized in a 1:1 ratio following stratification (time from prior systemic chemotherapy; Bellmunt criteria). Up to 2 prior systemic therapies are allowed. Treatment-arm patients receive three loading doses of apatorsen (600 mg) followed by up to ten 21-day treatment cycles (apatorsen 600 mg on Days 1, 8, and 15 and DOC 75 mg/M$^2$ IV on Day 1). Control-arm patients receive DOC 75 mg/M$^2$ IV on Day 1 of each cycle. Treatment may continue until disease progression, unacceptable toxicity, completion of ten cycles, or patient withdrawal. Patients who discontinue DOC due to toxicity after ≥2 cycles and do not have disease progression may receive maintenance therapy with apatorsen. One interim futility analysis will be performed. The trial will not be stopped early based on efficacy. Clinical trial information: NCT01780545.

**TPS4594 General Poster Session (Board #159B), Mon, 1:15 PM-5:00 PM**

**Phase II study of fosaprepitant plus 5HT3 receptor antagonists plus dexamethasone in patients with germ cell tumors undergoing 5-day cisplatin-based chemotherapy: Hoosier Oncology Group QL12-153.** *Presenting Author: Costantine Albany, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN*

**Background:** Germ cell tumors (GCT) account for 1% of malignancies of American males. Cisplatin combination chemotherapy is the cornerstone for curative therapy in metastatic GCT. Cisplatin is administered for 5 consecutive days, and it is appropriately categorized as highly emetogenic chemotherapy (HEC). Clinical and basic research over the past 25 years has led to steady improvements in the control of chemotherapy-induced nausea and vomiting (CINV). All of the guidelines (ASCO, MASCC and NCCN) unanimously suggest a combination of a 5-HT3RA, dexamethasone, and aprepitant for the prevention of acute and delayed CINV with single day HEC. However, there is paucity of studies and no clear guidelines evaluating multiday cisplatin-induced nausea and vomiting compared to single day cisplatin. We have published a randomized double-blind phase III trial testing whether the addition of aprepitant to standard 5HT3RA plus dexamethasone would provide additional protection in this patient population. Aprepitant was given for 5 consecutive days, starting on day 3 of chemotherapy; aprepitant 125mg PO (or matched placebo) was given on day 3, then 80mg PO on days 4-7. The complete response rate (CR) was 42% in the aprepitant arm vs. 13% in the placebo arm ($p<0.0001$), 80% of patients experienced no emetic episodes on days 1-5 on the aprepitant arm vs. just 52% on the placebo arm ($p<0.0001$).(*J Clin Oncol. 2012 Nov 10;30(32):3998-4003. doi: 10.1200/JCO.2011.39.5558.)* **Methods:** The current study is a single arm phase II study to evaluate the efficacy of combining fosaprepitant with a 5HT3RA + dexamethasone. This is the first clinical trial evaluating fosaprepitant in patients receiving multiday cisplatin. The primary objective is the Complete Response (CR) rate (no emetic episodes or use of rescue medications). Secondary objectives are the incidence of vomiting or retching via patient log and the patient's self-reported assessment of nausea Days 1-8 using a 0-100mm visual analog scale (VAS). Clinical trial information: NCT01736917.

**TPS4595^ General Poster Session (Board #160A), Mon, 1:15 PM-5:00 PM**

**ATLAS study: A randomized double-blind phase 3 study of adjuvant axitinib versus placebo in subjects at high risk of recurrent renal cell carcinoma (RCC).** *Presenting Author: Kwon Tae Gyun, Kyungpook National University Medical Center, Daegu, South Korea*

**Background:** Kidney cancer is diagnosed in approximately 270,000 people each year worldwide, and results in 120,000 deaths, with RCC as the most common form. Up to 30% of patients treated by nephrectomy for localized disease will relapse. 5-year survival rates for TNM stage II, III and IV are 65-80%, 40-60% and 0-20%, respectively. RCC is a high VEGF- and PDGF-expressing tumor. Axitinib, an oral, potent and selective inhibitor of vascular endothelial growth factor (VEGF) receptors 1, 2, and 3, is approved for the treatment of advanced RCC after failure of one prior systemic therapy. Preclinical data indicate higher potency and selectivity against the VEGFR family for axitinib compared to some other antiangiogenic agents. This phase 3 study tests the hypothesis that prevention of micro-metastases and tumor growth by anti-VEGF treatment with axitinib can prolong disease free interval after nephrectomy for patients with high risk of recurrent RCC. **Methods:** 692 patients, ECOG PS 0-1, with histologically confirmed preponderant clear cell RCC; treatment naïve and no residual or metastatic disease after nephrectomy will be randomized 1:1 to axitinib or placebo, 5mg PO BID for up to 3 years in a global, randomized, double blind placebo controlled trial. Patient will be stratified according their country and their stage of disease (any Fuhrman grade allowed): 1) pT2, pN0 or pNx, M0; 2) pT3, pN0 or pNx, M0; 3) pT4, pN0 or pNx, M0; or 4) any pT, pN1, M0; and ECOG PS 0-1. Primary objective is disease free survival as assessed by independent review committee. Key secondary objectives are overall survival as well as safety and tolerability of treatment. Efficacy analysis will be performed on the intention-to-treat population. This is a global, multi-center study with sites in Asia, US and Europe. As of January 2014, 167 subjects have been randomized and last patient enrollment is expected at the end of 2014. Clinical trial information: NCT01599754.

**TPS4596 General Poster Session (Board #160B), Mon, 1:15 PM-5:00 PM**

**Phase Ib study of axitinib in combination with crizotinib in patients with advanced solid tumors.** *Presenting Author: Dale Randall Shepard, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH*

**Background:** Antiangiogenic therapy is proven to be effective in the treatment of multiple advanced solid tumors, including renal cell carcinoma (RCC), colorectal cancer, and non-small cell lung cancer. However, the majority of patients treated with vascular endothelial growth factor (VEGF)-pathway inhibitors ultimately develop resistance to such treatments. Overexpression of mesenchymal-epithelial transition factor (c-MET), with or without upregulation of its ligand hepatocyte growth factor, has been implicated in tumor resistance to VEGF-pathway inhibitors. Results from preclinical models suggest that combining c-MET and VEGF receptor (VEGFR) inhibition provides added benefit compared with VEGF-pathway inhibition alone (Ciamporcero et al, AACR 2013:Abstr 1618). This study is evaluating axitinib (highly specific tyrosine kinase inhibitor of VEGFRs 1–3) in combination with crizotinib (c-MET/anaplastic lymphoma kinase [ALK] inhibitor). **Methods:** This ongoing, multicenter, phase Ib study (NCT01999972) employs a dose escalation phase exploring oral administration of axitinib (starting dose 3 mg twice daily [BID]; range 2–5 mg BID) plus crizotinib (starting dose 200 mg BID; range 250 mg once daily–250 mg BID) on a continuous schedule to ~25 patients with advanced solid tumors resistant to standard therapy or for which no standard therapy is available. Dose escalation/de-escalation decisions are based on the modified toxicity probability interval (mTPI) design. Following determination of the maximum tolerated dose (MTD) of the combination treatment, patients with advanced clear cell RCC will be enrolled in two cohorts of ~20 patients each (cohort 1: no prior systemic therapy; cohort 2: 1–2 prior systemic therapies) in a dose expansion phase. The primary study objective is to assess the tolerability of the combination treatment in order to determine the MTD and select the recommended phase II dose. Other objectives include characterization of pharmacokinetics and antitumor activity. Correlative biomarker studies on blood and tumor tissue (archival tissue and de novo biopsies) will be performed and will include evaluation of c-MET expression. Enrollment in the dose escalation phase began in Jan 2014. Clinical trial information: NCT01999972.

**TPS4597 General Poster Session (Board #161A), Mon, 1:15 PM-5:00 PM**

**A-PREDICT: A phase II study of axitinib in patients with metastatic renal cell cancer unsuitable for nephrectomy (CRUKE/11/061).** *Presenting Author: Rosalie A. Fisher, The Royal Marsden NHS Foundation Trust, London, United Kingdom*

**Background:** Patients presenting with metastatic renal cell carcinoma (mRCC) who cannot have palliative nephrectomy constitute a poor prognosis group. The vascular endothelial growth factor receptor (VEGFR) inhibitor axitinib has demonstrated a high response rate in mRCC, but its efficacy has not been evaluated in this patient group. Sustained disease control and predicting sensitivity to VEGFR inhibitors may be difficult to achieve in mRCC because of intra-tumour heterogeneity (ITH) and branched, subclonal tumour evolution. **Methods:** A-PREDICT is a single group phase II trial of axitinib in patients with newly diagnosed mRCC not considered suitable for immediate nephrectomy. The primary objective is to assess clinical activity of axitinib in this patient group. The study includes longitudinal sampling of tumour tissue during therapy to investigate the extent of ITH and track evolution of somatic mutational and copy number events. Key inclusion criteria are: clear cell histology and unsuitability for nephrectomy due to locally advanced primary tumour, high burden of metastatic disease or lack of fitness for surgery. Five core biopsies of the primary tumour are taken before the patient starts axitinib (starting dose 5 mg twice daily). After 8 weeks' treatment, multiple biopsies of the kidney tumour are repeated. Axitinib is continued for as long as the patient benefits. At treatment cessation, the progressing site is biopsied. Nephrectomy is offered to any patient who becomes suitable during the course of the trial and resected specimens are sampled. The primary endpoint is the proportion of participants free from disease progression 6 months from treatment start. The proportion of patients who become operable as a consequence of axitinib will be measured. To end 2013, 17 patients from 7 UK sites were recruited. The target accrual of 99 patients has 90% power to discount an 'ineffective' rate of freedom from progression at 6 months of 25% in favour of a rate of at least 40%. Serial tumour & blood samples will be evaluated by a functional genomics approach. Dynamic changes in expression of putative biomarkers during therapy will be compared between patients who respond to axitinib and those who are resistant. Clinical trial information: ISRCTN72679844.

**TPS4598 General Poster Session (Board #161B), Mon, 1:15 PM-5:00 PM**

**Dose adjustment of axitinib based on AUC monitoring in sunitinib-refractory advanced renal cell carcinoma.** *Presenting Author: Yuji Miura, Department of Medical Oncology, Toranomon Hospital, Tokyo, Japan*

**Background:** Axitinib is a standard second-line treatment after sunitinib in patients (pts) with metastatic or advanced renal cell carcinoma (RCC). The previous results of pharmacokinetic (PK) and pharmacodynamic (PD) analysis of axitinib showed that higher exposure and diastolic blood pressure (dBP) were independently associated with longer progression free survival (PFS) and overall survival in metastatic RCC pts (Rini et al., J Clin Pharmacol, 2013). These findings support that axitinib dose titration to increase plasma exposure in pts who tolerate axitinib, and also demonstrate dBP as a potential marker of efficacy. In clinical practice, axitinib dose titration based on dBP is recommended; however, it has limitations because underlying hypertension and anti-hypertensive agents usually affect daily dBP. Therefore, we hypothesize that the dose adjustment of axitinib based on its exposure is more adequate than that based on dBP. **Methods:** A prospective single arm trial is conducted at 6 institutions in Japan. The starting dose of axitinib is 5mg BID and blood samples are taken at 2h, 4h, 8h, and 12h after the first administration to assay axitinib levels and calculate the area under concentration-time curve from 0 to 12 hours ($AUC_{0\text{-}12}$) on day 1. We target $AUC_{0\text{-}12}$ value at the steady state over 150 ng*hr/mL, and suggest a sufficient dose to reach the 150 ng*hr/mL for each patient. After day 15, dose adjustment of axitinib to keep over the target value is performed according to adverse drug reaction for each patient. The primary endpoint is 6-month PFS rate based on axitinib AUC monitoring, and secondary endpoints include toxicity and objective response rate. The target $AUC_{0\text{-}12}$ value in sunitinib-refractory pts is also investigated, because the value of 150 ng*hr/mL is referred from the previous PK/PD analysis in which the first-line treatments were not only sunitinib. Major eligibility criteria include (1) metastatic or advanced clear cell RCC or RCC with clear cell component; (2) previously treated with sunitinib; and (3) disease progression on sunitinib or within 6 months of last dose of sunitinib. Prior treatment with cytokines is permitted. Twelve of planned 32 pts have been enrolled as of February 2014. Clinical trial information: UMIN000009579.

**TPS4599^ General Poster Session (Board #162A), Mon, 1:15 PM-5:00 PM**

**Enrollment insights in the synchronous mRCC population: An update from the ongoing ADAPT* phase 3 study experience.** *Presenting Author: Robert A. Figlin, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA*

**Background:** AGS-003 is an autologous immunotherapy designed to induce a T-cell response specific to a patient's tumor antigens. Sunitinib is a TKI and first-line therapy for mRCC that also reverses the immune suppression observed in these patients. In a single arm phase 2 study, AGS-003 plus sunitinib was safe and yielded a median overall survival (OS) of over 30 months in newly diagnosed mRCC patients. **Methods:** The ADAPT study is a randomized (2:1) international phase 3 study comparing standard targeted therapy plus AGS-003 to standard therapy alone. The primary objective is to compare the median OS between treatment arms. The study is enrolling adults with synchronous, metastatic, clear cell RCC who are good candidates for surgery and standard targeted therapy (initiating with, but not limited to, sunitinib), KPS $\geq$ 70%, life expectancy of at least 6 months, between 1-4 Heng risk factors, and adequate end organ function. Initial enrollment patterns were investigated in order to gain insight on the features of mRCC patients that are candidates for cytoreductive nephrectomy. More than 105 sites in North America and other select countries have been activated and >200 patients have been consented and tumor samples collected. Approximately 50% of these patients have been excluded from participation in the treatment phase of the ADAPT study after surgery with about half of these being excluded because of non-clear cell histology. Other major reasons include ineligibility for sunitinib and lack of measurable metastatic disease after nephrectomy. Clinical trial information: NCT 1582672.

**TPS4600^ General Poster Session (Board #162B), Mon, 1:15 PM-5:00 PM**

**Principal: A prospective observational study of real-world treatment patterns and treatment outcomes in patients with advanced or metastatic renal cell carcinoma (mRCC) receiving pazopanib.** *Presenting Author: Aristotelis Bamias, University of Athens Medical School, Athens, Greece*

**Background:** Pazopanib is an oral, selective, multikinase inhibitor of VEGF receptors 1/2/3, PDGF receptors $\alpha$/ß, and stem cell factor receptor (c-Kit) that is approved for first-line treatment of patients with advanced renal cell carcinoma (RCC) and for patients who received prior cytokine therapy. The COMPARZ study of pazopanib versus sunitinib as first-line treatment demonstrated noninferiority of pazopanib for progression-free survival (PFS) in the intention-to-treat population, and pazopanib statistically favored health-related quality of life (HRQoL) in 11 of the 14 domains measured (NEJM 2013;369:722-31). The PISCES patient preference study demonstrated that significantly more patients preferred pazopanib over sunitinib due to overall better HRQoL and less fatigue (JCO 2012;30 suppl 15:CRA4502). The purpose of the PRINCIPAL study is to evaluate the real-world effectiveness and safety of pazopanib in patients with advanced or mRCC. **Methods:** This is a global, multicenter, prospective, observational study (VEG115232, NCT01649778) designed to enrol up to 700 patients. Primary endpoints include PFS, overall response rate, overall survival, relative dose intensity data, HRQoL data, and safety data. Additional treatment strategies for RCC will be obtained post-progression. Key inclusion criteria include a clinical decision to initiate treatment with pazopanib (before enrolment in the study), no prior systemic therapy for advanced or mRCC, and no participation in an interventional trial. The study has enroled 339 patients to date and is currently recruiting in 15 countries, including Europe, Asia, Latin America, and the United States. This study will determine patient outcomes with pazopanib in a real-world setting in terms of efficacy, safety, and patient compliance outside the normal parameters of a controlled trial. PRINCIPAL will also provide further data in patient groups that were under-represented in the controlled clinical trials to date, such as the elderly and patients with co-morbidities. Clinical trial information: NCT01649778.

**TPS4601 General Poster Session (Board #163A), Mon, 1:15 PM-5:00 PM**

**Phase 3 randomized study of cabozantinib (XL184) versus everolimus in subjects with clear cell renal cell carcinoma (METEOR).** *Presenting Author: Toni K. Choueiri, Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA*

**Background:** Cabozantinib is an oral receptor tyrosine kinase inhibitor (TKI) with potent activity against MET and VEGFR2. Cabozantinib has demonstrated clinical activity in multiple solid tumor types, including heavily pretreated subjects with clear cell renal cell carcinoma (ccRCC) (Choueiri et al.; ASCO 2012, abstract 4504). In ccRCC, VHL tumor suppressor gene dysfunction results in impaired HIF degradation and consequent activation of MET and VEGF pathways. Moreover, MET has been implicated in adaptive resistance to VEGF-pathway targeted agents. Based on the clinical activity seen to date and the scientific rationale, there is strong interest in the evaluation of cabozantinib in ccRCC. **Methods:** This Phase 3, open-label, multicenter study evaluates the efficacy and safety of cabozantinib compared with everolimus in subjects with ccRCC (NCT01865747).The primary endpoint is progression-free survival (PFS) as evaluated by an independent radiology review committee (IRC). Secondary endpoints are overall survival (OS) and response rate. Exploratory endpoints are safety, tolerability, tumor MET status, circulating tumor cells, serum bone markers and plasma biomarkers, skeletal-related events (SRE), and health-related quality of life (HRQoL). Enrollment started in August 2013. Target recruitment is 650 subjects with ccRCC, which will provide power for both PFS and OS endpoints. Eligible subjects must have progressed after 1 or more prior VEGFR TKI therapy. Subjects are randomized 1:1 to receive either cabozantinib or everolimus. Stratification factors are the number of prior VEGFR TKI therapy and MSKCC prognostic criteria (Motzer et al.; J Clin Oncol 22:454-463, 2004). Radiographic assessments include CT/MRI and bone scintigraphy. PFS and response are determined by IRC using RECIST criteria version 1.1. SREs are defined as radiation therapy to bone, pathological fracture, spinal cord compression, and surgery to bone. The NCCN-Functional Assessment of Cancer Therapy (FACT) Kidney Symptom Index (FKSI-19) questionnaire and the EuroQol Health questionnaire (EQ-5D-5L) are being used to measure HRQoL. Subjects are being followed for survival. Clinical trial information: NCT01865747.

**TPS4602 General Poster Session (Board #163B), Mon, 1:15 PM-5:00 PM**

**Qualitative study of social and working life aspects of patients with metastatic renal cell carcinoma (mRCC) on palliative therapy.** *Presenting Author: Sandra Meyer-Moock, University Medicine Greifswald, Greifswald, Germany*

**Background:** The backbone of medical treatment of metastatic renal cell carcinoma (mRCC) consists of targeted agents. Inhibitors of VEGFR or mTOR with chronic exposure have led to the recent improvement in mRCC therapy. To assess health-related quality of life (HRQoL) of patients with mRCC, several generic and disease-specific instruments are available (eg. EQ-5D or the FKSI). Yet, little is known about the impact of mRCC on social and working life aspects as well as treatment-related decisions of patients on a palliative treatment. The aim of this study is to identify relevant dimensions as well as to develop and validate an instrument to close this gap. **Methods:** The study consists of three parts with qualitative and quantitative methods. In part I (development), we conducted 2 focus group interviews with 15 patients in patients support groups in Germany. In a pretest (part II), patients were asked to complete a draft questionnaire and to comment on it briefly during an interview. Qualitative data analysis (focus groups, field testing) consisted of content analysis methods (qualitative content analysis); software for qualitative data analysis (MAXQDA) was used. In part III (validation), the questionnaire will be validated by testing the psychometric properties in a sample of 100 patients with mRCC. Psychometric methods used will include factor analysis, assessment of distributional properties, floor and ceiling effects, percentage of missing values and subgroup analysis.

**TPS4604^ General Poster Session (Board #164B), Mon, 1:15 PM-5:00 PM**

**A phase I/II study to assess the safety and efficacy of pazopanib and MK-3475 in subjects with advanced renal cell carcinoma.** *Presenting Author: David F. McDermott, Beth Israel Deaconess Medical Center, Boston, MA*

**Background:** Pazopanib is an angiogenesis inhibitor targeting VEGFR-1, -2, and -3; PDGFR-$\alpha$ and -$\beta$; and the receptor c-Kit, and is indicated for the treatment of subjects with advanced RCC and advanced soft tissue sarcoma. MK-3475 (Merck) is a potent and highly-selective humanized mAb of the IgG4/kappa isotype designed to block directly the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Proangiogenic factors suppress various immune functions whereas antiangiogenic agents have potential to modulate the tumor microenvironment and improve immunotherapy. High expression of PD-L1 on tumor cells, and to a lesser extent of PD-L2, has been found to correlate with poor prognosis and survival in various cancer types including RCC [Thompson 2007]. An analysis of patients with RCC treated with paz demonstrated that elevated expression of PD-L1 correlates with shorter PFS [Figueroa 2013]. Additionally an objective response rate of 27% in RCC patients was reported in an early phase study with another antibody to PD-1 forall doses tested[Topalian 2012]. These findings suggest that MK-3475 may potentiate the activity of paz in patients with RCC. This Phase I/II trial has been undertaken to test the safety and tolerability of paz in combination with MK-3475 in advanced RCC, and assess the efficacy of the combination as compared with paz or MK-3475 alone. **Methods:** This is an open-label, 2-part multi-center study of paz and/or MK-3475 in treatment-naïve subjects with advanced predominantly clear cell RCC. Part 1 is Phase I dose escalation using a modified 3+3 design, with combination dosing starting at 800mg/day paz + 2mg/kgQ2W MK-3475, followed by an expansion cohort to confirm the maximum tolerated regimen and the recommended Phase 2 dose. Part 2 is a randomized 3-arm (1:1:1) Phase II study to evaluate the clinical efficacy and safety of paz + MK-3475 as compared to paz or MK-3475 alone. The primary endpoint in Part 2 is PFS by RECIST v1.1. Secondary endpoints are PFS rate at 18 months, PFS by modified RECIST criteria, overall response, stable disease $\geq$6 months, time to response, duration of response, overall survival, safety and tolerability. Part 1 has opened to enrollment. Clinical trial information: NCT02014636.

**TPS4605 General Poster Session (Board #165A), Mon, 1:15 PM-5:00 PM**

**A multicenter, open-label, single-arm, phase 2 study of the S1P inhibitor sonepcizumab (LT1009) in patients with previously treated metastatic renal cell carcinoma (mRCC).** *Presenting Author: Rupal Satish Bhatt, Beth Israel Deaconess Medical Center, Boston, MA*

**Background:** Sphingosine-1-phosphate (S1P), a key component of the sphingolipid signaling cascade, is a pleiotropic tumorigenic growth factor. S1P promotes tumor growth by stimulating cell proliferation, metastasis and cell survival while promoting tumor-associated angiogenesis by supporting the migration and survival of endothelial cells needed to form new blood vessels. Cancer cells promote conditions that favor the production of S1P through upregulation of sphingosine kinase (SphK) which appears responsible for release of S1P into the extracellular compartment. Data thus far implicate the type 1 isoform of SphK in chemoresistance and in the enhanced tumorigenicity adaptations to hypoxia, all of which correlate with poor patient outcomes in several cancer types. Sonepcizumab (LT1009) is a humanized murine-derived monoclonal antibody directed at S1P. Sonepcizumab slowed the progression of several orthotopic and subcutaneous human tumors in nude mice, including sunitinib-resistant renal tumors. Sonepcizumab was safe and well tolerated in a completed phase 1 study in 28 pts with advanced solid tumors up to 24 mg/kg weekly. Based on these data, we hypothesize that sonepcizumab may be effective in pts with advanced mRCC who failed previous therapies. **Methods:** A two-part, multi-center, open label phase 2 study is in progress to evaluate safety, tolerability, efficacy, and the pharmacokinetics (PK) and pharmacodynamics (PD) of sonepcizumab as a single agent when given at the dose of 24 mg/kg weekly in pts with previously treated mRCC. Two cohorts will be enrolled and dosed at the phase 1 maximum tolerated dose (MTD) of 24 mg/kg. If at least 12 out of the first 22 pts are progression-free at 2 months, then a second cohort will be enrolled for a total of approximately 60 pts. Key eligibility criteria include prior therapy with a VEGF/VEGFR targeted therapy (an mTOR inhibitor and/or prior immunotherapy are also permitted for a total of no more than 3 prior therapies); The primary endpoint is PFS. Secondary endpoints include response rate and serum PD biomarkers, including S1P. Clinical trial information: NCT01762033.

**TPS4606 General Poster Session (Board #165B), Mon, 1:15 PM-5:00 PM**

**Phase II efficacy trial of pazopanib in non-clear cell metastatic renal cell carcinoma (PINCR trial).** *Presenting Author: Brian Addis Costello, Mayo Clinic, Rochester, MN*

**Background:** Seven treatments for metastatic renal cell carcinoma (mRCC) have been FDA approved since December, 2005. Most of the trials evaluating these agents excluded non-clear cell histologies and therefore the efficacy of these agents remains unclear in patients with metastatic non-clear cell RCC. One such agent is pazopanib, an oral tyrosine kinase inhibitor; its effects are being studied in patients with metastatic non-clear cell RCC in this trial. The primary endpoint is to determine the overall survival rate at 12 months in patients with metastatic non-clear cell RCC. Secondary endpoints are to determine best tumor response rates after two cycles, progression free survival and toxicity profile. **Methods:** Main eligibility criteria include: (1) age ³ 18 years old; (2) histologic confirmation of non-clear cell renal cancer; (3) ECOG Performance Status (PS) 0, 1, or 2; (4) up to one prior treatment for metastatic non-clear cell renal cell carcinoma is allowed as long as the agent was not pazopanib; (5) measurable or nonmeasurable metastatic disease as defined by RECIST criteria. This is a single arm Phase II study designed to determine the efficacy of pazopanib in metastatic non-clear cell RCC. Treatment is pazopanib 800 mg by mouth daily until progression or intolerability of treatment. Dose reductions are allowed for toxicity with dose level -1 being 600 mg daily and dose level -2, 400 mg daily. Cycles are 28 days. Routine evaluation includes history, examination, adverse events assessment, serum studies, and ECG with every cycle. Research blood and urine specimens are being collected for future correlative studies. All eligible patients will be followed until death or for a minimum of two years. The sample size will be 35 evaluable patients with accrual of 4 additional patients to account for ineligibility or other reasons. Full accrual is anticipated to take 24 months. Final analysis will begin approximately 36 months after the trial begins which is the time point at which the last patient enrolled can be observed for at least 12 months. The Mayo Clinic Cancer Center Data Safety Monitoring Board is responsible for reviewing accrual and safety data. Supported in part by GSK. Clinical trial information: NCT01767636.

**TPS4607 General Poster Session (Board #166A), Mon, 1:15 PM-5:00 PM**

**Phase 1 study of ATR-101 in adrenocortical carcinoma (ACC): ATR-101-001.** *Presenting Author: Aung Naing, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** ATR-101 (Atterocor, Inc., Ann Arbor, MI, USA) is in clinical development for the treatment of adrenocortical carcinoma (ACC). ATR-101 is a selective inhibitor of ACAT1 (acyl coenzyme A:cholesterol acyltransferase). ACAT1 catalyzes cholesterol ester formation and, in the adrenals, is particularly important in creating a reservoir of substrate for steroid biosynthesis. ATR-101 is uniquely distributed to adrenal tissues and inhibition of adrenal ACAT1 by ATR-101 disrupts steroidogenesis and leads to selective apoptosis of steroid producing adrenocortical-derived cells. Similar effects have been seen in the human ACC cell line, H295R. ATR-101 has shown pre-clinical efficacy in H295R xenograft mouse models. ACC is an ultra-rare malignancy, occurring in about 2 per million population annually. ACC is frequently discovered in Stage 4 and the overall disease survival is approximately 17 months. Tumors often overproduce steroids normally produced in the adrenal cortex. Current therapies are toxic, difficult to administer, and poorly effective. **Methods:** ATR-101-001 is a phase 1, dose escalation "3+3" design study of ATR-101 in advanced ACC patients who have failed or declined standard therapy. The primary objectives are the safety and tolerability of once a day, orally administered ATR-101. Secondary objectives include the determination of MTD and pharmacokinetics, anti-tumor efficacy by RECIST, and evaluation of pharmacodynamic biomarkers, including steroid hormones and steroid intermediate production rates. Initial safety evaluation is after 28 days of therapy; subjects who appear to be deriving benefit may continue on ATR-101 indefinitely. The study is open at two centers in the United States to patients age 18 and over with advanced ACC. Patient's mitotane level must be 5 ng/ml or less; the QTcF 470 ms or less; and if present, CNS metastases must be treated and inactive. Clinical trial information: NCT01898715.

**5000 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Enzalutamide (ENZA) in combination with abiraterone acetate (AA) in bone metastatic castration resistant prostate cancer (mCRPC).** *Presenting Author: Eleni Efstathiou, Alexandra General Hospital of Athens, Oncology Department, Department of Clinical Therapeutics, Medical School, University of Athens, Athens, Greece*

**Background:** Co-targeting the androgen receptor (AR) and paracrine androgen biosynthesis in mCRPC may be more effective than either alone. This study aims to evaluate safety, pharmacokinetic (PK) drug-drug interactions (DDI), androgen signaling and steroid metabolome modulation and efficacy of ENZA with AA in mCRPC **Methods:** We enrolled patients (pts) with progressive bone mCRPC, castrate level serum testosterone (≤ 50 ng/dl) consenting to bone marrow (BM) biopsy. Pts were treated with ENZA 160 mg QD and AA 1g QD + prednisone 5 mg bid and monitored every 4-week with CBC, chemistry, physical exams. mCRPC was assessed clinically by PSA, ALP and imaging. Tumor was characterized by IHC and LC mass spectrometry (blood and BM). $C_{trough}$plasma concentrations of AA were measured on days 4 & 29, and ENZA and its active metabolite M2 on d29 in pt subset. **Results:** We enrolled (07/12-09/13) 60 pts with median age 66 yrs (range 40-82), PS-ECOG 1 (range 0-2) and PSA 20.8 ng/ml (range1-670). Gleason Score (GS) at diagnosis ≥ 8 in 38/53 (72%), [GS ≥ 9 29/53 (55%)/7 unknown]. Thirty (50%) had > 20 bone lesions, 19/60 (32%) lymph node lesions and 2/60 (3%) visceral metastases. Interim data on evaluable pts: PSA changes for 49 pts: maximum PSA decline ≥ 50% (37/49 [76%]), ≥ 90% (22/49 [45%]), PSA ≤ 0.1ng/ml (5/49 [10%]) and PSA progression (6 [12%]). Grade 3 adverse events: ALT rise (5), hypertension (5), ALP rise (4 ), arthralgia (3), bone pain (2). No Grade 4 AEs reported. At ENZA steady state (d29), $C_{trough}$ of AA was ~23% lower than d4 (pt n=14; LS means ratio 77.67 %; 90% CI 47.51-126.98) and $C_{trough}$for ENZA, M2, and the sum of both (pt n=15) were comparable to those reported previously. Following 8 weeks treatment, serum and BM testosterone were undetectable (<1pg/ml) in 29/39 (74%) and 31/36 (86%) evaluated pts respectively, and androstenedione in all pts. Nuclear AR expression was reduced following treatment in 5/6 of evaluable paired tumor specimens. **Conclusions:** ENZA+ AA combination has a favorable safety profile, without clinically meaningful PK DDI. Feedback mechanisms observed by either agent are dissipated. These promising findings are indicative of more efficacious androgen signaling inhibition in men with mCRPC. Clinical trial information: NCT01650194.

**5001 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Androgen receptor splice variant, AR-V7, and resistance to enzalutamide and abiraterone in men with metastatic castration-resistant prostate cancer (mCRPC).** *Presenting Author: Emmanuel S. Antonarakis, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

**Background:** Androgen receptor splice variant-7 (AR-V7) is a truncated form of the androgen receptor that lacks the ligand-binding domain, the target of enzalutamide and abiraterone, but remains constitutively active as a transcription factor. We hypothesized that detection of AR-V7 in circulating tumor cells (CTCs) from men with mCRPC may be associated with primary resistance to enzalutamide and abiraterone. **Methods:** We used quantitative reverse-transcription PCR (qRT-PCR) to interrogate CTCs for the presence or absence of AR-V7 from prospectively enrolled patients with mCRPC initiating treatment with enzalutamide or abiraterone. We examined associations between AR-V7 status and PSA response rates, PSA progression-free survival (PSA-PFS), and clinical/radiographic progression-free survival (PFS). Multivariable Cox regression analyses were performed to determine the independent effect of AR-V7 status on these clinical outcomes. 30 men (per cohort) were required to detect a difference in PSA response rates from 10% (in AR-V7–positive men) to 60% (in AR-V7–negative men), using a 2-sided $\alpha$=0.10 and $\beta$=0.15. **Results:** 31 enzalutamide-treated patients and 31 abiraterone-treated patients were enrolled, of which 38.7% and 19.4% had detectable AR-V7 from CTCs, respectively. Among men receiving enzalutamide, AR-V7–positive patients had inferior PSA response rates (0% *vs* 52.6%, *P*=0.004), PSA-PFS (median 1.4 *vs* 5.9 months, *P*<0.001), and PFS (median 2.1 *vs* 6.1 months, *P*<0.001) compared to AR-V7–negative patients. Similarly, among men receiving abiraterone, AR-V7–positive patients had inferior PSA response rates (0% *vs* 68.0%, *P*=0.004), PSA-PFS (median 1.3 months *vs* not reached, *P*<0.001), and PFS (median 2.3 months *vs* not reached, *P*<0.001). The negative prognostic impact of AR-V7 was maintained after adjusting for full-length AR expression levels. **Conclusions:** Detection of AR-V7 in CTCs from men with mCRPC is associated with resistance to enzalutamide and abiraterone. AR-V7 status may be used as a biomarker to predict resistance to AR-targeting agents, facilitate treatment selection, and fuel the development AR N-terminal domain inhibitors.

**5002 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**The site of visceral metastases (mets) to predict overall survival (OS) in castration-resistant prostate cancer (CRPC) patients (pts): A meta-analysis of five phase III trials.** *Presenting Author: Susan Halabi, Duke University Medical Center, Durham, NC*

**Background:** Recent studies have shown that metastatic site is an important predictor of overall survival, but the reports were based on small sample sizes and as such the estimates were unstable. We sought to test two hypotheses: 1) CRPC pts with lung mets have worse survival than pts with non-visceral mets; and 2) pts with liver mets have worse survival than pts with lung mets. **Methods:** We combined individual patient data from 3,993 chemotherapy-naive mets CRPC pts randomized to receive docetaxel (D) based therapy on 5 phase III trials: CALGB 90401 (D +/- Bevacizumab): SWOG 0421(D +/-atrasentan),ENTHUSE 33 (D +/- zibotentan), TAX327 (D 3 wks, D weekly) and SWOG 9916 (D + estramustine). Site of mets at baseline was categorized as: lymph node (LN) only, bone +/- LN with no visceral mets, any lung mets (but no liver), any liver mets, and other visceral. We used fixed-effects meta-analysis to estimate the pooled hazard ratios (pHR) and 95% confidence intervals (CI) for comparing pts with lung mets vs. non-visceral mets and liver mets vs. lung mets. **Results:** The pHR for death for pts with lung mets compared to pts with non-visceral mets was 1.3 (95% CI= 1.1-1.5, p<0.001) and the pHR for pts with any liver mets compared with pts with lung mets was 1.4 (1.2-1.7, p<0.001). The median overall survival by site of mets is presented in table below. f mets at baseline was categorized as: lymph node (LN) only, bone +/- LN with no visceral mets, any lung mets (but no liver), any liver mets, and other visceral. **Conclusions:** As anticipated, CRPC patients with liver mets had the worst OS (12.1 m). While pts with lung mets had better OS (16.5 months) compared to liver mets pts, they had significantly worse survival than pts with non-visceral bone mets (20 months). These data may help in treatment decisions and in the design of future clinical trials in mCRPC pts. Clinical trial information: NCT00110214.

| Metastatic Site | N (%) | Median OS in months (95% CI) |
|---|---|---|
| LN only | 187 (5) | 27.0 (24.7-32.4) |
| Bone/Bone with LN | 3334 (83) | 20.3 (19.7-21.0) |
| Lung (+/- bone), no liver | 300 (7) | 16.5 (14.8-18.4) |
| Liver (LM) (+/- bone) | 280 (7) | 12.1 (10.1-13.5) |
| Other Visceral (adrenal, brain) | 55 (1) | 14.4 (12.6-19.1) |

**5003 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Immediate versus deferred initiation of androgen deprivation therapy in prostate cancer patients with PSA-only relapse.** *Presenting Author: Xabier Garcia-Albeniz, Harvard School of Public Health, Boston, MA*

**Background:** The optimal timing to start androgen deprivation therapy (ADT) in patients with rising PSA as the only sign of relapse is unknown. ASCO guidelines state "the critical issue is to determine whether there is benefit and how large it is for starting ADT while patients are asymptomatic." **Methods:** We studied 2,022 men in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), a national prospective registry, staged < cT3aN0M0, treated with radical prostatectomy (RP) or radiotherapy (RT) and had a PSA relapse (> 0.2 ng/mL [RP] or three rising determinations one month apart [RT]). Exclusion criteria included ADT in the 12 months before inclusion, metastatic disease by CT scan or bone scan, and symptoms. We assigned patients to the "immediate" strategy if they initiated ADT within 3 months (grace period) of PSA relapse and to the "deferred" strategy if they initiated ADT 2 or more years after PSA relapse or when they presented with metastasis, symptoms or a short PSA doubling time. We did not allow a treatment other than ADT for PSA relapse (e.g., rescue RT). We censored patients when they deviated from the assigned strategy and adjusted for this censoring via inverse probability weighting where the weights are a function of time-varying confounders: PSA, Karnofsky, weight loss, and bone pain. **Results:** Of the 2,022 patients analyzed, median age was 69 (range 63 to 74) years, 33.8% had a Gleason score >7, 31.8% received radiotherapy as primary treatment, and median time from primary treatment to PSA relapse was 27 (range 14 to 51) months. After relapse, patients were followed a median of 53.2 months. All cause mortality HR for "immediate ADT" vs. "deferred ADT" was 1.06 (95% CI: 0.59 to 1.89), corresponding to a survival difference at 5 years of -5.5% (95% CI: -15.1 % to 4.2%). The prostate-cancer specific mortality HR was 1.48 (95% CI 0.69-3.16), corresponding to a 5-year survival difference of -5.6% (95% CI: -12.5% to 1.3%). **Conclusions:** Our study suggests little or no survival benefit of immediate ADT initiation for immediate ADT initiation compared with deferred ADT initiation (at clinical progression or at least two years after PSA relapse) among prostate cancer patients with PSA-only relapse.

**5004 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Main oncologic endpoints of the TROG 03.04 (RADAR) Trial for men with locally advanced prostate cancer** *Presenting Author: James William Denham, Calvary Mater Newcastle, University of Newcastle, Newcastle, Australia*

**Background:** To determine whether 18 months androgen suppression (AS) plus radiotherapy (RT) ± 18 months zoledronate (Z) is more efficacious than 6 months AS plus RT ± 18 months Z, and is associated with a widely acceptable morbidity profile in men with locally advanced prostate cancer (PC). **Methods:** Between 2003 and 2007 1071 men with locally advanced PC were randomly allocated in a 2X2 factorial trial design in a 1:1:1:1 ratio to short-term (6 months) neo-adjuvant AS using leuprolide (22.5mg i.m. every 3 months) and radiation (STAS) either alone, or followed by intermediate term (12 months) AS (ITAS) (22.5mg i.m. every 3 months), or accompanied by 18 months of zoledronate (4mg i.v. every 3 months) (STAS+Z), or by both (ITAS+Z). Eligibility included T2a-4, N0, M0 adenocarcinoma of the prostate, with PSA ≥10 and Gleason score (GS) ≥7 in T2a cases. The primary endpoint is time to prostate cancer specific mortality (PCSM). Secondary endpoints include time to PSA, all distant and bony progressions (PSAP, DP and BP), time to starting secondary therapeutic intervention (STI) and all-cause mortality (ACM). Analysis was by intention-to-treat. All endpoints were assessed using competing risks methodology (unadjusted Fine and Gray models) except ACM where the log-rank test was used. **RESULTS:** Median follow-up was 7.4 years IQR [6.5-8.4]. Important bi-directional interactions were identified. Compared to STAS, STAS+Z significantly increased BP SHR 1.85 [1.11-3.10] p=0.02. Compared to STAS, ITAS+Z significantly reduced PSAP SHR 0.71 [0.53-0.95] p=0.02 and STI SHR 0.67 [0.48-0.94] p=0.02, and further still in subjects with GS>7 tumours: PSAP SHR 0.59 [0.37-0.94] p=0.03 and STI SHR 0.49 [0.29-0.83] p=0.01 respectively. ITAS was superior to STAS only in subjects with GS≤7 tumours; PSAP SHR 0.65 [0.43-0.98] p=0.04, STI SHR 0.49 [0.29-0.84] p=0.01. Corresponding reductions in DP, PCSM and ACM did not reach significance. Apart from two mandibular osteonecroses, no increases in morbidity or adverse patient reported outcomes were attributable to 18 months AS or Z. **CONCLUSIONS:** Ten year data is required to confirm and quantify reductions in DP, PCSM and ACM from the use of ITAS and ITAS+Z. STAS+Z cannot be recommended. Clinical trial information: NCT00193856.

**5005 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Docetaxel-estramustine in localized high-risk prostate cancer: Results of the French Genitourinary Tumor Group GETUG 12 phase III trial.** *Presenting Author: Karim Fizazi, Department of Cancer Medicine, Gustave Roussy, University of Paris Sud, Cancer Campus, Grand Paris, Villejuif, France*

**Background:** Docetaxel-estramustine improves survival in patients (pts) with castrate-resistant prostate cancer (CaP). This phase III trial assessed docetaxel-estramustine in pts with high-risk localized CaP. **Methods:** Eligibility included non-pretreated high-risk localized CaP, defined as ≥1 of the following criteria: T3-T4, Gleason score (GS)≥8, PSA≥ 20 ng/mL, pN+ (stratification factors). All pts had a staging pelvic lymph node dissection. Pts were randomly assigned to either goserelin 10.8 mg every 3 months for 3 years and 4 cycles of docetaxel 70 mg/m$^2$ q3w + estramustine 10 mg/kg/d d1-5 (ADT+DE arm) or goserelin alone (ADT arm). Local therapy was administered at 3 months. The primary endpoint is progression-free survival (PFS); events=PSA relapse, radiographic relapse, death. The planned number of pts was 400, to detect a 12% difference at 4 years with a power of 80% and a type I error of 0.05 (two-sided Logrank test). Preliminary results indicated a better PSA response rate (PSA ≤ 0.2 ng/mL: 34% in the ADT+DE arm vs 15% in the ADT arm [p< 0.0001]), neutropenic fever in 2%, and no negative impact on QoL at 1 year in the ADT+DE arm (Fizazi, Eur J Cancer 2012; 48:209-17). Here we report PFS results. **Results:** 413 pts were accrued. With a median follow-up of 7.6 years, PFS was marginally improved in the ADT+DE arm: 8-year PFS rate: 62% [55–69] in the ADT+DE arm vs 53% [45–60] in the ADT arm (adjusted HR: 0.75 [0.55-1.01], p=0.06). In pts with a GS<8, the 8-year PFS rate was 69% [60-78] (ADT+DE) and 51% [41-61] (ADT) (HR: 0.55 [0.36-0.84], interaction test =0.06 for GS). A non-significant trend favoring ADT+DE was found for clinical PFS (HR: 0.79 [0.55-1.13]). No long-term toxicity signal was detected, with no toxic death. The 8-year cumulative incidence of second cancers (11% vs 10%) was similar in the two arms. The 8-year OS rate is 83% [77–89] with no difference between treatment arms (HR: 0.94 [0.60-1.49]). In pts with a GS<8, the 8-year OS rate was 94% [89-98] (ADT+DE) and 85% [78-92] (ADT) (HR: 0.40 [0.17-0.91], interaction test: p=0.02). **Conclusions:** Docetaxel-estramustine is associated with a borderline significant reduction in the risk of relapse or death in high-risk prostate cancer. Clinical trial information: NCT00055731.

**5006 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**SWOG S0925: A randomized phase 2 study of androgen deprivation combined with cixutumumab versus androgen deprivation alone in patients with new metastatic hormone-sensitive prostate cancer.** *Presenting Author: Evan Y. Yu, University of Washington/Seattle Cancer Care Alliance, Seattle, WA*

**Background:** Cixutumumab (CIX), formerly IMC-A12, is a fully recombinant human monoclonal IgG$_1$ antibody that specifically targets insulin-like growth factor 1 receptor (IGF-IR). Pre-clinical studies have shown interaction between IGF-IR and the androgen receptor, with greatest anti-tumor activity in castration-sensitive xenografts. **Methods:** Patients with new metastatic prostate cancer were randomized within 30 days of initiation of LHRH agonist plus bicalutamide (AD) to CIX with AD versus AD alone. With 180 eligible patients randomized and one-sided alpha=0.10 there would be 90% power to detect an absolute difference of 20% in the primary endpoint, undetectable PSA (≤0.2 ng/mL) rate at 28 weeks (relative risk (RR)=1.44) using an intent-to-treat analysis; this endpoint was previously shown to be strongly correlated with survival. Secondary endpoints included the proportion of patients with 0.3 ≤ PSA ≤4.0 ng/mL, safety and tolerability, circulating tumor cell levels (CTCs) and multiple plasma IGF biomarkers. Fisher's exact test was used for the primary endpoint, and extended MH chi-square was used for 3 PSA response categories. **Results:** The trial accrued 210 eligible patients (105 randomized to each arm). Patient characteristics were similar in both arms. The undetectable PSA rate was 42/105 (40.0%) for CIX with AD and 34/105 (32.3%) for AD alone (RR=1.24, one-sided p=0.16). When separating out the PSA ≤4.0 ng/mL rate (see Table), there was no significant difference in PSA response rates between arms (p=0.17). CTCs were obtained at baseline prior to AD for 39 patients. Lower CTC (<5 vs. ≥ 5/7.5 mL whole blood) levels were associated with higher rate of PSA response (3 categories) (p=0.03). IGF-associated biomarkers will be reported at the meeting. **Conclusions:** CIX with AD did not significantly increase the proportion of men with an undetectable PSA in men with new metastatic hormone-sensitive prostate cancer. CTCs at baseline may carry prognostic value for this population. Clinical trial information: NCT01120236.

| | PSA response | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | PSA<=0.2 | | 0.2<PSA<=4.0 | | PSA>4.0 | | Total | |
| | n | % | n | % | n | % | n | % |
| **Treatment** | | | | | | | | |
| **CIX + AD** | 42 | 40.0% | 17 | 16.1% | 46 | 43.8% | 105 | 100.0% |
| **AD** | 34 | 32.3% | 15 | 14.2% | 56 | 53.3% | 105 | 100.0% |

**5007 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Primary, secondary, and quality-of-life endpoint results from PREVAIL, a phase 3 study of enzalutamide in men with metastatic castration resistant prostate cancer (mCRPC).** *Presenting Author: Andrew J. Armstrong, Duke University, Durham, NC*

**Background:** Enzalutamide (ENZ), an androgen receptor inhibitor, improved overall survival (OS) in men with mCRPC who had received prior docetaxel therapy (Scher, N Engl J Med 2012;367:13). The PREVAIL study examined whether ENZ could prolong OS and radiographic progression-free survival (rPFS) in men with mCRPC who had progressed on androgen deprivation therapy (ADT). **Methods:** In this randomized double-blind, placebo-controlled, multinational study (NCT01212991), asymptomatic or mildly symptomatic patients were randomized 1:1 to ENZ 160 mg/day or placebo (PBO). OS and rPFS were co-primary endpoints and analyzed for the intent-to-treat population. Key prespecified secondary and exploratory endpoints are noted in the table below. **Results:** 872 men were randomized to ENZ and 845 to PBO, with respective median treatment durations of 16.6 and 4.6 months. Based on a planned interim analysis at 540 deaths the Data Monitoring Committee recommended stopping the study and crossing PBO patients to ENZ. Efficacy results are shown in the Table. The most common adverse events with a higher incidence in the ENZ arm than PBO were fatigue (35.6% vs 25.8%), back pain (27.0% vs 22.2%), constipation (22.2% vs 17.2%), and arthralgia (20.3% vs 16.0%). Seizure was reported in 1 patient in each treatment arm (0.1%). **Conclusions:** In men with mCRPC who progress on ADT, treatment with enzalutamide has a favorable safety profile and significantly improves OS, rPFS, and secondary measures of disease response and progression. Clinical trial information: NCT01212991.

| | Est. median (95% CI) months | | | |
|---|---|---|---|---|
| **Co-primary endpoints** | **ENZ** | **PBO** | **HR (95% CI)** | **P value** |
| **OS** | 32.4 (31.5, NYR) | 30.2 (28, NYR) | 0.71 (0.60, 0.84) | < 0.0001 |
| **rPFS** | NYR (13.8, NYR) | 3.9 (3.7, 5.4) | 0.19 (0.15, 0.23) | < 0.0001 |
| **Other efficacy endpoints** | | | | |
| **Time to cytotoxic chemotherapy** | | | 0.35 (0.30, 0.40) | < 0.0001 |
| **Time to antineoplastic treatment**[a] | | | 0.27 (0.24, 0.31) | < 0.0001 |
| **Time to first SRE** | | | 0.72 (0.61, 0.84) | < 0.0001 |
| **Time to PSA progression** | | | 0.17 (0.15, 0.20) | < 0.0001 |
| **Time to FACT-P degradation** | | | 0.63 (0.54, 0.72) | < 0.0001 |
| **Best objective response (CR+PR)** | | | ENZ = 58.8%<br>PBO = 5.0% | < 0.0001 |
| **PSA decline from baseline** | | | ENZ | PBO |
| **≥ 50%** | | | 78.0% | 3.5% < 0.0001 |
| **≥ 90%** | | | 46.8% | 1.2% < 0.0001 |

[a] Cytotoxic, hormonal, or investigational therapy.

**5008 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Phase 3, randomized, placebo-controlled trial of orteronel (TAK-700) plus prednisone in patients (pts) with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) (ELM-PC 4 trial)** *Presenting Author: Ronald De Wit, Erasmus University Medical Center, Rotterdam, Netherlands*

**Background:** Orteronel, an investigational, non-steroidal, selective 17,20-lyase inhibitor, demonstrated improved radiographic PFS (rPFS) but not OS in men with mCRPC post-docetaxel (Dreicer et al, ASCO GU 2014, Abstract 7). The double-blind ELM-PC 4 trial (NCT01193244) evaluated orteronel in pts with chemotherapy-naïve mCRPC. **Methods:** Men with progressive mCRPC (rising PSA and/or radiographic evidence) and testosterone $<$ 50 ng/dL (post-orchiectomy or with maintained GnRH suppression) were randomized 1:1 to orteronel 400 mg twice daily (BID) + prednisone 5 mg BID (O+P) or placebo + prednisone (P), stratified by region and radiographic progressive disease at baseline. Co-primary endpoints were OS and rPFS. Based on 90% power to test OS ($>$ 90% for rPFS), an initial HR of 1.25 in favor of orteronel was anticipated with 1454 pts and 900 deaths (pre-assigned alpha: OS 0.045, rPFS 0.005). The final analysis for rPFS was conducted at an interim analysis (IA) for OS; the final analysis for OS was conducted at 600 deaths, with 78% power. **Results:** 1560 pts were randomized. The study met the co-primary endpoint of rPFS; at the IA (final for rPFS), median rPFS with O+P *v* P was 11 *v* 8.3 months (HR 0.7; 95% CI: 0.5–0.8; $P < .001$). At the final analysis for OS the updated median rPFS benefit with O+P *v* P had increased to 5.1 months (median 13.8 *v* 8.7 mo; HR 0.7; 95% CI: 0.6–0.8; $P < .00001$). The co-primary endpoint of OS was not met. Median OS with O+P *v* P was 31.4 *v* 29.5 months (HR 0.9; 95% CI: 0.8–1.1; $P = .314$), with no notable differences across regions. More pts had a $\geq$ 50% PSA decrease (43% *v* 25%, $P < .00001$) and a favorable circulating tumor cell count (15% *v* 9%, $P = .00016$) at 12 weeks with O+P *v* P. Common all-grade adverse events with O+P *v* P included nausea (36% *v* 15%), fatigue (34% *v* 20%), constipation (33% *v* 15%), and diarrhea (28% *v* 14%); 30% *v* 18% of pts discontinued due to AEs. In O+P *v* P groups, 45% *v* 51% of pts received subsequent therapy, including docetaxel/abiraterone/enzalutamide in 31%/14%/6% *v*33%/20%/6%. **Conclusion:** O+P demonstrated a significant improvement in rPFS but no statistically significant improvement in OS *v* P in chemotherapy-naive mCRPC. Clinical trial information: NCT01193244.

**5009 Clinical Science Symposium, Sat, 3:00 PM-4:30 PM**

**Nivolumab for metastatic renal cell carcinoma (mRCC): Results of a randomized, dose-ranging phase II trial.** *Presenting Author: Robert J. Motzer, Memorial Sloan-Kettering Cancer Center, New York, NY*

**Background:** Nivolumab, a fully human IgG4 programmed death-1 immune checkpoint inhibitor antibody, restores T-cell immune activity and showed objective responses in mRCC in a phase I trial (*NEJM* 366:2443). This phase II trial (NCT01354431) assesses three nivolumab doses in mRCC patients (pts) pretreated with agents targeting the VEGF pathway. **Methods:** Pts with clear-cell mRCC ($\geq$1 agent targeting VEGF pathway; $\leq$3 prior systemic therapies) were randomized (blinded 1:1:1) to nivolumab 0.3, 2 or 10 mg/kg IV Q3W until progression or toxicity. The primary objective was to evaluate the dose-response relationship measured by progression-free survival (PFS). Secondary objectives included overall survival (OS), objective response rate (ORR) and safety assessment. **Results:** All pts (N=168) received prior systemic therapy (70% received $\geq$2) including VEGFR TKIs (98%), mTOR inhibitors (38%) and immunotherapy (24%). 25% were MSKCC poor risk. All had $>$16 months of follow-up. No dose-response relationship was noted for PFS (stratified trend test, $P$=0.9). PFS and ORR were similar across doses (Table). For 0.3 mg/kg, median duration of response was 15.7 months and median OS was 18.2 months; for other doses medians were not reached. Across doses 19/35 responders (54%) had objective responses lasting $>$12–20+ months. Rates of grade 3–4 related adverse events (AEs) were $\leq$17% for all doses (Table). There was no grade 3–4 pneumonitis. For 0.3, 2 and 10 mg/kg, 1 (2%), 6 (11%) and 4 (7%) pts, respectively, had treatment-related AEs that led to discontinuation. **Conclusions:** Antitumor activity was observed with nivolumab in this pretreated mRCC population including objective responses of long duration. No dose-response relationship for PFS was noted and the safety profile was acceptable. Median OS was 18.2 months for the 0.3 mg/kg dose and was not reached for 2 or 10 mg/kg; updated OS will be presented. Clinical trial information: NCT01354431.

| | 0.3 mg/kg n=60[a] | 2 mg/kg n=54 | 10 mg/kg n=54 |
|---|---|---|---|
| **Median PFS, months (80% CI)** | 2.7 (1.9, 3.0) | 4.0 (2.8, 4.2) | 4.2 (2.8, 5.5) |
| **ORR, n (%)** | 12 (20) | 12 (22) | 11 (20) |
| **Median OS, months (80% CI)** | 18.2 (16.7, NR) | NR | NR |
| **Treatment-related AE, n (%)** | 44 (75) | 36 (67) | 42 (78) |
| **Grade 3–4** | 3 (5) | 9 (17) | 7 (13) |

[a] Safety analysis included 59 treated pts; CI=confidence interval; NR=not reached.

**5010 Clinical Science Symposium, Sat, 3:00 PM-4:30 PM**

**Nivolumab (anti-PD-1; BMS-936558, ONO-4538) in combination with sunitinib or pazopanib in patients (pts) with metastatic renal cell carcinoma (mRCC).** *Presenting Author: Asim Amin, Levine Cancer Institute, Charlotte, NC*

**Background:** Antiangiogenic agents sunitinib (S) and pazopanib (P) are SOC for mRCC, but new therapies are needed as pts advance through therapy with limited survival benefit. We report preliminary results of a phase I trial of nivolumab, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody, in combination with S or P in pts with mRCC. **Methods:** mRCC patients ($\geq$1 prior systemic therapy) received nivolumab in combination with S (50 mg, 4 wks on, 2 wks off; arm S) or P (800 mg daily; arm P), until progression/unacceptable toxicity. Starting dose of nivolumab was 2 mg/kg IV Q3W (N2), with planned escalation to 5mg/kg IV Q3W (N5). Based on tolerability, arm S N5 cohort was expanded to treatment-naïve pts. Primary objectives were safety/tolerability and determination of maximum tolerated dose (MTD) for the combinations; secondary objective was antitumor activity (objective response rate [ORR] and duration of response [DOR]). **Results**: 7 pts were assigned to each of arms S N2 and N5. No dose-limiting toxicities (DLTs) were observed and MTD was not reached thus N5 was expanded with 19 additional pts (total n=33). Arm P enrolled 20 pts at N2; 4 DLTs (elevated ALT/AST [n=3], fatigue [n=1]) were observed, leading to closure of this arm. Grade 3–4 related AEs were observed in 24/33 pts (73%) in arm S and 12/20 pts (60%) in arm P. Most common related grade 3–4 AEs included elevated ALT (18%), hypertension and hyponatremia (15% each) in arm S and elevated ALT/ AST (20% each) and fatigue (15%) in arm P. Hepatotoxicities were manageable using treatment algorithms. Grade 3 pneumonitis occurred in 1 pt (arm S, N5). Grade 3–4 related AEs led to therapy discontinuation in 8/33 pts (24%; 1 N2, 7 N5) in arm S and 4/20 pts (20%) in arm P. ORR was 52% (17/33) in arm S and 45% (9/20) in arm P. Responses occurred by first assessment (6 wks) in 41% (arm S) and 56% (arm P) of responding pts and were durable (range: arm S: 12.1+ to 54 wks; arm P: 12.1 to 69.1+ wks). Stable disease rate was 33% (n=11) in arm S and 35% (n=7) in arm P. PFS rate at 24 wks was 78% for arm S and 55% for arm P. **Conclusions:** Nivolumab plus S or P showed encouraging antitumor activity and a manageable safety profile in pts with mRCC. Additional follow up will be presented. Clinical trial information: NCT01472081.

**5011 Clinical Science Symposium, Sat, 3:00 PM-4:30 PM**

**Inhibition of PD-L1 by MPDL3280A and clinical activity in pts with metastatic urothelial bladder cancer (UBC).** *Presenting Author: Thomas Powles, Barts Cancer Institute, Queen Mary University Hospital of London, London, United Kingdom*

**Background:** Metastatic UBC is associated with a poor prognosis and limited treatment options. PD-L1 expression is prevalent in this disease and may protect cancer cells from immune-mediated destruction by binding to its receptors PD-1 and B7.1. MPDL3280A is a human anti-PD-L1 mAb with an engineered Fc-domain designed for optimized efficacy and safety. **Methods:** In a Ph I study, UBC pts received MPDL3280A 15 mg/kg IV q3w for up to 1 y. Objective response rate (ORR; including unconfirmed responses) was assessed by RECIST v1.1. In parallel, tumor and circulating biomarkers were evaluated to study MPDL3280A immune correlates. **Results:** As of Sep 19, 2013, 31 UBC pts were treated with MPDL3280A. Pts were 84% male, had a median age of 66 y (42-86), 57% were ECOG PS 1 and 68% had visceral metastases. 71% received $\geq$ 2 prior therapies; 97% received prior platinum-based chemotherapy. Pts had received MPDL3280A for a median duration of 43 d (1-153); the majority remained on treatment as of the data cutoff. The G1-4 treatment-related AEs occurring in $\geq$ 2 pts were pyrexia, anemia, decreased appetite, fatigue and nausea. Related G3-4 AEs occurred in 3.2% of pts. There were no immune-related AEs. 20 PD-L1+ pts were evaluable for efficacy at time of analysis with a median follow up of 2.8 m (1.4-5). The ORR was 50% (1 CR and 9 PRs) with a median time to response of 43 d (39-82), corresponding to the first radiographic assessment. Responders included pts with visceral metastases at baseline. All responders were still responding at the time of clinical cutoff. Treatment resulted in transient increases in circulating CD8+Ki-67+ T cells and plasma proteins (eg, IL-18) upstream of IFN$\gamma$ signaling, representing pharmacodynamic biomarkers of activity. Gene expression data from pretreatment tumors showed that pts who progressed had a proportionally higher myeloid gene signature (eg, IL8, CCL2). Updated data will be presented, including data from PD-L1–neg pts. **Conclusions:** MPDL3280A was well tolerated in this pretreated UBC population. 50% of pts treated responded to treatment. Responses were rapid and on-going. Biomarker analysis revealed pharmacodynamic markers, as well as markers of potential mechanisms of resistance to therapy. Clinical trial information: NCT01375842.

**5012 Clinical Science Symposium, Sat, 3:00 PM-4:30 PM**

**Immunomodulatory activity of nivolumab in previously treated and untreated metastatic renal cell carcinoma (mRCC): Biomarker-based results from a randomized clinical trial.** *Presenting Author: Toni K. Choueiri, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Nivolumab, a fully human IgG4 programmed death-1 (PD-1) inhibitor antibody, has shown encouraging activity in mRCC. This trial assessed the immunomodulatory and clinical activity, and safety of nivolumab in patients (pts) with mRCC. **Methods:** Ninety-one pts received nivolumab IV Q3W: pretreated pts (1–3 prior therapies; ≥1 anti-angiogenic agent) received 0.3 (n=22), 2 (n=22), or 10 mg/kg (n=23); 24 treatment-naïve pts received 10 mg/kg. Fresh biopsies and serum were obtained at baseline (BL) and nivolumab cycle 2 day 8 (C2D8; biopsy) and cycle 4 day 1 (C4D1; serum). Primary objective was to assess the immunomodulatory activity of nivolumab on serum chemokines (CXCL9, CXCL10) and tumor T cell infiltrates from BL to post treatment. Secondary/exploratory objectives included safety and tolerability, antitumor activity (ORR; RECIST 1.1), BL and treatment-induced changes in PD-1 ligand (PD-L1) expression (Dako immunohistochemistry assay; PD-L1 positivity: >5% tumor membrane staining at any intensity) and association of clinical activity with BL PD-L1 expression. **Results:** Mean increase from BL to C4D1 was 191% for CXCL9 and 90% for CXCL10. T cell infiltrates increased by a median of 70% (CD3+; range 53–220%) and 88% (CD8+; 61–257%) from BL to C2D8. Of 56 evaluable fresh pretreatment biopsies, 18 (32%) were PD-L1+. ORR was 22% (4/18) for PD-L1+ pts vs 8% (3/38) for PD-L1–. In 5/27 (19%) matched biopsy pairs PD-L1 expression increased >5% by C2D8. For evaluable pts ORR was 16% (14/90); 16% in previously treated pts, 13% in untreated pts. Median duration of response was 15 months; 6 (43%) responses are ongoing. 14/91 (15%) pts had grade 3–4 related AEs, most commonly colitis and elevated AST (n=2 each), diarrhea and pneumonitis (n=1 each), all grade 3. **Conclusions:** In this prospective biomarker-based study, nivolumab showed clinical activity and manageable safety in pts with previously treated and untreated mRCC. Responses were numerically higher in PD-L1+ pts but also seen in PD-L1– pts. Changes in biomarkers were consistent with PD-1 inhibition and provided evidence of immunomodulatory effects in serum and in the tumor microenvironment. Clinical trial information: NCT01358721.

**5013 Poster Highlights Session (Board #27), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Validation of a prognostic model for metastatic castrate-resistant prostate cancer (mCRPC) patients receiving abiraterone acetate (AA).** *Presenting Author: Praful Kumar Ravi, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*

**Background**: A prognostic model based on clinical parameters has been derived from the population of the COU-AA-301 Phase 3 trial for mCRPC patients treated with AA after docetaxel. It relies on the presence of six clinical parameters: ECOG-PS=2, presence of liver metastases, time from start of initial LHRH agonist therapy to AA therapy ≤36mths, low albumin, high alkaline phosphatase and high LDH (1 point per parameter) to stratify patients into 3 risk groups. We sought to validate this model in an independent cohort of patients treated with AA post-docetaxel, and to explore its utility in patients treated with AA in the pre-chemotherapy setting. **Methods**: We reviewed all mCRPC patients who received AA between January 2006 and June 2013 at our centre who either received AA post-docetaxel outside of a clinical trial (group A, validation set) or were treated with AA prior to chemotherapy (group B, exploratory analysis). Clinical data at the time of starting treatment with AA and outcome was collected from electronic patient records. Patients were assigned into 'good' (0-1), 'intermediate' (2-3), and 'poor' (4-6) prognostic groups as per the published model (Chi KN et al, J Clin Oncol 2013;abstr 5013). Differences in median overall survival (mOS) were assessed using the log-rank test. **Results**: A total of 158 patients were eligible for this analysis (group A: n=94, group B: n=64). Median duration of AA therapy and mOS were 4.7mths and 13.3mths (group A), and 15.3mths and 40.4mths (group B) respectively. When considering the validation set of patients post-docetaxel, mOS was significantly different across the three prognostic groups (good: n=39, mOS=21.8mths; intermediate: n=44, mOS=10.6mths; poor: n=7, mOS=6.8mths; p=0.0001). Analysis of group B confirmed the ability of the model to prognosticate for OS in the pre-chemotherapy setting: (good: n=44, mOS=45.6mths; intermediate or poor: n=20, mOS=34.5mths; p=0.042). **Conclusions**: These results serve to validate the prognostic model in an independent, unselected population treated with AA post-docetaxel and support clinical implementation of the score. Additionally, the model remains valid in the pre-chemotherapy setting.

**5014 Poster Highlights Session (Board #28), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Circulating tumor cells (CTCs) and LDH as prognostic factors in patients with metastatic castration-resistant prostate cancer (mCRPC) progressing during or following docetaxel treated in the orteronel phase 3 ELM-PC 5 trial.** *Presenting Author: Howard I. Scher, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Results from a global phase 3 study demonstrated that orteronel 400 mg BID /prednisone 5 mg (O+P), vs placebo/prednisone alone (P), improved radiographic progression (rPFS) and increased PSA50 response but resulted in no overall survival (OS) benefit (HR 0.89) (Dreicer et al., ASCO GU 2014). **Methods:** Whole blood samples for CTC enumeration (Veridex Cell Search, Esoterix) were obtained from 1,038 pts at baseline and 635 at end of wk 12 (primary CTC endpoint). Results were reported as number counted CD45-/EpCam+ cells/7.5 mL whole blood. **Results:** Baseline distribution of favorable (< 5 cells/7.5 mL) to unfavorable (≥ 5 CTCs/7.5 mL) were balanced in the two groups (40% favorable in each). In cross sectional analysis, the percent favorable remained unchanged with P at wk 12 (96/214) (45%) but increased to 62% (262/421) with O+P. Patient shift analysis showed that 99 of 231 (43%) of pts on O+P converted to favorable vs. 17 of 113 (15%) on P. A trichotomous surrogate biomarker panel (Scher et al, ESMO 2013) based on 12-wk data categorized patients as low-risk (CTC ≤ 4), intermediate-risk (CTC ≥ 5, LDH ≤ 225 U/L) or high-risk (CTC ≥ 5, LDH > 225 U/L). Distribution of risk at 12 wks by treatment was for O+P vs. P: low, 262 (36%) vs. 96 (26%); intermediate, 63 (9%) vs. 54 (15%); and high, 93 (13%) vs. 59 (16%). At 12 wks, the overall survival (OS) HRs for the three risk categories adjusted for treatment and other baseline characteristics are shown in the table. Addition of treatment effect to the K-M estimates for risk groups did not give additional predictive value at that 12-wk timepoint. Results with a dichomotous CTC-only model were similar: OS % at 1 and 2 yrs was 87 and 61 vs. 51 and 15 for ≤ 4 vs. ≥ 5 respectively (P < 0.0001). **Conclusions:** O+P resulted in a more favorable risk redistribution of CTCs at 12 wks and the risk categories were strongly predictive of OS. The findings support the therapeutic impact of O+P relative to P as well as the prognostic potential for CTC at 12 wks. Clinical trial information: NCT01193257.

| Risk at 12 wks | HR | CI | P-value |
|---|---|---|---|
| Intermediate- vs. low-risk | 2.596 | (1.742, 3.870) | < 0.0001 |
| High- vs. low-risk | 6.218 | (4.329, 8.931) | < 0.0001 |

**5015^ Poster Highlights Session (Board #29), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Association of serum (SR) and tissue (TX) abiraterone (ABI) levels with intraprostatic steroids and pathologic outcomes in men with high-risk localized prostate cancer (PCa).** *Presenting Author: Elahe A. Mostaghel, Fred Hutchinson Cancer Research Center, Seattle, WA*

**Background:** Factors influencing efficacy of ABI in suppressing SR and TX androgens and inhibiting tumor growth in PCa are unknown. We examined the relationship of SR and TX ABI levels with SR and TX steroid levels and pathologic responses. **Methods:** Steroid and ABI levels were measured by mass spectrometry in SR and TX from 58 men with localized PCa in a clinical trial of castration with 3 or 6 months (mo) of ABI prior to prostatectomy. **Results:** Median ABI levels in SR and TX were 31 ng/ml (range 2.8-414) and 18 pg/mg (1.3-265) respectively. SR and TX ABI levels were positively correlated with SR and TX steroids upstream of CYP17A (pregnenolone [Preg], progesterone [Prog]) and inversely correlated with downstream steroids (17OH Preg, DHEA, all p<0.05). Two men at 3 mo and six at 6 mo had undetectable ABI in SR and TX, and did not show changes in steroids up or downstream of CYP17A. In men with undetectable vs detectable TX ABI levels, there was a trend toward higher cross-sectional tumor dimension, TX cellularity, tumor PSA staining and SR PSA (all p<0.10). TX ABI levels were significantly lower at 6 vs 3 mo (7.8 vs 62 pg/mg, p<0.001) while SR ABI levels were similar. At 3 mo 0/25 men had TX dihydrotestosterone (DHT) levels >1 (range 0.08-0.57 pg/mg), while at 6 mo 22% (10/46) had TX DHT >1 (1-17 pg/ml). At 3 mo TX Preg was strongly correlated with TX DHEA, while DHT was correlated with androstenedione (AED) and testosterone (T) (r>0.5, all p<0.01). At 6 mo the intraprostatic correlations of up- and downstream steroids were markedly increased (r>0.5 for TX Preg with downstream DHEA, AED, T and DHT; and for TX DHT with upstream T, AED, DHEA and Preg, all p<0.01). **Conclusions:** Prostate TX ABI levels are associated with TX steroids and pathologic responses in localized PCa. At 6 mo TX ABI levels decreased nearly 10-fold vs 3 mo (despite stable SR ABI levels), DHT levels markedly increased in >20% of samples, and intraprostatic correlations of DHT with steroids upstream of CYP17A inhibition became highly significant. These findings suggest that potential mechanisms of ABI resistance are induction of drug export or metabolism, and intraprostatic conversion of upstream precursors to DHT. Clinical trial information: NCT00924469.

**5016 Poster Highlights Session (Board #30), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Pathologic correlation of 18F-16β-fluoro-5α-dihydrotestosterone (FDHT) and FDG PET in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC).** *Presenting Author: Jarett Lawrence Feldman, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** We have demonstrated the feasibility, pharmacokinetic properties, tumor targeting, and the preliminary prognostic value of FDHT as a PET tracer for prostate cancer (PCa). As part of an imaging trial, we performed biopsies (bx) to assess the tumor-detection rate of FDHT and compared it with FDG PET. **Methods:** Pts with progressive mCRPC identified on standard imaging (CT, MRI, and bone scintigraphy) from 2007 to 2013 underwent FDHT and FDG PET/CT. Bx locations were selected by a consensus panel prioritized on the basis of: FDHT & FDG positivity, FDHT & FDG mismatch, and standard imaging positivity & any PET mismatch. Bx were considered positive (pos) if PCa was identified and negative (neg) if benign tissue or a secondary malignancy was sampled. **Results:** A total of 64 bx (28 soft tissue, 36 bone) were obtained from 54 pts of which 62 were evaluable (2 were non-diagnostic). 53/62 (85%) bx were pos and 9/62 (15%) were neg for PCa. FDHT and pathology correlated (pos/pos or neg/neg) in 56/62 (90%). FDG and pathology correlated in 57/62 (92%). All 47 FDHT pos lesions were pos for PCa. Notable mismatches were: FDHT neg/biopsy pos appeared in 6/53 (11%) cases of which 3 displayed neuroendocrine (NE) features and 2 were poorly-differentiated (PD) adenocarcinoma. FDG pos/bx neg for PCa appeared in 5/62 (8%) cases; 3 were secondary malignancies. The histopathologic correlation is provided in the table below. **Conclusions:** FDHT is highly effective at identifying adenocarcinoma of the prostate as demonstrated by pathology. A subset of lesions that are not detected on FDHT, but present on FDG imaging, represent neuroendocrine/poorly-differentiated PCa; these require further investigation in regards to prognosis and response to treatment. Clinical trial information: NCT00588185.

**Biopsy correlation of evaluable lesions with imaging findings (N=62).**

| Imaging results | | | Biopsy pos for PCa | | Biopsy neg for PCa | | Total lesions (# of pts[a]) |
|---|---|---|---|---|---|---|---|
| FDHT | FDG | CT/MRI or BS | Soft tissue | Bone | Soft tissue | Bone | |
| + | + | + | 18 | 29 | 0 | 0 | 47 (44) |
| + | - | + | 0 | 0 | 0 | 0 | 0 |
| - | + | + | 4[b] | 2[c] | 5[d] | 0 | 11 (10) |
| - | - | + | 0 | 0 | 1 | 3 | 4(4) |

[a]8pts obtained > 1 bx [b]2bxs had NE features and 2bxs had PD PCa [c]1bx had NE features [d] 3bxs had a secondary malignancy (2 gastrointestinal, 1 sarcoma) and 2 had benign pathology.

**5017 Poster Highlights Session (Board #31), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Comparison of plasma microRNAs with CTCs and PSA in patients treated on SWOG S0925, a randomized phase II study of androgen deprivation combined with cixutumumab versus androgen deprivation alone for patients with new metastatic hormone-sensitive prostate cancer.** *Presenting Author: Heather H. Cheng, University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA*

**Background:** Circulating, blood-based microRNAs (miRNAs), like circulating tumor cells (CTCs), are promising prostate cancer biomarker candidates. However, circulating miRNAs have yet to be examined in prospective clinical trials. Here, we examine the correlation between baseline plasma miRNAs and CTCs with 7-month PSA (previously shown to be strongly correlated with overall survival in SWOG 9346) in patients from SWOG 0925. **Methods:** Plasma and CTCs were collected prior to initiation of androgen deprivation (AD) from patients on SWOG 0925. miRNA was extracted and measured from plasma using miRCURY RNA Isolation kit and miRNA Ready-to-Use PCR, Human panel I, V1.M qRT-PCR arrays (Exiqon). CTC measurements were performed using the CellSearch® platform (Veridex). **Results:** Correlation between miRNA cycle threshold and CTCs are shown (Table). Baseline plasma miR-375 levels were associated with stratified 7-month PSA response (≤0.2, 0.2 to ≤4.0, or >4.0, P=0.0071, Friedman test). Using ROC curve analysis, there was no significant difference between baseline miR-375 and baseline CTC in predicting 7-month PSA response (≤0.2 vs. >0.2). **Conclusions:** Baseline plasma miR-141, miR-200a, miR-200c and miR-375 levels were significantly correlated with baseline CTC count. Baseline plasma miR-375 was similar to baseline CTCs in ability to predict 7-month PSA in a prospective, multi-center clinical trial.

**Correlation of baseline miRNA (cycle threshold) and CTC counts.**

| MicroRNA | N | Spearman correlation | 95% CI | p-value |
|---|---|---|---|---|
| **miR-141** | 35 | -0.60 | -0.78 to -0.34 | 0.0001 |
| **miR-200a** | 31 | -0.51 | -0.73 to -0.19 | 0.0035 |
| **miR-200c** | 36 | -0.34 | -0.59 to -0.01 | 0.0447 |
| **miR-210** | 35 | -0.18 | -0.48 to 0.16 | 0.3123 |
| **miR-375** | 36 | -0.46 | -0.68 to -0.15 | 0.0051 |

**5018 Poster Highlights Session (Board #32), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Effect of HOXB13 and FOXA1 on the AR cistrome during prostate tumorigenesis in primary human tissue.** *Presenting Author: Mark M Pomerantz, Dana-Farber Cancer Institute, Boston, MA*

**Background:** The androgen receptor (AR) is central to prostate carcinogenesis and cancer progression. Current understanding of the prostate AR cistrome - the genome-wide set of AR binding sites (ARBS) - is driven largely by tumor model systems. The role of the AR cistrome in prostate tumorigenesis in human tissue is unknown. We map the AR cistrome in 20 normal and tumor human prostate samples using chromatin immunoprecipitation followed by high-throughput sequencing (ChIP-seq). **Methods:** Chromatin was extracted from 13 tumor and 7 matched histologically normal foci (>70% enrichment) from fresh-frozen radical prostatectomy specimens. Tissue was pulverized, fixed and sonicated then immunoprecipitated with antibody to AR; DNA was isolated; libraries were constructed for the Illumina platform; sequencing reads were aligned to the human genome using MACS (false discovery rate 0.01) **Results:** Median 19,602 ARBS were called per sample. In unsupervised pairwise analysis of each AR cistrome, specimens clustered distinctly into tumor and normal groups. 9,181 ARBS were consistently enriched in tumor relative to normal (T-ARBS) and 2,690 were enriched in normal relative to tumor (N-ARBS). DNA binding motif analysis showed that AR itself is the most significantly enriched motif in N-ARBS, while FOXA1, and HOXB13 and AR were most significantly enriched in T-ARBS (z-score < -15). HOXB13 ChIP and FOXA1 ChIP in VCaP cell line showed substantial overlap with T-ARBS (68% and 76% of T-ARBS, respectively) and their knockdown via shRNA adversely affects prostate cell line survival. We identified genes within 1 megabase of T-ARBS or N-ARBS that are differentially expressed in tumor and normal. Expression levels of these genes in large clinically annotated patient cohorts are highly associated with multiple clinical parameters, including tumor grade and development of metastasis. **Conclusions:** We performed the most comprehensive study of the AR cistrome in human tumor and normal prostate tissue. We demonstrate that the AR cistrome is dynamic and implicate HOXB13 and FOXA1 as factors that reprogram the AR during transformation. These findings attest to the power of performing epigenetic analysis in both normal and tumor human tissue.

**5019 Poster Highlights Session (Board #33), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Concordance of ETS fusion status of matched metastatic castration-resistant prostate cancer and primary prostate cancer: Data from NCI 9012, a randomized ETS fusion-stratified phase II trial.** *Presenting Author: Lakshmi Priya Kunju, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI*

**Background:** Fusions of androgen-regulated genes with ETS transcription family members have been reported in 50% of localized pPCa patients (pts), with *TMPRSS2-ERG* fusions being the most common. ETS fusion products functionally depend upon Poly (ADP-ribose) polymerase 1 (PARP1), and its inhibition is preferentially cytotoxic to ETS translocation positive disease in preclinical models. We hypothesized that targeting ETS gene fusions will improve response rate in pts with these molecular subtypes and in pts with ETS fusion positive tumors, targeting the promoter and transcription factor of ETS fusion is more effective than targeting a single aspect of the fusion. **Methods:** Eligible mCRPC pts undergo a metastatic site biopsy to determine ETS fusion status by immunohistochemistry (ERG), fluorescent in-situ hybridization and/or RNA in-situ hybridization (ETV1) and sequencing (ETV4). Pts are stratified by ETS status and randomized to abiraterone (ABI) +/- the PARP inhibitor veliparib. Soft tissue biopsies are done using 18-gauge needle: 1-cm core (≥ 6 specimens), 2-cm core (≥4 specimens). For bone biopsy: 2-8 cores. We report interim results on rates of positive biopsy, ETS status/type and concordance between primary PCa and metastasis. **Results:** To date, 86 pts (Caucasians: 80%, African Americans 14%) with a median age 70 years and a median PSA 36.3 ng/ml have been enrolled. Of the 86 pts, 1 had an unreachable bone lesion, 36 had soft tissue and 49 had bone biopsies; all soft tissue and 36/49 (73%) bone biopsies were evaluable for analysis (13 had no tumor), ETS fusion status is positive in 36% pts: ERG positive (31%), ETV1 positive (4%), ETV4 positive (1%). Concordance of ETS status between primary PCa and metastatic site was found in 30/31 pts (97 % [95% CI: 83-99.9%]. **Conclusions:** This trial represents one of the first prospective predictive biomarker-driven trials in mCRPC. Results indicate feasibility of real time biopsy (adequate tissue yield including from bone) and biomarker determination, and demonstrates significant concordance of ETS status between primary PCa and metastasis in the subset analyzed to date. Clinical trial information: NCT01576172.

**5020 Poster Highlights Session (Board #34), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Androgen receptor (AR) amplification in patients with metastatic castration-resistant prostate cancer (mCRPC) refractory to therapy with abiraterone acetate or enzalutamide: Preliminary results from the SU2C/PCF/AACR West Coast Prostate Cancer Dream Team (WCDT).** *Presenting Author: Eric Jay Small, University of California, San Francisco, San Francisco, CA*

**Background:** The mechanisms of resistance to androgen signaling inhibitors such as Abiraterone (Abi) or Enzalutamide (Enz) are poorly understood. AR amplification (AR+) has been observed in Abi/Enz naive mCRPC patients (pts), but its role in Abi/Enz resistant pts is not known. Progressive mCRPC has historically been challenging to biopsy and characterize on a molecular basis because of its bone tropism. As part of the WCDT project which aims to identify genetic pathways underlying primary and acquired resistance to Abi and Enz, AR+ was assessed in mCRPC biopsies. **Methods:** Following central radiologic review, eligible mCRPC pts underwent biopsy at one of 5 WCDT clinical sites, using a uniform biopsy protocol. Tissue was both frozen, and formalin fixed/paraffin embedded (FFPE). FFPE tissue underwent a CLIA-certified assessment of a mutational panel, IHC for PTEN, and fluorescence in situ hybridization (FISH) for AR+. **Results:** 60 of 300 planned mCRPC pts have undergone a metastasis biopsy. To date, 33 pts have had biopsies successfully evaluated by AR FISH, including 12 from bone, 11 from lymph nodes, 8 from liver and 2 from other soft tissues. Of 16 Abi and Enz naive pts, 13 (81%) were AR+. By contrast, only 1/11 Abi resistant pts (9%) was AR+. 4/6 Enz resistant pts (67%) were AR+. Of 6 AR+ patients that went on to receive Abi or Enz, 3 (50%) had a response (PCWG2 criteria), whereas of 5 pts without AR+ who went on to receive Abi/Enz, just 1 (20%) had a response. **Conclusions:** AR amplification can be evaluated by FISH in small biopsies of mCRPC, including bone, and it was observed in 18/33 samples (55%). AR+ was common in mCRPC patients prior to therapy with Abi or Enz (81%). However, once resistance developed, Abi resistant pts had a far lower likelihood of AR+ (9%) than Enz resistant pts (67%). These data support the hypothesis that treatment with Abiraterone selects for non-AR amplified cells, whereas Enzalutamide does not. In this relatively small cohort, mCRPC pts with AR+ are more likely to respond to subsequent AR targeted therapeutics than pts without AR+.

**5021 Poster Highlights Session (Board #35), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Genomic analysis of circulating tumor DNA (ctDNA) in plasma of metastatic castration-resistant prostate cancer (mCRPC) patients (pts) treated with abiraterone acetate (abi) and enzalutamide (enza).** *Presenting Author: Arun Azad, British Columbia Cancer Agency, Vancouver, BC, Canada*

**Background:** CollectingctDNA represents a promising and minimally invasive approach for profiling the cancer genome of mCRPC pts, which may reveal key resistance mechanisms to agents such as abi and enza. **Methods:** Plasma was collected from 51 mCRPC pts at cessation of abi (n=26), enza (n=17) or other agents (n=8) due to any of biochemical, objective or clinical progression. DNA was extracted and subjected to array Comparative Genomic Hybridization (aCGH) for chromosome copy number analysis and next generation sequencing of exon 8 of the androgen receptor (AR) ligand-binding domain (LBD). **Results:** Sufficient DNA was available for aCGH in 48 of 51 pts (94%). 8p loss, 8q gain and AR gain were seen in 29% (14/48), 40% (19/48) and 54% (26/48) of pts respectively, with AR amplification status being concordant between ctDNA and fluorescence in situ hybridization (FISH) of concurrent metastatic tumour biopsies in 3 of 4 pts. Other copy number changes detected included high CCND1 and CCNE1 gain (4% each). Correlation of clinical and genomic data showed that AR amplification was significantly more frequent in pts progressing on enza compared to those progressing on abi (76% vs. 39%, p=0.027; Chi-square). In 26 pts switched onto enza after ceasing abi/other agents, those with AR amplification at initiation of enza were significantly more likely to have enza-refractory disease (i.e. no PSA decline on treatment) compared to pts without AR amplification (60% vs. 19%, p=0.046; Chi-square). AR sequencing in 29 pts detected several high frequency mutations including T877A and F876L in 41% (12/29) and 10% (3/29) of pts respectively. The F876L mutation, linked with resistance to enza pre-clinically, was detected in two enza-naïve pts, both of whom progressed within 3 months on subsequent enza therapy. **Conclusions:** Genomic analysis of ctDNA from mCRPC pts identified key aberrations that may be associated with therapeutic resistance including AR amplification and the F876L AR mutation. Our data illustrate the potential utility of profiling ctDNA to characterize the genomic landscape of mCRPC.

**5022 Poster Highlights Session (Board #36), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**A randomized, open label, multicenter, phase 3, 2-arm study of androgen deprivation with leuprolide (L), ± docetaxel (D) for clinically asymptomatic prostate cancer (PC) subjects with a rising PSA following definitive local therapy: Safety results.** *Presenting Author: Michael J. Morris, Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** The optimal approach to PC patients (pts) who biochemically relapse following a radical prostatectomy (RP) is not known. Pts with a rapidly rising PSA are at high risk of early metastasis and death. We conducted a phase III study in such pts to determine the clinical benefit of adding chemotherapy to early hormonal therapy (ADT). All pts have been treated. Here we report the safety results. **Methods:** Pts with PC who underwent a RP ± salvage RT and developed a rising PSA with a doubling time ≤ 9 months (mo) and no evidence of metastasis were eligible. PSA ≥ 1 ng/mL and testosterone (T) ≥ 100 ng/dl were required. Prior ADT ≤ 6 mo was allowed. Pts were randomized (1:1) to receive L 22.5 mg q3 mo x 18 mo, bicalutamide 50 mg x 30 days, with (Arm A) or without (Arm B) D 75 mg/m2 q3 weeks x 10 cycles. The primary endpoint was PFS at 18 mo post treatment (tx), with T recovery > 50 ng/dl. A sample size of 412 was calculated to detect a HR of 1.6 with 90% power. **Results:** 400 pts received tx (Arm A = 196, Arm B = 204) and 352 pts completed tx (Arm A = 170, Arm B = 182). 87% of pts treated in Arm A and 89% of pts treated in Arm B completed tx. Pts in Arm A received a mean of 9 cycles of D (range: 1-10), with 79.1% receiving all cycles. Pt compliance for L and bicalutamide was 100%. A greater % of Arm A pts experienced tx-related adverse events (AEs) (93.9 vs. 66.7%), AEs ≥ Gr 3 (48 vs. 10.8%), and serious AEs (25 vs. 9.8%). Most common AEs in Arm A were alopecia (Gr 1-2), fatigue, hot flush, edema, and diarrhea (Gr 1-4), and in Arm B were hot flush (Gr 1-4) and fatigue (Gr 1-2). Most common Gr ≥ 3 AEs in Arm A were neutropenia (15.8%), febrile neutropenia (6.6%), fatigue (4.6%), hyperglycemia (2.6%), and peripheral neuropathy (2.0%). In Arm B, no AE of Gr ≥ 3 occurred in more than 1 pt. **Conclusions:** ADT for 18 mo ± D for 10 cycles is feasible when given to pre-metastatic castration-sensitive PC pts. As expected, tx in Arm A was concordant with the known D safety profile. Collection of data for analysis of the primary endpoint is ongoing. Clinical trial information: NCT01813370.

**5023 Poster Highlights Session (Board #37), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**A phase 2 trial of prostate-specific membrane antigen antibody drug conjugate (PSMA ADC) in taxane-refractory metastatic castration-resistant prostate cancer (mCRPC).** *Presenting Author: Daniel Peter Petrylak, Yale University Medical Center, New Haven, CT*

**Background:** PSMA expression on prostate cancer cells provides a rationale for ADC therapy. PSMA is a clinically validated target. PSMA ADC is a fully human antibody to PSMA linked to the microtubule disrupting agent MMAE. It induces cell cycle arrest and apoptosis specifically in PSMA-positive cells. We have completed enrollment in a multicenter phase 2 trial of PSMA ADC in mCRPC pts progressing after taxane and antiandrogen. **Methods:** Pts with progressive mCRPC following taxane and abiraterone (ABI) and/or enzalutamide (ENZ) regimens and ECOG PS 0, 1 or 2 were eligible. PSMA ADC was administered Q3 wk IV for up to 8 cycles. Safety, tumor response by PSA, circulating tumor cells (CTC), imaging, biomarkers and clinical progression were assessed. Dosing was initiated at 2.5 mg/kg and adjusted for tolerability. **Results:** 34 pts received PSMA ADC at 2.5 mg/kg. Due to neutropenia, 49 pts subsequently received 2.3 mg/kg. 39% had both docetaxel and cabazitaxel (CAB); and 58% had both ABI and ENZ. 30% had visceral or soft tissue metastases. Duration of therapy on 2.3 mg/kg was longer than on 2.5 mg/kg. Any related adverse event (AE) grade ≥3 was 37% (2.3) and 59% (2.5 mg/kg). Related, grade 3/4 AEs occurring in ≥10% were fatigue, neutropenia and decreased electrolytes (16% vs 15%, 6% vs 18%, and 8% vs 21% at 2.3 and 2.5 mg/kg, respectively). 2 pts at 2.5 mg/kg died of sepsis. PSA decline of ≥30% was noted in 36% (2.3) and 16% (2.5 mg/kg), and CTC decline of ≥50% was noted in 74% pts in both 2.3 and 2.5 mg/kg. CTC conversion from ≥5 to <5 cells/7.5 ml blood occurred in 48% (2.3) and 50% (2.5 mg/kg). PSA and CTC responses were associated with higher PSMA+CTC and PSA responses with lower neuroendocrine markers. Stable disease was seen in 80% of RECIST evaluable pts (n=15). Pts with prior CAB had lower CTC responses. Responses in pts with prior ABI did not differ from pts with prior ENZ. **Conclusions:** PSMA ADC at 2.3 mg/kg was active and well tolerated in heavily pretreated mCRPC pts. Updated safety and secondary efficacy endpoints from the 2.3 and 2.5 mg/kg cohorts will be presented. These data warrant further evaluation in this population. A taxane-naïve cohort is ongoing. Clinical trial information: NCT02020135.

**5024 Poster Highlights Session (Board #38), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**A phase I study of DSTP3086S, an antibody-drug conjugate (ADC) targeting STEAP-1, in patients (pts) with metastatic castration-resistant prostate cancer (CRPC).** *Presenting Author: Daniel Costin Danila, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

**Background:** Six-transmembrane epithelial antigen of the prostate-1 (STEAP1) protein is a cell-surface protein frequently overexpressed in prostate cancer. The ADC DSTP3086S contains the humanized IgG1 anti-STEAP1 monoclonal antibody linked to the potent anti-mitotic agent MMAE. **Methods:** This study evaluated safety and activity of DSTP3086S (0.3-2.8 mg/kg IV) given every 3 weeks (q3w) to pts with CRPC. A traditional 3+3 design was used to determine maximum-tolerated dose, followed by cohort expansion at the recommended Phase II dose (RP2D). Clinical activity was evaluated per PCWG2 criteria. **Results:** As of 18 Dec 2013, 59 pts were enrolled with a median age of 68 (43-87), all ECOG PS 0-1, and with a median of 6 prior systemic regimens (71% received prior taxanes). Pts received a median of 3 doses (range 1-14) of DSTP3086S, with 14 pts (24%) still ongoing. Two patients in dose escalation (1 at 2.25 mg/kg and 1 at 2.8 mg/kg) had dose limiting G3 transaminitis. Cohort expansion started at 2.8 mg/kg (n=10). Frequent dose reductions at 2.8mg/kg led to testing 2.4 mg/kg (n=22) which had increased tolerability. The most common related AEs (>10%) across all doses were fatigue, nausea, constipation, peripheral neuropathy, anorexia, vomiting, diarrhea, and abdominal pain. There were 9 treatment-related serious AEs in 6 pts, including DVT (G3) at 1.5 mg/kg, sepsis (G5) and GI hemorrhage (G3) at 2.25 mg/kg, bacteremia (G4), neutropenia (G3 and G4), presyncope (G2), and constipation (G2) at 2.4 mg/kg; and abdominal pain (G3) at 2.8 mg/kg. Approximately 60% of archival tumor tissues from Ph1 dose escalation patients were STEAP1 IHC high (2+/3+), while STEAP1 IHC high was required in the expansion cohort. PSA declines by >50% were obtained in 1/7 at 2.25 mg/kg, 3/21 at 2.4 mg/kg, and 5/16 at 2.8 mg/kg; 2 pts at 2.8 mg/kg also had RECIST responses. CTC conversions from unfavorable to favorable (<5) occurred in 1/5 at 2.25 mg/kg, 3/5 at 2.4 mg/kg, and 7/10 at 2.8 mg/kg. **Conclusions:** DSTP3086S at dose levels between 2.25 and 2.8 mg/kg demonstrated anti-tumor activity and the RP2D is 2.4 mg/kg q3w. Clinical trial information: NCT01283373.

**5025 Poster Highlights Session (Board #40), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Phase 1b study of abiraterone acetate (AA) and docetaxel (D) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC).** *Presenting Author: Scott T. Tagawa, Weill Cornell Medical College, New York, NY*

**Background:** Coadministration of D and AA may be beneficial due to complementary mechanisms of action. A phase 1b safety and pharmacokinetic (PK) study assessed the safety and efficacy of D + AA. **Methods:** 3 cohorts (C) of chemo-naive mCRPC pts received escalating doses of D + AA. Primary end point: proportion of pts with dose-limiting toxicity (DLT) between Wks 2 and 7, defined as grade (Gr) ≥ 3 non-heme toxicity, Gr 4 neutropenia > 7 days (or febrile neutropenia), Gr 4 thrombocytopenia, or other intolerable toxicity. Pts could continue AA after discontinuing D. D + AA was deemed safe if ≤ 2 pts/C experienced DLT; the maximum tolerated dose (MTD) was the highest safe combination of D + AA. PSA changes and PK parameters were evaluated. **Results:** 22 pts were treated; 18 pts were evaluable for DLT assessment. The combination dose received by C3 (1 pt had DLT) was deemed the MTD. With treatment ongoing, 90% and 70% of pts had ≥ 50% and ≥ 90% PSA decline from baseline, respectively (Table). With median follow-up of 11.8 months, there were 5 PSA progression events. PK parameters were comparable for both abiraterone and D alone and in combination. **Conclusions:** D + AA was well tolerated at full doses of each drug. PK was comparable when D and AA were given alone and in combination. The efficacy signal may justify further study. Clinical trial information: NCT01400555.

| Baseline characteristics | C1<br>D 60 mg/m$^2$ + AA 500 mg[a]<br>n = 7 | C2<br>D 75 mg/m$^2$ + AA 500 mg[a]<br>n = 8 | C3<br>D 75 mg/m$^2$ + AA 1000 mg[a]<br>n = 7 |
|---|---|---|---|
| **ECOG PS, n (%)** | | | |
| **0** | 4 (57) | 2 (25) | 2 (29) |
| **1** | 2 (29) | 6 (75) | 5 (71) |
| **2** | 1 (14) | 0 | 0 |
| **PSA, μg/L, median (range)** | 85.2 (5.9-234.3) | 33 (4.8-62.6) | 10 (2-504.8) |
| **LDH, U/L, median (range)** | 187 (139-463) | 207.5 (134-344) | 237 (136-768) |
| **ALP, U/L, median (range)** | 97 (76-513) | 91 (64-392) | 124 (42-242) |
| **Hemoglobin, g/dL, median (range)** | 121 (113-144) | 120 (110-153) | 129 (101-136) |
| **Lesions, n (%)** | | | |
| **Bone** | 7 (100) | 7 (88) | 5 (71) |
| **Measurable target** | 2 (29) | 4 (50) | 4 (57) |
| **Nontarget** | 4 (57) | 4 (50) | 2 (29) |
| **Efficacy outcomes** | | n = 20 | |
| **PSA decline[b], n (%)** | | | |
| **≥ 90%** | | 14 (70) | |
| **≥ 50%** | | 18 (90) | |
| **Safety outcomes** | n = 6 | n = 6 | n = 6 |
| **DLT, n (%)** | | | |
| **Syncope** | 1 (17) | 0 | 0 |
| **Hypertension** | 1 (17) | 0 | 0 |
| **Neutropenia** | 0 | 1 (17) | 0 |
| **Hematuria[c]** | 0 | 0 | 1 (17) |

[a]AA and prednisone taken daily. D administered once q3wk; [b]C3 data is limited; [c]Pt had elective cystolitholapaxy for preexisting hematuria.

**5026 Poster Highlights Session (Board #41), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**ARN-509 in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) with and without prior abiraterone acetate (AA) treatment.** *Presenting Author: Dana E. Rathkopf, Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

**Background:** ARN-509 is a second-generation antiandrogen that selectively binds to the ligand-binding domain of the androgen receptor, blocks its nuclear translocation and impairs DNA binding to androgen response elements. ARN-509-001 is a phase 1/2 study evaluating ARN-509 activity in 3 cohorts: 1) nonmetastatic CRPC; 2) mCRPC; and 3) mCRPC post-abiraterone acetate (AA). Phase 2 results for the mCRPC cohorts as of July 2013 are presented. **Methods:** All pts with mCRPC had progressive disease based on rising prostate-specific antigen (PSA) and/or imaging. Prior chemotherapy for mCRPC was an exclusion. The post-AA cohort required treatment with AA for ≥ 6 mos. All pts received 240 mg/d ARN-509, the phase 2 recommended dose (Rathkopf et al. J Clin Oncol. 2013). The primary end point was PSA response at 12 wks, using Prostate Cancer Working Group 2 (PCWG2) criteria. Secondary end points were safety, time to PSA progression, objective response rate, and progression-free survival (PFS). PSA was assessed every 4 wks and tumor imaging was performed every 12 wks. **Results:** Enrolled pts included 25 mCRPC and 21 post-AA mCRPC pts with median age of 68 yrs (range 48-91). At baseline 57% had ECOG score 0; 52% had Gleason score ≥ 8; median PSA 14.7 (mCRPC) and 58.4 (post-AA) ng/mL. Median duration on ARN-509 treatment is 9.2 mos (range 1.8-25.8). 31 pts have discontinued the study due to disease progression (n = 18), adverse events (n = 5), consent withdrawal (n = 4), or other reasons (n = 4). The most common treatment-related adverse events were fatigue (n = 21), nausea (n = 13), diarrhea (n = 10) and abdominal pain (n = 8). **Conclusions:** ARN-509 is safe and well tolerated, with evidence of activity in chemo-naïve mCRPC, including in 24% of pts who have received prior AA. Clinical trial information: NCT01171898.

| | mCRPC | mCRPC post-AA |
|---|---|---|
| **N** | 25 | 21 |
| **Efficacy measures** | | |
| **PSA response[a], n (%)** | | |
| **12 wks** | 22 (88) | 5 (24) |
| **24 wks** | 19 (76) | 2 (10) |
| **36 wks** | 17 (68) | 0 |
| **Median time to PSA progression, mos (95% CI)** | 16.3 (8.3, NE) | 3.7 (2.8, 7.1) |
| **Pts with measurable disease, N** | 8 | 11 |
| **Partial response[b], n (%)** | 4 (50) | 0 |
| **Stable disease[b], n (%)** | 2 (25) | 4 (36) |
| **Median PFS, mos (95% CI)** | 19.2 (NE, NE) | 8.3 (4.2, NE) |

NE, not estimable. [a]Per PCWG2, % of pts with ≥ 50% decline in PSA from baseline. [b]Objective response.

**5027^ Poster Highlights Session (Board #42), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Phase 1 dose-finding study of cabozantinib (cabo) plus abiraterone (abi) combination therapy in castration resistant prostate cancer (CRPC): An investigator-sponsored study.** *Presenting Author: Christopher Sweeney, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Abi (CYP17A1 and lyase inhibitor) and cabo (multi-tyrosine kinase inhibitor including MET and VEGFRs) have complementary mechanisms of action. Both have single agent activity in CRPC. Preclinical in vivo work with LAPC4-CR (castration and abi resistant cell line) has shown the combination has enhanced activity. **Methods:** A phase 1 dose escalation trial using a 3 + 3 design with a fixed dose of abi 1,000 mg daily and prednisone 5mg BID with escalating daily doses of cabo (20mg, 40mg, 60mg) in pts with progressive metastatic CRPC (pre or post chemo). Cycles were 28 days. The dose expansion cohorts alternated between the 20 and 40mg doses. **Results:** 21 patients were enrolled. Median age was 60 yrs. All had ECOG PS 0 or 1. 6 pts had prior docetaxel for CRPC. 3 patients were enrolled at each dose level. No DLTs were observed in the first 4 week cycle. The 60 mg cabo cohort had grd 2 adverse events (AEs) of myalgias (2), fatigue (2) and DVT (1) in cycles 2 and 3 necessitating a dose reduction to 40 mg (no change to abi). Due to a preferable tolerability profile over the 60mg dose, the 20mg and 40mg cohorts were expanded (9 pts each). See Table for key activity data. At time of report, 9 patients had >8 mos of combination therapy. The most common grd 1/2 AEs (n≥2) in the 20mg cohort were myalgias (5), nausea (2) , fatigue (3), edema (2), and hypertension (htn, 2). At the 40mg dose, grd 1/2 AEs (n≥2) included nausea (2), diarrhea (2), fatigue (4), mylagias (2), hand-foot syndrome (2), and htn (2). 6 pts had cabo-related grd 3 AEs (20mg: diarrhea, anemia, increased AST/ALT; 40mg: HTN, low phosphate, increased lipase). Five 40mg cohort pts required dose reductions but none were needed in the 20mg cohort. **Conclusions:** Cabo at either 20mg or 40 mg is tolerable when combined with standard dose abi/prednisone. The long term tolerability and preliminary efficacy data support the investigation of this combination for further clinical development in metastatic CRPC. A phase 2 study is underway. Clinical trial information: NCT01574937.

| | 20 mg N=9 | 40 mg N=9 |
|---|---|---|
| **Median baseline PSA** | 21 | 14 |
| **PSA decline** | (n=8) | (n=8) |
| **> 90%** | 50% | 13% |
| **> 75%** | 63% | 13% |
| **Median time on therapy** | (n=9) | (n=9) |
| **Months (min, max)** | 7.3 (0.6+,20.3+) | 5.3 (0.5, 15.5+) |
| **- 13 pts still on combination** | | |

**5028 Poster Highlights Session (Board #43), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Everolimus plus bicalutamide in men with castration-resistant prostate cancer (CRPC): Final results of a phase II trial.** *Presenting Author: Chong-xian Pan, VA Northern California Health Care System, Mather, CA*

**Background:** We previously reported that the mammalian target of rapamycin (mTOR) pathway was upregulated in CRPC, and that inhibition of mTOR was ineffective in killing prostate cancer cells likely due to its effect on upregulating the androgen receptor (AR) pathway (Wang et al. Oncogene. 2008; 27:7106). We hypothesized that simultaneous blockade of both AR and mTOR pathways would be effective against CRPC. **Methods:** Eligible patients (pts) must have progressive CRPC with serum testosterone <50 ng/dl. No prior bicalutamide (except to prevent flare) or everolimus was allowed. Treatment regimen included bicalutamide 50 mg and everolimus 10 mg po, both qd. Primary endpoint was prostate specific antigen (PSA) response (≥30% reduction). Sample size of 23 pts would have the power of 0.8 and $\alpha$ error of 0.05 (one-sided) if the combination had a PSA response rate of 50% vs. a historical rate of 25% with bicalutamide alone. Molecular correlative studies were performed. **Results:** Twenty four pts were enrolled. Mean age was 71.1 years (range: 53.0-87.0). Mean PSA at the study entry was 43.4 ng/dl (2.5-556.9). Mean number of treatment cycles was 7.9 (1.0-23.0). Of 24 pts, 18 had a PSA response (75%, 95% CI: 0.53-0.90). Of these, 15 had a PSA decrease of ≥ 50% (62.5%, 95% CI 0.41-0.81). Median overall survival was 28 months (95% CI 14.1-42.7). Fourteen pts (54%, 95% CI 0.37, 0.78) developed Grade 3 (13 pts) or Grade 4 (1 pt with sepsis) adverse events attributable to the treatment. Serum ErbB3 increased by 5.16 folds in non-responders vs a 60% decrease in responders ($p<0.001$). **Conclusions:** The combination of bicalutamide and everolimus has very encouraging efficacy in men with bicalutamide-naïve CRPC. These results are contrary to the results of a similar phase II trial that predominantly enrolled pts previously treated with bicalutamide, and reported limited efficacy for this doublet (Nakabyashi, BJU Intl 2012; 110:1729). A substantial number of pts experienced everolimus-related toxicity. ERBB3 appears to be a candidate marker of response to therapy and deserves further study. A randomized Phase III trial of bicalutamide +/- everolimus in bicalutamide-naïve CRPC is warranted. Clinical trial information: NCT00814788.

**5029 Poster Highlights Session (Board #44), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Galeterone in men with CRPC: Results in four distinct patient populations from the ARMOR2 study.** *Presenting Author: Robert B. Montgomery, University of Washington, Seattle, WA*

**Background:** Galeterone is a 1st in class oral small molecule that disrupts androgen receptor (AR) signaling via multi-targeted mechanism of action (1) selective inhibition of CYP17 lyase; (2) competitive antagonism of androgen binding to AR; and (3) degrading of AR protein. CYP17 enzyme inhibition (abiraterone) and AR antagonism (enzalutamide) separately have shown significant activity in metastatic castrate resistant prostate cancer (mCRPC) and considered standard treatment for these pts. Galeterone is a single molecule that has the potential advantage to target both mechanisms. **Methods:** ARMOR2 (*NCT# 01709734*) is a 2 Pt Phase 2 study designed to confirm dose of reformulated galeterone (spray dry dispersion; SDD) (Pt 1) and assess the safety and efficacy of the dose, 2550 mg QD for 12 wks, in 4 distinct CRPC pt cohorts; non-metastatic tx naïve (M0 TN, n= 7, median PSA=15.6 ng/dL, median PSA DT=2.30 mo), metastatic tx naïve (M1 TN, n=24, median PSA = 22.9 ng/dL, median PSA DT=2.3 mo), abiraterone refractory (Abi-R, n=11, median PSA=35.8 ng/dL, median PSA DT=1.57 mo) and enzalutamide refractory (Enza-R, n=2, median PSA = 72.85 ng/dL, median PSA DT=1.97 mo). This abstract presents interim results of the 2550 mg dose for pts treated in both Pt 1 and 2. **Results:** Response was seen at 2550 mg in all tx groups, including decreases in PSA. In the most mature dataset of 24 M1 TN pts, PSA decreases of 30% (92%), and 50% (83%) were reached. Data on the M1 group showed encouraging preliminary objective responses (ORR) in 7 of 8 (86%) evaluable pts at 3 months. Safety: Drug was well tolerated by all tx groups. 94% of all adverse events (AE) were gr1 or 2 in severity. Most common < gr 2 AEs were GI (nausea, diarrhea), fatigue and pruritis with no mineralocorticoid excess (ME) or seizures. **Conclusions:** SDD Galeterone has shown significant biochemical activity and preliminary clinical activity and is well tolerated with no ME or seizures. These data support continued testing of this unique compound in pts with prostate cancer. Clinical trial information: NCT01709734.

**PSA response by tx group.**

| Tx Group | N | Pts with >30% n (%) | Pts with > 50% n (%) |
|---|---|---|---|
| M0 TN | 6* | 5 (83) | 4 (67) |
| M1 TN | 24* | 22 (92) | 20 (83) |
| Abi-R | 5** | 2 (40) | 0 (0) |
| Enza-R | 2 | NA | NA |

*N= # of pts completing 12 wks, reached PSA 50 or terminated early. **N= # of pts completing 12 wks.

**5030 Poster Highlights Session (Board #45), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Primary outcomes of the placebo-controlled phase 2 study PERSEUS (NCT01360840) investigating two dose regimens of abituzumab (DI17E6, EMD 525797) in the treatment of chemotherapy-naive patients (pts) with asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer (mCRPC).** *Presenting Author: Maha Hussain, University of Michigan, Comprehensive Cancer Center, Ann Arbor, MI*

**Background:** The humanized monoclonal IgG2 antibody abituzumab inhibits $\alpha$v integrins expressed on CRPC cells, tumor vessels, and osteoclasts involved in bone (B) metastasis. It showed antitumor effects in in vivo CRPC models and was well tolerated in a phase 1 study in mCRPC pts previously treated with docetaxel. **Methods:** PERSEUS is an exploratory double-blind trial with 180 pts randomized 1:1:1 to placebo, abituzumab 750, or 1,500 mg i.v. given every 3 weeks in addition to standard of care. Eligible pts had radiologic disease progression (rPD) of B lesions <28 days prior to randomization. Pts were treated until rPD in either B or soft tissue (ST) lesions, skeletal event, death, or unacceptable toxicity. Primary endpoint was progression-free survival (PFS). In addition, overall response (OR, RECIST 1.0) and safety were assessed. **Results:** Baseline characteristics were balanced across arms. In pts treated with placebo, abituzumab 750, and 1500 mg, median PFS (ITT) was 3.3 (95% CI: 2.8, 4.8), 3.4 (95% CI: 2.8, 5.6; HR = 0.89 [95% CI: 0.57, 1.39]), and 4.3 months (95% CI: 2.8, 6.6; HR = 0.81 [95% CI: 0.52, 1.26]), respectively. Progression occurred in 72, 68, and 65% of pts, respectively, incl. B lesion progression observed in 42% of pts in the control arm and in 23% of pts in each abituzumab arm. Of 74 OR-evaluable pts with confirmed ST lesions at baseline, 2 achieved partial responses (placebo: 1/28 pts; abituzumab 1500 mg: 1/24 pts). Treatment-emergent adverse events (TEAEs) occurred in 92, 85, and 88% of pts in the placebo, abituzumab 750, and 1500 mg arms, respectively, incl. serious TEAEs in 27, 22, and 23% and TEAEs with fatal outcomes in 3, 3, and 5% (treatment-related AE: 1 pt in the placebo arm). **Conclusions:** Median PFS with abituzumab 1500 mg was above the duration observed with 750 mg or placebo. Compared with placebo, pts receiving abituzumab experienced B progression less frequently. Considering these favorable trends, further investigation of abituzumab efficacy is needed. Its previously observed safety profile was confirmed. Clinical trial information: NCT01360840.

**5031 Poster Highlights Session (Board #46), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Adjuvant radiation, androgen deprivation, and docetaxel for high-risk prostate cancer post-prostatectomy: Results of RTOG 0621.** *Presenting Author: Mark Hurwitz, Department of Radiation Oncology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA*

**Background:** Phase III trials have shown benefit in progression-free survival and in some cases overall survival with adjuvant radiation therapy (ART) in men with adverse pathologic findings at radical prostatectomy (RP). Despite ART, a high-risk group of patients has been defined with 50% risk of progression at 3 years, a risk factor for prostate cancer specific mortality. RTOG 0621 is a single-arm phase II trial that assessed whether addition of androgen deprivation (ADT) and docetaxel to ART would increase freedom from progression (FFP) at 3 years from 50% to ≥ 70% in these high-risk patients. **Methods:** Eligible subjects had prostatic adenocarcinoma who underwent RP with PSA nadir > 0.2 and Gleason score ≥ 7 or PSA nadir ≤ 0.2 with Gleason score ≥ 8 and ≥ pT3. Subjects received 6 months of ADT + RT to the pelvis with prostatic fossa boost to 66.6 Gy followed in one month with 6 cycles of docetaxel 75 mg/m$^2$ every 21 days. The primary objective was to assess whether addition of ADT and docetaxel to ART results in FFP of ≥70% as defined as PSA < 0.4 ng/ml, and no clinical failure or death from any cause at 3 years. Multivariate logistic regression was used to model association of factors with the occurrence of FFP. Odds ratios and respective 95% confidence intervals were computed. **Results:** 76 patients with median age 62 meeting eligibility criteria were enrolled on the study. 3 year FFP was 71%, (95% CI:61-81%), p-value<0.001. In univariate and multivariate models, only post-RP PSA was statistically significantly associated with FFP. Two deaths occurred of which only 1 was related to prostate cancer. The most common significant chemotherapy side effects were peripheral neuropathy (12 grade 2 and 1 grade 3) and febrile neutropenia in 3 patients. Six subjects (8%) experienced late grade 3-4 treatment related toxicities. **Conclusions:** Addition of ADT and docetaxel to ART for men as high risk of failure despite ART alone following prostatectomy resulted in a significant improvement in FFP as compared to historical controls. Phase III trials assessing chemotherapy in this high-risk population are warranted. This work was supported by RTOG grant U10 CA21661 and CCOP grant U10 CA37422 from the NCI and Sanofi-Aventis. Clinical trial information: NCT00528866.

**5032 Poster Highlights Session (Board #47), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**First double-blind placebo-controlled, multicenter, randomized trial of stabilized natural sulforaphane in men with rising PSA following radical prostatectomy.** *Presenting Author: Bernard G Cipolla, CH Privé Saint Grégoire, Saint Gregoire, France*

**Background:** Sulforaphane (SF) is a natural compound present in cruciferous vegetables. It has demonstrated molecular targets. Its main problem is its instability in its free form. We have assessed the efficacy of a natural, stabilized SF in recurrent prostate cancer patients (pts) after radical prostatectomy (RP) ± adjuvant or salvage external radiotherapy (RT). **Methods:** In this multicenter trial, 81 pts, mean age 69 ± 6 years with a rising prostate-specific antigen (PSA) >0.2 ng/ml (and <5 ng/ml) after RP ± RT, without metastasis, a Gleason score ≤7, a PSA doubling time (PSADT) >5 and <36 months (M) participated in a double-blind, randomized, placebo (P) controlled study. Treatment consisted in 60 mg daily SF during six-months (M0-M6). A two months washout period (M6 to M8) followed. Clinical and biological assessments were performed at M0, M1, M3, M6 and M8. The study was designed to detect a 0.012 log(ng/ml)/month decrease in Log PSA slope in the SF arm compared to P. **Results:** Baseline parameters did not differ between the 2 groups considering pathological stage and Gleason score, PSA, PSADT, Log PSA slope and serum testosterone. Three non-complying pts were excluded. The ITT population was 78 patients (40 P and 38 SF). Log PSA slope in the SF group (0.0298±0.0096) was significantly lower between M0 and M6 (p=0.036, 0.0285 log(ng/ml)/month =-49%) than in the P group (0.0583±0.0093) and most particularly (-83%) between M3 and M6 (p=0.011). The difference in PSA levels observed at M6 between the two groups was preserved during the washout period. A 78 % PSA DT increase was observed in the SF group (21.9 vs 12.1 months) compared to P. The mean change in PSA levels between M6 and M0 was significantly lower in the SF group compared to P (0.099±0.341 vs 0.620±1.417 ng/ml; p=0.03). Testosterone levels did not differ between the two groups. Observance was excellent (96% in each group). Safety was very good with a few more GI tract side effects in the SF arm (17 vs 10). **Conclusions:** The stabilized SF used in this study was shown to significantly delay PSA progression after RP ± RT. These encouraging results both on efficacy and safety indicate more extensive studies of this SF. Clinical trial information: ID-RCB: 2011- A00347-34.

**5033 Poster Highlights Session (Board #48), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**15-year survival outcomes following primary androgen deprivation therapy for localized prostate cancer.** *Presenting Author: Grace L. Lu-Yao, Rutgers Cancer Institute of New Jersey, Robert Wood Johnson Medical School, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ*

**Background:** Primary androgen deprivation therapy (ADT) for early stage prostate cancer has been widely utilized for localized prostate cancer, especially among older patients, despite a lack of data supporting its use. This study presents long-term survival outcomes following primary ADT in older men with localized (T1/T2) prostate cancer as a follow up to our prior study. **Methods:** Instrumental variable analysis was used to assess the impact of primary ADT in a population-based cohort consisting of residents in areas covered by the Surveillance, Epidemiology, and End Results (SEER) Program. **Results:** The cohort consisted of 66,717 patients aged ≥66 years diagnosed in 1992-2009 who received no definitive local therapy within 180 days of prostate cancer diagnosis. After a median follow-up of 9.2 years, primary ADT was not associated with improved 15-year overall or prostate cancer-specific survival. Among patients with moderately differentiated cancers, 15-year overall survival was 20.0% in high-use regions vs. 20.8% in low-use regions (difference 95% CI -2.2% to 0.4%), and 15-year prostate cancer survival was 90.6% in both high- and low- use regions (difference 95% CI -1.1% to 1.2%). Among patients with poorly differentiated cancers, the 15-year cancer-specific survival was 78.6% in high-use regions versus 78.5%, in low-use regions (difference 95% CI -1.8% to 2.4%), and 15-year overall survival was 8.6% in high-use regions vs. 9.2% in low-use regions (difference 95% CI -1.5% to 0.4%). **Conclusions:** Primary ADT is not associated with improved long-term overall or disease-specific survival for localized prostate cancer.

**5034 Poster Highlights Session (Board #49), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**The risk of second malignancies after treatment for localized prostate cancer.** *Presenting Author: Elizabeth J. Davis, University of Michigan Medical School, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI*

**Background:** Prostate cancer has an excellent prognosis with a 10-year relative survival of 99.7%. The long survival for this common cancer raises questions about the risk of second primary malignancies after initial therapy for localized disease. **Methods:** A population-based cohort of 441,504 men diagnosed with prostate cancer between 1992 and 2010 was identified from Surveillance, Epidemiology and End Results Program data (SEER13). Standardized incidence ratios (SIR) were calculated as an estimate of the risk of a second primary malignancy based on the incidence in the general population according to whether or not men received radiation therapy (external beam radiation therapy or EBRT) as their initial treatment for prostate cancer. Only new primary cancers that arose 10 years or more after prostate cancer treatment were considered. **Results:** Compared to men who were not treated with radiation, men treated with EBRT were significantly more likely than the general population to be diagnosed with rectal ($SIR_{radiation}$=1.70 versus $SIR_{noradiation}$=0.74, p <0.0001) and bladder cancer ($SIR_{radiation}$=1.42 versus $SIR_{noradiation}$=0.76; p<0.0001). Both groups were at reduced risk of second primary malignancy and second solid tumors overall, but the magnitude of the reduction was less among men who received radiation (e.g., for solid tumors SIR=0.72; 95% CI=0.69,0.76 for those treated with EBRT compared to SIR=0.51; 95% CI=0.49,0.52 for those not exposed to radiation). **Conclusions:** Men who receive ERBT for localized prostate cancer have a significantly increased risk of later diagnoses of bladder and rectal cancer. Although the absolute risk of developing these cancers is small, physicians should discuss this information with patients before decisions are made on primary treatment for localized prostate cancer.

**5036 Poster Highlights Session (Board #51), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**The natural history of progression to PSA recurrence and metastasis among at risk men following radical prostatectomy.** *Presenting Author: Ashley E. Ross, Brady Urological Institute, John Hopkins Medical Institute, Baltimore, MD*

**Background:** Active surveillance for low risk disease has been gaining acceptance with the aim of preferentially treating men with NCCN intermediate and high risk prostate cancer. Currently used outcome estimates however, were developed using cohorts, which included a high proportion of men with low or very low- risk disease. Here we describe the natural history of intermediate and high-risk prostate cancer treated only by radical prostatectomy (RP). **Methods:** Men who underwent RP in the PSA era, initially had undetectable PSAs after surgery, and received no post-RP therapy prior to metastasis were included (1,739 men). Biochemical recurrence (BCR) was defined by a PSA of ≥0.2 ng/ml and metastasis was diagnosed by axial imaging or bone scan. **Results:** Median follow up was 10 years and 17% developed BCR with a median time to BCR of 3 years (range 1-18). Of men with BCR, 41% developed metastasis (median time 3 years (range 0-11) after BCR). Median time from metastasis to death was 4 years (range 0-11). Men with metastasis had higher median CAPRA-S and Stephenson scores than those without metastatic progression (6 vs. 2 and 0.28 vs. 0.04, respectively, p<0.001 for both) but the range of scores was broad (1-12 vs. 0-10 and 0.02-0.95 vs. 0.01-0.71 respectively). Following BCR, the cumulative incidence of metastasis among intermediate and high-risk men was similar (p=0.57) as was the cumulative incidence of death after metastasis (p=0.69). The AUC for predicting metastasis after BCR was 0.67 for the Stephenson and 0.55 for CAPRA-S scores. **Conclusions:** As practice patterns shift towards the treatment of higher risk localized disease, point estimates for the time to BCR, metastatic progression, and death shorten accordingly. In addition, the predictive ability of clinicopathologic variables and nomograms is significantly diminished. This highlights the need for additional information (i.e. molecular markers) to help guide treatment decisions among at risk men following radical prostatectomy.

**5037 Poster Highlights Session (Board #52), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**A multicenter yearlong randomized controlled trial of different exercise modalities in prostate cancer survivors on androgen deprivation therapy.** *Presenting Author: Daniel Abido Galvao, Edith Cowan University, Perth, Australia*

**Background:** It is well recognized that androgen deprivation therapy (ADT) for prostate cancer is associated with a number of substantial adverse effects including a reduction in muscle mass and strength, increased fat mass and poorer physical function. Recently, undertaking purposeful physical exercise has been proposed as an effective strategy to counter many of these ADT-related adverse effects. The purpose of this multi-centre, year-long randomized controlled trial was to extend these findings by assessing the effects of two varying exercise regimens, one targeting the musculoskeletal system (impact loading + resistance training; ILRT) and the other the cardiovascular and muscular systems (aerobic + resistance training; ART), on body composition, lower body muscle strength and physical function in men currently undertaking ADT. **Methods:** One hundred and sixty three men aged 42-90 years with a BMI of 24.8 kg/m$^2$ completed baseline testing and were randomized to ILRT (n=58), ART (n=54) or delayed exercise (CON, n=51) for 12 months. Training was undertaken for ~1 hour twice weekly under supervision at a moderate-to-high intensity. Lean and fat mass were determined by DXA, muscle strength by the 1-RM test, and lower body physical function by a battery of tests (6-m walk, 6-m backwards walk, 400-m walk, chair rise, stair climb). **Results:** There were no differences among the groups for any variable at baseline. Between pre and post-intervention, lean mass increased in ILRT by 1.4 kg ($p<0.001$) and 0.6 kg ($p=0.030$) in ART with no change in CON. Fat mass also increased in ILRT and CON by1.1 kg ($p<0.001$) with no significant change in ART (0.6 kg, $p=0.156$). Upper and lower body muscle strength increased by 17-45% in ILRT which was greater than that in ART and CON ($p<0.001$). Compared to pre-intervention, ILRT and ART generally improved in most physical function tasks ($p<0.050$). **Conclusions:** The combination of impact loading and resistance training produced superior gains in lean mass and muscle strength compared to aerobic plus resistance exercise in prostate cancer survivors on ADT. Strategies to implement this novel training protocol are warranted. Clinical trial information: ACTRN12609000200280.

**5038 General Poster Session (Board #167), Mon, 1:15 PM-5:00 PM**

**Long-term versus short-term androgen deprivation combined with high-dose radiotherapy for intermediate and high-risk prostate cancer: A randomized controlled trial (DART01/05).** *Presenting Author: Almudena Zapatero, Department of Radiation Oncology, Hospital Universitario de la Princesa, Madrid, Spain*

**Background:** Androgen deprivation (AD) combined with radiotherapy (RT) is an established treatment for locally advanced prostate cancer (PCa). However, the timing and optimal duration of AD associated with dose escalation RT remains controversial. This trial was designed to determine whether long-term AD (LTAD) is superior to short-term AD (STAD) when combined with high-dose radiotherapy (HDRT). **Methods:** Between 2006 and 2010, 362 assessable patients were enrolled. Eligible patients had cT1c-T3aN0M0 adenocarcinoma of prostate with intermediate risk (IR) and high risk (HR) factors according to 2005 NCCN criteria and PSA less than 100 ng/ml. All patients received 4 months of neoadjuvant and concomitant AD (STAD) + HDRT (median RT dose 78 Gy) before randomization to adjuvant gosereline for two years (LTAD). Stratification was performed according to risk group (IR versus HR). Study endpoints included biochemical-disease free survival (bDFS), metastasis free survival (MFS) and overall survival (OS). **Results:** Three hundred and fifty two patients (STAD =177, LTAD=175) were eligible with 57 months median follow-up.There were188 HR patients (STAD = 97, LTAD = 91) and 164 IR patients (STAD = 80, LTAD = 84) ($p=0.669$). Twenty-three patients in the STAD group and 7 patients in the LTAD group had biochemical failure according to Phoenix Consensus definition ($p=0.003$). Median OS has not been reached. At 5 years bDFS was significantly improved in the LTAD group (95.4%, 95% CI: 93.2-97.6), compared to the STAD group (86.1%, 95% CI: 83.5-88.7). Five-year MFS was 85.5% (95% CI: 82.9-88.1) for STAD and 93.2% (95% CI: 91.0-95.4) for LTAD, and OS was 88.8% (95% CI: 86.3-91.3) for STAD and 94.0% (95% CI: 91.9-96.1) for LTAD. **Conclusions:** The results of the present study indicate that the combination of HDRT with LTAD is superior to HDRT plus STAD in terms of bDFS. Further follow-up is needed to confirm these data and to assess the effect on MFS, OS and CSS. Clinical trial information: 2005-000417-36.

**5039 General Poster Session (Board #168), Mon, 1:15 PM-5:00 PM**

**Activity of abiraterone acetate (AA) in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) previously treated with ketoconazole (keto): A prospective phase II study from the Prostate Cancer Clinical Trials Consortium.** *Presenting Author: Won Kim, University of California, San Francisco, San Francisco, CA*

**Background:** AA, like keto, inhibits CYP17, the rate-limiting enzyme in androgen synthesis. Since pts with prior keto were excluded from the pivotal phase III AA trials, the utility of AA following keto is not well understood. This prospective study evaluated the efficacy of AA in pts previously treated with keto. **Methods:** Pts with progressive mCRPC, prior keto ≥28 days, and normal baseline organ function were treated with AA 1000mg PO daily and prednisone 5mg PO BID. Pts with prior chemotherapy were excluded. Serum androgen levels, including dehydroepiandrosterone (DHEA), were measured by liquid chromatography/mass spectrometry (LC/MS) at baseline and during treatment for exploratory analyses. Radiographic progression-free survival (rPFS) was defined as freedom from death, radiographic progression, or unequivocal clinical progression. **Results:** 42 pts were enrolled. Median duration of prior keto was 38 weeks (wks). 40 pts discontinued keto due to disease progression, and 2 due to toxicities. AA resulted in ≥30% PSA decline at 12 wks in 20 pts (48%, 95% CI 32-63%), and ≥50% PSA decline at 12 wks in 16 pts (38%, 95% CI 24-54%). Median time on prior keto was significantly shorter in pts who had ≥30% PSA decline compared to those who had <30% decline (20 vs. 58 wks, $p=0.003$). Median time to PSA progression (TPP) was 16 wks (range, 4-64). Median rPFS was 24 wks (range, 1-88). Baseline serum DHEA levels were measured in 40 pts. 9 pts had DHEA < limit of quantitation (LOQ, 0.250ng/mL), and 31 pts had DHEA ≥LOQ. 1 pt with DHEA <LOQ (1/9, 11%) had PSA decline ≥30% at 12 wks, compared to 17 pts (17/31, 55%) with DHEA ≥LOQ ($p=0.027$). Median TPP was 6 wks (range, 4-32) for pts with DHEA <LOQ, compared to 16 wks (range 4-64) for pts with DHEA ≥LOQ ($p=0.017$). Median rPFS was 12 wks (range, 4-36) for pts with DHEA <LOQ, compared to 31.5 wks (range, 1-88) for pts with DHEA ≥LOQ ($p=0.0009$). 4 pts remain on AA. **Conclusions:** AA retains clinical activity in a significant proportion of pts previously treated with keto. DHEA levels via LC/MS merits further study as a biomarker in pts treated with androgen synthesis inhibitors.

**5040 General Poster Session (Board #169), Mon, 1:15 PM-5:00 PM**

**Time to chemotherapy following treatment with sipuleucel-T: Data from PROCEED.** *Presenting Author: Christopher Michael Pieczonka, Associated Medical Professionals, Syracuse, NY*

**Background:** Sipuleucel-T (sip-T) is an autologous cellular immunotherapy that targets prostatic acid phosphatase and is approved by the US FDA and EMA for the treatment of certain patients (pts) with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. PROCEED is an ongoing multicenter Phase 4 registry in the US that enrolled pts treated with commercial sip-T. PROCEED is collecting information on chemotherapy treatments (C) after sip-T treatment; these data will allow us to assess C predictability and determine characteristics associated with time to C after sip-T treatment. **Methods:** PROCEED enrolled >1,900 mCRPC pts who were treated with sip-T within the prior 6 months. Demographics, disease characteristics, and prior and ongoing prostate cancer treatments were recorded at baseline. We further characterized data from patients who received C after sip-T and used statistical modeling to identify predictors of time to first C. **Results:** As of May 2013, 1,254 enrolled pts had completed sip-T treatment. Time to first C ranged from 0.4 – 19.2 months. Median time to first C was shorter at oncology vs. urology practices (11.6 vs. 18.0 months, Kaplan-Meier method; HR= 2.154; $p<0.001$). A stepwise Cox model for time to C was developed from preliminary analysis of several baseline factors. **Conclusions:** The final stepwise Cox model indicates that pts who are younger, have lower baseline hemoglobin, have higher baseline PSA, or who received prior C, receive subsequent C sooner. Clinical trial information: NCT01306890.

**Predictors of time to C[1].**

| | | |
|---|---|---|
| Kaplan-Meier estimate of median time (95% CI[2]) to first C, months[3] | | 13.1 (12.2, 15.4) |
| Final Stepwise Cox model for time to first C | | |
| Baseline covariate[4] | Hazard ratio (95% CI[4]) | P value |
| Age, yrs (median = 72.0) | 0.604 (0.480, 0.758) | <0.001 |
| Baseline hemoglobin, g/dL (median = 12.7) | 0.703 (0.561, 0.881) | 0.002 |
| Prior C (15.4%) | 1.341 (1.005, 1.788) | 0.046 |
| Baseline PSA[5], ng/mL (median = 16.1) | 1.704 (1.360, 2.135) | <0.001 |

[1]Chemotherapy. [2]Confidence interval. [3]Changes in the enrolled population over time may result in the time to C differing in subsequent analyses. [4]Continuous variables dichotomized at median value. [5]Prostate-specific antigen.

**5041 General Poster Session (Board #170), Mon, 1:15 PM-5:00 PM**

**A randomized phase 2 study evaluating optimal sequencing of sipuleucel-T (sip-T) and androgen deprivation therapy (ADT) in biochemically recurrent prostate cancer (BRPC): Preliminary clinical data.** *Presenting Author: Emmanuel S. Antonarakis, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

**Background:** Sip-T is an autologous cellular immunotherapy targeting prostatic acid phosphatase (PAP) that is approved by the FDA and EMA for the treatment of certain patients with asymptomatic/minimally symptomatic metastatic castration-resistant prostate cancer. The STAND trial (NCT01431391) evaluated optimal sequencing of sip-T and ADT in men with BRPC at high risk of developing metastases (PSA-DT ≤12 mos). **Methods:** Men (N=68) were randomized (1:1) to Arm 1: sip-T followed by ADT (2 wks after infusion 3) or Arm 2: ADT (3 mo lead-in) followed by sip-T. Men received 3 doses of sip-T and 12 mos of ADT (leuprolide). The primary endpoint was cellular immune response to target antigen (ELISPOT to PA2024). Secondary endpoints included humoral and cytokine responses, product parameters, clinical efficacy, and safety. Here we report preliminary clinical data and longer-term immune responses. **Results:** 65 men have been followed for ≥9 mos from last ADT injection: 10/32 (31.3%) in Arm 1 and 14/33 (42.4%) in Arm 2 achieved undetectable PSA (<0.02 ng/mL) and testosterone (T; <0.35 ng/mL) at 9 mos from last ADT injection; 4/65 men (6.2%) developed PSA progression (2 consecutive PSA measurements, 4 wks apart, ≥50% above nadir, >5ng/mL). In both arms, sip-T induced robust and prolonged immune responses to PA2024 and PAP (measured by T cell memory and ELISA antibody responses), although no significant differences have yet emerged between arms. There appear to be higher levels of serum cytokines in Arm 2 vs Arm 1, with a pattern suggesting a mixed $T_H1/T_H2$ cellular immune response; significant increases were seen in $T_H1$ (IFNg, IL-12), $T_H2$ (IL-4, IL-10, IL-13), and $T_H17$ (IL-17) subsets (P<0.05). **Conclusions:** These data suggest that tumor-specific T cell responses and broad-based immune responses are augmented in both arms, and cytokine responses may be superior when sipuleucel-T is given after (rather than before) ADT initiation. In addition, augmented PA2024- and PAP-specific humoral responses have persisted for at least 12 mos, and are equally robust in both groups. Longer-term T cell responses and cytokine responses will be presented. Clinical trial information: NCT01431391.

**5042 General Poster Session (Board #171), Mon, 1:15 PM-5:00 PM**

**Regional differences observed in the phase 3 trial (ELM-PC 5) with orteronel (TAK-700) plus prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) that has progressed during or following docetaxel.** *Presenting Author: Karim Fizazi, Institut Gustave Roussy, University of Paris Sud, Villejuif, France*

**Background:** Orteronel is an investigational, nonsteroidal, selective 17,20-lyase inhibitor. ELM-PC 5 (NCT01193257) did not meet the primary endpoint of OS (P = 0.1898) despite improvement in radiographic PFS (rPFS; P = 0.00038) (Dreicer, ASCO GU 2014, Abstract #7). Here we analyze baseline characteristics and outcomes across study regions (Europe [E], North America [NA], and non-E/NA). **Methods:** Men with progressive mCRPC who had received prior docetaxel but not orteronel, abiraterone or ketoconazole were randomized 2:1 to orteronel 400 mg BID plus prednisone 5 mg BID (O+P) or placebo plus prednisone (P). Enrollment (N = 1099) was stratified by region (E, n = 590; non-E/NA, n = 397; NA, n = 112). The primary endpoint was OS; other key endpoints were rPFS, ≥50% prostate-specific antigen (PSA50) decrease and pain response. **Results:** Baseline characteristics were generally balanced, except for pain score, ≥2 prior chemotherapies, PSA and lacate dehydrogenase (LDH). Substantial regional differences were noted in OS, rPFS and PSA50 rates.Regional data are summarized below (Table). **Conclusions:** Substantial differences in efficacy were seen across regions, with differences in OS possibly being related to subsequent therapies. Clinical trial information: NCT01193257.

| | E | | non-E/NA | | NA | |
|---|---|---|---|---|---|---|
| | O+P N = 394 | P N = 196 | O+P N = 265 | P N = 132 | O+P N = 75 | P N = 37 |
| **Baseline characteristics** | | | | | | |
| Median time from diagnosis, yrs | 5.3 | 5.7 | 5.3 | 5.6 | 7.5 | 7.3 |
| Median Brief Pain Inventory-Short Form worst pain score | 3.0 | 3.0 | 4.0 | 3.5 | 2.0 | 2.5 |
| Pts with ≥2 prior chemotherapies, % | 18 | 23 | 32 | 34 | 7 | 27 |
| Median PSA, ng/mL | 138.0 | 127.5 | 131.0 | 169.0 | 53.6 | 51.6 |
| LDH >225 U/L, % | 42 | 34 | 54 | 52 | 28 | 38 |
| **Outcomes** | | | | | | |
| Median treatment duration, mos | 5.7 | 4.6 | 5.7 | 4.7 | 5.95 | 3.7 |
| Median OS, mos | 18.3 | 17.8 | 15.3 | 10.1 | 20.9 | 16.9 |
| P value | 0.721 | | 0.019 | | 0.680 | |
| Median rPFS, mos | 8.3 | 6.4 | 6.7 | 5.2 | 11 | 8.3 |
| P value | 0.0745 | | 0.00076 | | 0.5387 | |
| PSA50 response at 12 wks, % | 27 | 9 | 20 | 13 | 35 | 5 |
| P value | <0.0001 | | 0.0965 | | 0.00083 | |
| Pain response at 12 wks, % | 12 | 9 | 14 | 11 | 7 | 3 |
| P value | 0.204 | | 0.540 | | 0.385 | |
| **Subsequent therapy** | N = 392 | N = 194 | | | | |
| Pts with ≥1 subsequent therapy, % | 49 | 61 | 35 | 44 | 53 | 54 |
| Abiraterone, % | 26 | 32 | 9 | 5 | 27 | 24 |
| Abiraterone or enzalutamide, % | 30 | 35 | 9 | 5 | 36 | 27 |
| Abiraterone, enzalutamide, or cabazitaxel, % | 38 | 48 | 15 | 16 | 44 | 41 |

**5043 General Poster Session (Board #172), Mon, 1:15 PM-5:00 PM**

**The impact of baseline serum testosterone and duration of first-line androgen deprivation therapy on the efficacy of docetaxel in patients with metastatic castration-resistant prostate cancer (mCRPC).** *Presenting Author: Robert J. van Soest, Erasmus University Medical Center, Rotterdam, Netherlands*

**Background:** The TAX 327 study was conducted in 1,006 men with mCRPC who were randomized to receive 3-weekly docetaxel (D3), weekly docetaxel, or 3-weekly mitoxantrone (M), each with prednisone. Survival and symptom control were superior following D3 as compared to M. In this post hoc analysis, we aimed to identify factors that could characterize subgroups of patients who obtain the greatest benefit from the use of D3. **Methods:** Using a Cox model, we investigated the OS benefit obtained from D3 as compared to M in subgroups of baseline testosterone (T) ≥ median and < median, and in subgroups of duration of first-line ADT ≥ median and < median. Duration of first-line ADT was defined as the time from start date of first-line ADT to the start date of subsequent treatment. **Results:** Baseline characteristics known to predict OS including visceral metastases and Karnofsky performance score were well balanced between patient groups. The analysis demonstrated that D3 was superior to M irrespective of baseline T and the duration of first-line ADT, but demonstrated greater and statistically significant OS benefit in patients with a baseline T ≥ median (14.5 ng/dl) (p=0.035, see table) and in patients with a duration of first-line ADT <median (15 months) (p=0.022). **Conclusions:** In conclusion, docetaxel is effective in patients with mCRPC irrespective of baseline T and duration of first-line ADT, but demonstrated superior OS benefit in patients with high baseline T and in patients with a short duration of first-line ADT. These results will be further investigated in the dataset of the VENICE study, and require validation in a prospectively designed fashion.

| | Duration of first-line ADT ≥ median | | Duration of first-line ADT <median | | Baseline T ≥ median | | Baseline T < median | |
|---|---|---|---|---|---|---|---|---|
| | D3 | M | D3 | M | D3 | M | D3 | M |
| Number of patients | 182 | 166 | 153 | 166 | 164 | 173 | 171 | 159 |
| Median OS, months (95% CI) | 21.1 (16.7-23.7) | 18.6 (14.8-20.8) | 18.3 (15.9-20.8) | 14.8 (12.3-17.0) | 21.1 (16.8-NR) | 17.1 (14.8-20.7) | 17.4 (15.8-19.8) | 15.2 (13.2-18.4) |
| Hazard ratio (95% CI) | 0.84 (0.63-1.14) | | 0.71 (0.54-0.95) | | 0.72 (0.53-0.98) | | 0.80 (0.61-1.06) | |
| P value | 0.261 | | 0.022 | | 0.035 | | 0.124 | |

**5044 General Poster Session (Board #173), Mon, 1:15 PM-5:00 PM**

**Changes in androgen deprivation therapy overuse: Reimbursement response and characteristics of persistent overusers.** *Presenting Author: Shellie D. Ellis, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

**Background:** Reimbursement cuts driven by the Medicare Modernization Act of 2003 are associated with declining androgen deprivation therapy (ADT) overuse in prostate cancer; yet, 25.7% of men for whom ADT was not recommended still received it in 2005. We examined physician-level prescribing changes and characteristics of persistent overusers among urologists. Understanding characteristics of urologists who persistently overuse ADT can improve quality of care and inform current efforts to limit reimbursement. **Methods:** We conducted a population-based, retrospective study of 2,138 urologists treating 12,943 men with early stage and lower grade prostate cancer diagnosed between 2000 and 2007. SEER-Medicare data was matched to American Medical Association physician data. Mixed effects regression modeling controlled for patient and provider characteristics. **Results:** We observed 3 distinct patterns of overuse. Static users (69%) had low levels of ADT overuse in 2000 and maintained infrequent overuse. Decreasing users (18%) had the highest levels of ADT overuse in 2000, but overuse decreased sharply in 2004, matching levels of use of static users by 2008. Increasing users (13%),increased ADT overuse in 2004 adopting levels higher than any user in 2000. Urologists' time in practice was not associated with ADT overuse (OR 0.89; 95% CI 0.75-1.05). However, solo practice type (OR 1.65; 95% CI 1.34-2.02), lack of medical school affiliation (OR 1.35; 95% CI 1.23-1.45), and patient race were. Compared to non-Hispanic whites, non-Hispanic blacks (OR 1.76; 95% CI 1.37-2.27), Hispanics (OR 1.41; 95% CI 1.12-1.79) and men of "other" race (OR 1.44; 95% CI 1.04-1.99) had greater odds of receiving unnecessary ADT. **Conclusions:** ADT overuse remains high among some urologists who may be professionally isolated and difficult to reach by usual means. These urologists may treat more vulnerable populations, which may contribute to health disparities in prostate cancer treatment quality. Finally, efforts to limit reimbursement may not have uniform effects, warranting careful assessment of subsequent quality and potential disparate impact.

**5045 General Poster Session (Board #174), Mon, 1:15 PM-5:00 PM**

**Obesity and the odds of weight gain following androgen deprivation therapy for prostate cancer: Toward a risk adapted approach for ADT use.** *Presenting Author: Lior Zvi Braunstein, Harvard Radiation Oncology Program, Boston, MA*

**Background:** Increasing BMI is associated with an increased risk of mortality; however, quantifying weight gain in men undergoing ADT for prostate cancer (PC) as stratified by baseline BMI remains unexplored and was the subject of the current study. **Methods:** Between 1995 and 2001, 206 men with unfavorable-risk prostate cancer were enrolled on a randomized trial evaluating the impact on survival of adding 6-months of ADT to radiotherapy (RT). BMI, both at baseline and after therapy, was available in 171 men who formed the study cohort. The primary endpoint was weight gain of ≥10 lbs by the 6-month follow-up. Logistic regression multivariable analysis was performed to assess whether baseline BMI or treatment-received was associated with this endpoint adjusting for comorbidity and known PC prognostic factors. **Results:** By the 6 month follow-up, 12 men were observed to have gained ≥10 lbs of which 10 (83%) were treated with RT and ADT and, of these, 7 (70%) were obese at randomization. As shown in the table, men treated with RT as compared to RT and ADT were significantly less likely to experience a weight gain of ≥ 10 pounds (adjusted odds ratio (AOR): 0.18 [95% confidence interval (CI) 0.04 - 0.89]; p = 0.04); whereas this risk was significantly increased with increasing BMI (AOR: 1.15 [ 95% CI 1.01 – 1.31]; p = 0.04). Moreover, weight gain persisted at 2 years for the obese men who gained ≥ 10 lbs after treatment with RT and ADT (median: 13.0 lbs; range: 9.0 to 21.0). **Conclusions:** Consideration should be given to avoiding ADT use in obese men with low or favorable-intermediate risk PC where improved cancer control has not been observed, but a shortened life expectancy from weight gain is expected. Clinical trial information: NCT00116220.

| | | | Multivariable analysis | |
|---|---|---|---|---|
| **Clinical factor** | **No. of men** | **No. of men who gained ≥ 10 lbs by EOT** | **AOR (95% CI)** | **P value** |
| **RT** | 85 | 2 | 0.18 (0.04, 0.89) | 0.04 |
| **RT + AST** | 86 | 10 | 1 (Ref) | - |
| **BMI increase per kg/m$^2$** | 171 | 12 | 1.15 (1.01, 1.31) | 0.04 |
| **PSA increase per ng/mL** | 171 | 12 | 0.97 (0.87, 1.08) | 0.57 |
| **Age** | 171 | 12 | 0.95 (0.85, 1.06) | 0.38 |
| **Gleason score 8 to 10** | 26 | 3 | 1.17 (0.17, 7.93) | 0..87 |
| **7** | 94 | 6 | 0.55 (0.10, 3.06) | 0.49 |
| **6 or less** | 51 | 3 | 1 (Ref) | - |
| **T2** | 88 | 8 | 1.99 (0.49, 7.99) | 0.33 |
| **T1** | 83 | 4 | 1 (ref) | - |
| **Mod to sev comorbidity** | 41 | 5 | 2.11 (0.54, 8.26) | 0.28 |
| **No or min comorbidity** | 130 | 7 | 1 | - |

**5046 General Poster Session (Board #175), Mon, 1:15 PM-5:00 PM**

**The in vivo efficacy of docetaxel and cabazitaxel in a cell-line based xenograft of castration-resistant prostate cancer (CRPC) previously treated with enzalutamide.** *Presenting Author: Robert J. van Soest, Erasmus University Medical Center, Rotterdam, Netherlands*

**Background:** With the rapid evolvement of treatment options for metastatic CRPC, it has become of critical importance to determine the optimal sequencing of therapies. We recently reported in vitro cross-resistance between the taxanes docetaxel and cabazitaxel, and the AR targeting agents abiraterone and enzalutamide (Eur J Cancer 2013;49(18):3821-30). In the present study, we investigated the efficacy of docetaxel and cabazitaxel in an in vivo model of CRPC previously treated with enzalutamide. **Methods:** The enzalutamide-resistant prostate cancer cell line PC346Enza was derived by continuous culturing of PC346C cells in the presence of enzalutamide (1 $\mu$M). PC346Enza cells were subcutaneously inoculated in nude mice. Castrated mice were treated with a single intraperitoneal dose of docetaxel 33 mg/kg, cabazitaxel 33 mg/kg, or placebo when a tumor volume of 300 mm$^3$ was reached. Uncastrated male mice received oral enzalutamide 60 mg/kg daily or placebo. Mean tumor volumes at the time of analysis were calculated after 46 and 25 days of follow-up and compared using an unpaired 2 sample t-test. **Results:** Cabazitaxel demonstrated a greater antitumor effect as compared to docetaxel in the PC346Enza xenograft. Mean tumor volumes after 46 days of treatment were 61 mm$^3$ (95% CI 24-98) for cabazitaxel versus 258 mm$^3$ (95% CI 95-421) for docetaxel (p=0.01). The mean tumor volume of the placebo treated mice was 743 mm$^3$(95% CI 345-1142). Although the PC346Enza cell line demonstrated complete resistance to enzalutamide in vitro, xenografts still responded to high dose enzalutamide in vivo (60mg/kg). **Conclusions:** Our in vivo data demonstrated that cabazitaxel was more effective as compared to docetaxel in a model of CRPC previously treated with enzalutamide. Our current findings provide the rationale for a clinical study investigating the efficacy of cabazitaxel versus docetaxel, given as first-line chemotherapy in patients previously treated with enzalutamide. These data and are concordant with clinical studies demonstrating that cabazitaxel retains activity as second-line chemotherapy, even after prior AR-targeted treatment in metastatic CRPC.

**5047 General Poster Session (Board #176), Mon, 1:15 PM-5:00 PM**

**Prognostic role of derived neutrophil to lymphocyte ratio (dNLR) in men with metastatic castration resistant prostate cancer (mCRPC) treated in a phase 3 trial (VENICE).** *Presenting Author: Arnoud J. Templeton, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada*

**Background:** We evaluated retrospectively the prognostic impact of derived neutrophil to lymphocyte ratio (dNLR), a marker of host inflammation, in men with progressive metastatic castration-resistant prostate cancer (mCRPC) treated in VENICE, a phase 3, multicenter, trial of aflibercept versus placebo in combination with docetaxel and prednisone funded by Sanofi and Regeneron (Tannock et al. Lancet Oncology 2013). **Methods:** The arms were combined for analysis, since no difference was observed in the primary endpoint of overall survival (OS). dNLR was calculated as the absolute count of neutrophils divided by the absolute white cell count minus the absolute count of neutrophils. A logarithmic transformation was applied to non-normal factors. The Kaplan-Meier method was used for OS estimation. To adjust for baseline patient and tumor characteristics we used Cox proportional hazards regression with backward stepwise selection, stratifying for ECOG PS (0 vs. 1-2) and treatment group. **Results:** Complete data for construction of a prognostic model were available in 876 men. Patients with a dNLR greater than the median (2.0) had significantly worse survival (2y OS: 38% vs. 54%, log-rank $P$<0.001; HR (univariate) 1.48 [95% CI 1.29 - 1.69], $P$for stratified Cox model <0.001). The factors that remained individually significant for OS in multivariable analysis are shown in the Table. **Conclusions:** High dNLR was associated with worse survival in men with mCRPC treated with docetaxel. These data warrant external validation.

| | **HR** | **95% CI** | **P value** |
|---|---|---|---|
| **Age ≥ 68 years (median)** | 1.24 | 1.06-1.44 | 0.01 |
| **Alkaline phosphatase ≥ 142 U/L (median)** | 1.58 | 1.35-1.86 | <0.001 |
| **Duration of first ADT < 15 months (median)** | 1.39 | 1.20-1.62 | <0.001 |
| **Hemoglobin < 127 g/L (median)** | 1.40 | 1.20-1.63 | <0.001 |
| **Pain (PPI) ≥ 2** | 1.47 | 1.25-1.72 | <0.001 |
| **Number of metastatic organs involved ≥ 2** | 1.20 | 1.03-1.40 | 0.02 |
| **dNLR ≥ 2.0 (median)** | 1.31 | 1.13-1.52 | <0.001 |

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; PPI, Present Pain Intensity scale from the McGill–Melzack questionnaire, which uses verbal descriptors; scores can range from 0 to 5, with higher scores indicating greater pain.

**5049 General Poster Session (Board #178), Mon, 1:15 PM-5:00 PM**

**The potential of peripheral blood HERV-K expression as a biomarker for diagnosis with prostate cancer in older men.** *Presenting Author: Sharon A. Glynn, Prostate Cancer Institute, National University of Ireland Galway, Galway, Ireland*

**Background:** Aberrant expression of human endogenous retrovirus-k (HERV-K) has been observed in prostate cancer (PCa). HERV-K is unique as it encodes sequences in the human genome containing open reading frames for near intact retroviruses. We hypothesized that HERV-K reactivation could serve as a non-invasive early disease detection marker. **Methods:** We evaluated HERV-K *gag* mRNA expression in PBMCs of African-American (AA) and European-American (EA) men via qRT-PCR (294 PCa cases and 135 male controls). We examined HERV-K env protein expression in PCa by immunohistochemistry. Fisher's exact test and logistic regression were used to analyze continuous and dichotomized data and calculate odds ratios (ORs). Multivariable models adjusted for age at diagnosis and race/ethnicity. Mann-Whitney test was used to compare HERV-K $C_t$-based expression values between groups. **Results:** HERV-K *gag* expression in PBMCs was significantly higher in PCa cases than controls (Table). Men with *gag* in the highest quartile had > 12-fold increased odds [OR = 12.87 (95% CI 6.3-26.25)] of PCa than those in the lowest quartile. Additionally, HERV-K may perform better in older than younger men (sensitivity of PSA testing decreases with age). HERV-K envelope protein was up-regulated in PCa, with the most abundant expression observed in AA patients (61% versus 40%, $P < 0.01$). **Conclusions:** Combining non-invasive HERV-K testing with PSA testing may improve the efficacy of PCa detection specifically among older men.

**Association between HERV-K *gag* mRNA levels in PBMC and a PCa diagnosis.**

| | Univariate analysis† | | | | Multivariable analysis* | | | |
|---|---|---|---|---|---|---|---|---|
| | **OR** | **95% CI** | **P value** | **n** | **OR** | **95% CI** | **P value** | **n** |
| **Logistic regression as a continuous variable (per $C_t$ value)** | | | | | | | | |
| **Gag mRNA** | 1.33 | 1.24-1.43 | <0.0001 | 429 | 1.36 | 1.26-1.47 | <0.0001 | 427 |
| **Logistic regression evaluating dose response effect**** | | | | | | | | |
| **1$^{st}$ Quartile** | 1 | | | 48 | 1 | | | 48 |
| **2$^{nd}$ Quartile** | 1.38 | 0.61-3.11 | 0.433 | 57 | 1.58 | 0.69-3.62 | 0.280 | 57 |
| **3$^{rd}$ Quartile** | 4.14 | 1.98-8.67 | <0.0001 | 98 | 5.90 | 2.69-13.0 | <0.0001 | 96 |
| **4$^{th}$ Quartile** | 12.87 | 6.30-26.3 | <0.0001 | 226 | 17.3 | 8.07-37.0 | <0.0001 | 226 |
| | | Ptrend | <0.0001 | | | | Ptrend | <0.0001 |

†294 cases and 135 controls. *Adjusted for age at diagnosis and ethnicity. ***HERV-K *gag* levels were divided into quartiles based on control population.

**5050 General Poster Session (Board #179), Mon, 1:15 PM-5:00 PM**

**The effect of change in PSA velocity on overall survival (OS) in men with biochemically recurrent prostate cancer (BRPC) treated with nonhormonal agents: Combined analysis of four phase 2 trials.** *Presenting Author: Daniel L. Suzman, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

**Background:** Multiple phase 2 trials in men with BRPC have assessed the impact of non-hormonal agents on PSA kinetics. We have previously demonstrated that changes in PSA kinetics are correlated with metastasis-free survival; however, it is unknown whether these changes may also correlate with overall survival (OS). **Methods:** We performed a combined retrospective analysis of 146 men with BRPC treated on phase 2 trials using one of four investigational drugs: lenalidomide (n=60), marimastat (n=39), ATN-224 (n=22), and imatinib (n=25). We examined factors influencing OS, including within-subject changes in PSA kinetics (PSA slope, PSA doubling time, and PSA velocity) before and 6 months after treatment initiation. **Results:** After median follow up of 137 months, 48 men had died. In univariate Cox regression analysis, four factors were associated with OS: prior androgen deprivation therapy (ADT), prior local radiotherapy, baseline PSA velocity, and change in PSA velocity after therapy. In a landmark multivariable model, stratified by study, which also controlled for age and Gleason score (<7 vs ≥7): prior radiotherapy, baseline PSA velocity, and increase in PSA velocity remained independent predictors of OS (Table). Median OS for men with an increase in PSA velocity on treatment was 9.4 years vs not-yet-reached for men with a decrease in PSA velocity (HR 2.2; 95% CI 1.10-4.39; *P*=0.03). **Conclusions:** This hypothesis-generating study suggests that within-subject changes in PSA velocity after initiation of non-hormonal therapy may correlate with OS in men with BRPC. If validated in prospective trials using OS as the primary endpoint, change in PSA velocity may represent a reasonable intermediate endpoint for screening new agents in these patients.

| | Multivariate | |
|---|---|---|
| Variable | HR (95% CI) | P |
| Age, y (continuous) | 0.97 (0.93, 1.02) | 0.26 |
| Gleason score | | |
| ≥7 | 0.95 (0.38, 2.38) | 0.92 |
| ≤7 | 1 | |
| Prior radiotherapy | | |
| Yes | 2.20 (1.03, 4.73) | 0.04 |
| No | 1 | |
| Prior use of ADT | | |
| Yes | 0.79 (0.36, 1.73) | 0.55 |
| No | 1 | |
| Baseline PSA velocity | | |
| Above median | 2.49 (1.33, 4.65) | 0.004 |
| Below median | 1 | |
| Δ in PSA velocity | | |
| Increase | 2.20 (1.10, 4.39) | 0.03 |
| No increase | 1 | |

**5051 General Poster Session (Board #180), Mon, 1:15 PM-5:00 PM**

**Safety results of the enzalutamide expanded access program in the United States and Canada for patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel.** *Presenting Author: Anthony M. Joshua, Princess Margaret Hospital, University Health Network, Toronto, ON, Canada*

**Background:** In the Phase 3 AFFIRM trial, the androgen receptor inhibitor enzalutamide improved overall survival compared with placebo in patients (pts) with mCRPC who had received prior docetaxel. The aim of this open-label single-arm study was to monitor safety and provide access to enzalutamide for mCRPC pts pending marketing approval in the U.S. and Canada. **Methods:** 507 pts with mCRPC were treated at 54 sites. Pts received enzalutamide 160 mg/d in the study until disease progression, intolerable adverse event (AE), or commercial availability. AEs, serious AEs (SAEs), vital signs, and laboratory measurements were assessed on day 1, wk 4 and 12, and every 12 wks thereafter. No efficacy data were collected. **Results:** Median age was 71 yr (range 43-97). Baseline ECOG PS was 0, 1 and 2 in 27.8%, 56.1%, and 15.9% of pts, respectively. Prior treatments for prostate cancer included abiraterone (76.0%), and cabazitaxel (28.6%); 24.8% of pts received both prior abiraterone and cabazitaxel. Median enzalutamide treatment duration in the study was 2.6 mo (range 0.03-9.07); data following transition to commercial drug was not collected. Common AEs (≥10%) included fatigue (39.1%), nausea (22.7%), anorexia (14.8%), anemia (11.8%), peripheral edema (11.4%), back pain (10.3%), vomiting (10.3%), and arthralgia (10.1%). SAEs reported in ≥1% of pts were disease progression (7.9%), pneumonia (2.0%), asthenia (1.8%), anemia (1.6%), and back pain (1.4%). Drug-related AEs leading to permanent discontinuation occurred in 3.7% of pts. Grade ≥3 drug-related AEs were reported in 14.2 % of pts and drug-related AEs leading to death occurred in 4 pts: 1 cerebrovascular accident, 2 myocardial infarctions and 1 death not otherwise specified. Seizure was reported in 4 (0.8%) pts, of whom 3 had brain metastases. **Conclusions:** In this expanded access population of pts with progressive mCRPC who had previously received docetaxel, enzalutamide was well tolerated. The safety profile was consistent with that seen in the AFFIRM trial. Median treatment duration was shorter than in AFFIRM (2.6 vs 8.3 mo); duration on subsequent commercial drug was not collected. Clinical trial information: NCT01606982.

**5052 General Poster Session (Board #181), Mon, 1:15 PM-5:00 PM**

**A pilot study of supraphysiologic testosterone (T) and oral etoposide (E) in men with castrate-resistant prostate cancer (CRPC).** *Presenting Author: Michael Thomas Schweizer, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

**Background:** Prostate cancer (PC) cells become resistant to chronic castration via an adaptive increase in androgen receptor (AR) expression, a liability that can be exploited therapeutically. Mechanistically, supraphysiologic androgens can induce PC cell death through topoisomerase 2 (topo2) mediated double-strand DNA breaks and disruption of DNA relicensing due to persistence of AR at origins of replication during the cell cycle. **Methods:** We evaluated parenteral T in combination with the topo2 inhibitor E in men with CRPC and low metastatic burden (≤5 bone and <10 soft tissue metastases). To rapidly cycle from supraphysiologic (>1500 ng/dL) to near castrate T levels, men received intramuscular T cypionate 400 mg on day (D) 1 and oral E 100 mg D 1-14 of a 28 D cycle. After 3 cycles, men with declining PSA could continue T alone every 28 D. The primary endpoint was PSA response, defined as a PSA below baseline, after cycle 3. Secondary endpoints included objective response rates and safety. **Results:** Sixteen men enrolled of which 14 completed 3 cycles of T+E and were evaluable for response. 7/14 went on the T-only expansion stage. After 3 cycles, 6/14 men had a PSA response. 7 (50%) had a PSA response at any timepoint [4 (29%) had PSA declines ≥50%] (Table). In men with RECIST-evaluable disease, 2 had progressive and 3 had stable disease (SD), 4 had partial (PR) and 1 had a complete response (CR). Median response duration was 343 D (95% CI, 91 to 434 D). Post T, 12/12 men had a PSA decline to subsequent androgen ablative therapies. Most adverse events (AEs) were ≤grade 2 and considered effects of E. One man died from neutropenic sepsis before completing the 1st cycle. AEs possibly related to T included lower extremity edema (n=1), priapism (n=1) and asymptomatic pulmonary embolism (n=2). No one developed new pain on T. **Conclusions:** T with or without E demonstrated preliminary efficacy in patients with CRPC as manifested by PSA and objective responses. This regimen is generally safe. Cyclic T-based therapies warrant further study. Clinical trial information: NCT01084759.

**PSA/radiographic response summary.**

| Subject | Cycles (N) | Maximum PSA change relative to baseline (%) | RECIST response |
|---|---|---|---|
| **4** | 15 | -86 | PR |
| **6** | 12 | -48 | PR |
| **8** | 3 | -46 | SD |
| **9** | 16 | -78 | NA |
| **13** | 14 | -97 | PR |
| **15** | 8 | -18 | PR |
| **16** | 5 | -98 | CR |

**5053 General Poster Session (Board #182), Mon, 1:15 PM-5:00 PM**

**15-year outcomes following conservative management among patients with screen-detected localized prostate cancer.** *Presenting Author: Grace L. Lu-Yao, Rutgers Cancer Institute of New Jersey, Robert Wood Johnson Medical School, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ*

**Background:** An understanding of the natural history of screen-detected prostate cancer is essential for making appropriate treatment decisions; however, such data are few and far between **Methods:** We assembled a population-based cohort consisting of 12,271 men aged >65 years diagnosed with screened detected (T1c) localized prostate cancer during 1992 - 2009 who did not receive surgery, radiotherapy, or androgen deprivation therapy (ADT) within 6 months of diagnosis. Competing risk analyses were used to assess cancer-specific mortality and use of cancer-related interventions. **Results:** Compared to outcomes of pre-PSA era patients, 15-year survival has improved considerably for conservatively managed patients diagnosed in the PSA era. The 15-year risk of prostate cancer specific mortality for men aged 66-74 diagnosed with T1C Gleason 5-7 prostate cancer was 6.1% (95% CI 3.6-8.8% ) compared to 17 - 23% among men diagnosed in the pre-PSA era. Similarly, substantial improvement was observed for patients with T1c Gleason 8-10 prostate cancer: 15-year prostate cancer mortality was 21.4% (95% CI 11.9 – 44.2%) compared to 56-65% in the pre-PSA era. The 15-year prostate cancer mortality for patients aged 75+ was 9.8% (95% CI 7.7-12.1%) for Gleason 5-7 and 25.2% (95% CI 18.4-33.2%) for Gleason 8-10. Among patients aged 66-74 with T1c Gleason 5-7 cancer, 53.6% (95% CI 50.6 – 56.9%) received cancer therapy (42.3% attempted curative therapy, 22.5% ADT, 6.6% palliative therapy) within 15 years of cancer diagnosis. Among those who received attempted curative cancer therapy, the majority did so within the first 3 years of follow-up. **Conclusions:** To our knowledge, this is the largest US population-based long-term study on screen-detected prostate cancer initially treated with conservative management. Fifteen-year disease-specific mortality following conservative management among men with screen-detected cancer has decreased by more than 60% as compared with results from the pre-PSA era. The risk of death due to prostate cancer for men diagnosed with T1c Gleason 5-7 disease in the PSA era is low.

**5054 General Poster Session (Board #183), Mon, 1:15 PM-5:00 PM**

**Sensitivity analyses for radiographic progression-free survival (rPFS): Results from the phase 3 PREVAIL trial comparing enzalutamide to placebo.** *Presenting Author: Michael J. Morris, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

**Background:** In the PREVAIL trial, enzalutamide (ENZ), an androgen receptor inhibitor, significantly improved overall survival (HR: 071, $P<0.0001$) and rPFS (HR: 0.19, $P<0.0001$) compared with placebo in asymptomatic/mildly symptomatic chemotherapy-naive men with mCRPC (Beer, ASCO GUCS 2014, LBA1). Sensitivity analyses (SA) were performed to assess the impact of different sources of progression on the prespecified rPFS analysis. We also analyzed concordance between central and local reviewers. **Methods:** In this double-blind, placebo-controlled, multinational study (NCT01212991), 1,717 patients were randomized 1:1 to ENZ 160 mg/day (n=872) or placebo (n=845). rPFS was a co-primary endpoint defined as time from randomization to the earliest objective evidence of radiographic progression by central review or death within 169 days of treatment discontinuation. Radiographic progression was defined by PCWG2 guidelines for bone disease or by RECIST 1.1 for soft tissue disease; bone progression was captured using a validated bone scan data capture assay. The primary rPFS analysis was event driven (at least 410 events). Characteristics of representative SA are reported in the Table. **Results:** Concordance between central and local assessment of progression was 87.6%. Results of the SA were statistically significant in favor of ENZ (see Table). **Conclusions:** rPFS sensitivity analyses in PREVAIL demonstrated a consistent and robust treatment benefit with ENZ. Central and local assessment showed good concordance using a quantitative definition of radiographic progression and validated bone scan data assay. Clinical trial information: NCT01212991.

| Analysis | Modifications from primary analysis | Total events | Hazard ratio* (95% CI) |
|---|---|---|---|
| **Primary** | None | 439 | 0.19 (0.15, 0.23) |
| **SA 1** | · Skeletal-related events, initiation of radiotherapy, and new anti-neoplastic therapy counted as PFS events | 621 | 0.18 (0.15, 0.22) |
| **SA 2** | · Investigator assessment used in lieu of central review | 413 | 0.22 (0.18, 0.27) |
| **SA3** | · Investigator assessment with same data cutoff as OS analysis | 889 | 0.31 (0.27, 0.35) |
| **SA4** | · Discontinued for clinical progression counted as PFS event | 482 | 0.18 (0.14, 0.22) |

*All p values <0.0001.

**5055 General Poster Session (Board #184), Mon, 1:15 PM-5:00 PM**

**Comparison of prostate health index and PCA3 values in patients with clinical or biologic suspicion of prostate cancer.** *Presenting Author: Pierre-Jean Lamy, Institut Régional du Cancer Montpellier, Montpellier, France*

**Background:** The Prostate Health Index (PHI) and the Prostate CAncer gene 3 (PCA3) have shown to have predictive values for early detection of PCa. The aim of this prospective observational study was to compare the values of the both markers in patients consulting for a suspicion of PCa **Methods:** Samples of 573 consecutive patients presenting a suspicion of PCa were included in a biobank between 2010 and 2012. Total PSA (tPSA),Free PSA (fPSA) and -2proPSA (Beckman Coulter) were performed on serum to calculate the PHI ([-2proPSA/fPSA] X [tPSA]$^{1/2}$). Urine samples were collected after digital rectal examination (DRE) by an urologist in order to calculate the PCA3 score ([PCA3 mRNA]/[PSA mRNA] X 1,000). Prostate biopsies were performed for 235 men according usual clinical practice. Correlation between PSA, PHI, PCA3 score and clinico-pathological factors were studied with the Kruskall-Wallis tests. ROC–derived area under the curve (AUC) was used to quantify the predictive accuracy of the tests predicting pathologic findings in biopsies specimens. **Results:** PCA3 score was only correlated with age (Spearman's rho = 0.21; p=0.001) and PHI was only correlated with tPSA (Spearman's rho = 0.35; p<0.0001). PHI and PCA3 were slightly correlated (Spearman's rho = 0.16; p=0.01). Comparing biomarkers values in patients with positive (P+; n=60, 25.5%) and negative biopsy (P-; n=175, 74.5%), PHI and PCA 3 were statistically different according to patients status. **Conclusions:** In this large series of patients consulting for a suspicion of PCa, tPSA is hardly more effective than a coin toss to predict PCa. PHI, an independent biological marker, presented a higher predictive value for positive biopsy prediction than PCA3, a marker slightly correlated with age.

| | Negative biopsies | Positive biopsies | p | AUC | AUC IC |
|---|---|---|---|---|---|
| **235 men** | 74.5% | 25.5% | | | |
| **tPSA (median)** | 6.7 [0.6-36.6] | 6.8 [2.5-43.0] | p=0.19 | 0.56 | 95% [0.47; 0.64] |
| **fPSA (median)** | 1 [0.1-7.6] | 0.8 [0.3-4.8] | p=0.02 | 0.60 | 95% [0.52; 0.69] |
| **PHI (median)** | 37.0 [11.4-117.1] | 49.3 [16.8-114.5] | p<0.001 | 0.71 | 95% [0.63; 0.79] |
| **PCA3 (median)** | 30 [2-371] | 47 [10-333] | p<0.001 | 0.65 | 95% [0.57; 0.72] |

**5056 General Poster Session (Board #185), Mon, 1:15 PM-5:00 PM**

**Development and validation of a prognostic index for fracture risk in older men undergoing prostate cancer treatment.** *Presenting Author: Tisheeka Graham-Steed, Yale School of Medicine, New Haven, CT*

**Background:** Although men treated with androgen deprivation therapy (ADT) or radiation therapy (RT) for prostate cancer are at an increased risk for fractures, it is unclear whether specific factors can be used to identify men at increased risk. We therefore developed a prognostic index for risk of fracture in this population. **Methods:** We used the Surveillance, Epidemiology, and End Results-Medicare database to identify men diagnosed with -localized prostate cancer in 2007-2009 who received ADT or RT. Potential risk factors for fracture included age, comorbidity (including osteoporosis), medication use, and functional status. Cox proportional hazards models tested the association of potential risk factors on fracture. In a derivation group (n=2,912), hazard ratios were used to assign points for factors independently related to fracture. The prognostic index was then applied to a validation group (n=2,912). **Results:** The sample of 5,824 men had a mean age of 74.2 years; 82.9% were white and 8.6 % had a fracture within 2 years of treatment for prostate cancer. The Cox model identified 8 variables (age, race, hormone treatment, Elixhauser score, anxiety, Parkinson's, fall-inducing medications, disability score) independently associated with fracture; data not shown. Fractures in the derivation cohort included 4.3% in the low-risk group, 8.9% in the intermediate group, and 19.2% in the high-risk group (C statistic, 0.749). The incidence of fractures in the validation cohort ranged from 6.2% in the lowest-risk, 10.6% in the intermediate-risk, and 16.5% in the high-risk group (C statistic, 0.782). **Conclusions:** These data underscore the importance of identifying risk factors for fracture, given the substantial variation in fracture risk in men treated with ADT or RT. The prognostic index can help to inform treatment decisions (e.g., identifying patients at increased risk for fracture).

**5057 General Poster Session (Board #186), Mon, 1:15 PM-5:00 PM**

**Longitudinal assessment of general health-related QOL in patients undergoing active surveillance (AS) for low-risk prostate cancer: Interim results of the PRIAS-JAPAN cohorts.** *Presenting Author: Mikio Sugimoto, Department of Urology, Kagawa University Faculty of Medicine, Kagawa, Japan*

**Background:** Japan is participating in the Prostate cancer Research International: Active Surveillance (PRIAS) study as PRIAS-JAPAN since 2010. QOL has been assessed annually as an independent side study of PRIAS-JAPAN. The objective of this study is to measure the base-line QOL and the longitudinal changes in QOL status of Japanese AS cohorts. **Methods:** PRIAS-JAPAN study was launched since January 2010. Until July 2013, 354 patients were enrolled into the study from 33 institutions. Participants' general health related QOL (HRQOL) have been assessed using SF-8 at enrollment and annually thereafter. QOL subscales and summary scores were compared with norm-based scoring (general population) and also between each evaluation points over time. A paired t-test served to compare the data, and $p< 0.05$ was considered to indicate statistical significance. **Results:** Of the 354, 325 could be able to follow in PRIAS protocol. Median age of participants was 68 (45-87 yr.), median PSA was 5.27ng/ml (1.5-9.93). 220 patients were remained on the AS program with median observation period of 15 months. Of the 325 patients, QOL was evaluable in 315, 183, 48 and 18 patients at enrollment, 1-year, 2-year and 3-year after, respectively. Almost all domains of QOL at enrollment revealed better QOL than that of general population. At 1 and 2-year after starting of AS, there was no significant QOL deterioration and favorable QOL was maintained. When it stratified by median baseline QOL score, the physical and mental component summary score in favorable baseline QOL group were deteriorated over time ($p<0.01$ and $p<0.05$ respectively). On the other hand, those of unfavorable baseline QOL group revealed significant improvements over time ($p<0.05$ and $p<0.01$ respectively). **Conclusions:** QOL of the Japanese patients who choose AS as initial treatment is relatively better than that in general population and it has been maintained at 2-year after AS. However, there is a possibility of QOL deterioration with time, especially for better QOL patients at baseline. Clinical trial information: UMIN000009876.

**5058 General Poster Session (Board #187), Mon, 1:15 PM-5:00 PM**

**Predicting response to abiraterone acetate (AA): mRNA biomarker analysis of study COU-AA-302.** *Presenting Author: Deborah Sokol Ricci, Janssen Research and Development, Raritan, NJ*

**Background:** AA is metabolized to abiraterone, a CYP17 inhibitor that blocks testicular, adrenal, and tumoral androgen biosynthesis. AA is approved for the treatment of metastatic castration-resistant prostate cancer (mCRPC). We examined the predictive value of mRNA biomarkers in determining clinical response to AA therapy in chemo-naive pts with mCRPC. **Methods:** 1,088 pts were randomized 1:1 to AA 1000 mg + prednisone (P) 5 mg po BID vs placebo + P and stratified by Eastern Cooperative Oncology Group (ECOG) score 0 or 1. Co-primary end points: radiographic progression-free survival (rPFS) and overall survival (OS). 329 pts provided optional consent for biomarker analysis of pretreatment FFPE tumor samples. Of these, 110 pts were evaluable for mRNA analysis using Taqman array microfluidic cards. We tested 94 biomarkers relevant to androgen receptor (AR) signaling, steroidogenesis, and AA response or resistance. Association analysis of single biomarkers or predetermined biomarker groups with rPFS (independent review) and OS was done by Cox regression within each treatment group and stratified by ECOG score. **Results:** Six biomarkers (SF1, HSD17B10, SRD5A1, UBE2C, NUSAP1, ANLN) were significantly associated with rPFS in the AA ($p < 0.05$) but not the P ($p \geq 0.2$) group; none were significant based on false discovery rate (FDR) $\geq 0.15$. Higher AR expression was significantly associated with longer rPFS in the AA group, HR (95% CI): 0.80 (0.65-0.98), $p = 0.03$, FDR = 0.2. Androgen-regulated genes and CYP17 cofactors were associated with longer rPFS and OS in the biomarker group analysis (Table). **Conclusions:** This exploratory analysis shows that gene expression of androgen-regulated genes and CYP17 cofactors at the time of diagnosis may be predictive of outcome to AA therapy. The current study is limited by sample size and lack of independent validation datasets and requires confirmation in planned additional studies. Clinical trial information: NCT00887198.

| | rPFS, AA + P | | OS, AA + P | |
|---|---|---|---|---|
| **Biomarkers** | HR (95% CI) | p value (FDR) | HR (95% CI) | p value (FDR) |
| **Androgen-regulated genes (AKR1C3, FKB5, PCNA)** | 0.57 (0.37-0.88) | 0.01 (0.11) | 0.31 (0.14-0.69) | 0.004 (0.07) |
| **CYP17A1 and cofactors (CYB5A, CYP17A1, CYP3A5, DUSP5, HNF1A, NR0B1, POR)** | 0.43 (0.21-0.89) | 0.02 (0.13) | 0.33 (0.13-0.86) | 0.02 (0.12) |

**5059 General Poster Session (Board #188), Mon, 1:15 PM-5:00 PM**

**Validation of an RNA cell cycle progression (CCP) score for predicting prostate cancer death in a conservatively managed needle biopsy cohort.** *Presenting Author: Jack M. Cuzick, Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, London, United Kingdom*

**Background:** The natural history of prostate cancer is highly variable and difficult to predict accurately. Better markers are needed to guide management and avoid unnecessary treatment. To validate the predictive value of a cell cycle progression (CCP) score and a pre-specified linear combination of the CCP score with standard clinical variables (CAPRA) to form a combined clinical cell cycle risk (CCR) score for predicting prostate cancer death in a cohort of conservatively managed patients diagnosed by needle biopsy. **Methods:** A retrospective cohort study of 585 men diagnosed by needle biopsy in the UK from 1990-2003 using UK cancer registry data - supplemented by hospital records and histopathology review of diagnostic needle biopsies. The primary endpoint was prostate cancer death. Clinical variables consisted of centrally reviewed Gleason score, baseline PSA, age, clinical stage, and extent of disease. These were combined into a single predefined risk assessment (CAPRA) score. **Results:** In univariate analysis, the CCP score hazard ratio (HR) was 2.08 (95% CI (1.76, 2.46), $P < 10^{-13}$) for a one unit change of the score and in a bivariate analysis including CAPRA, the CCP score HR was only marginally decreased (HR=1.76, 95% CI (1.44, 2.14)), and remained highly significant ($P < 10^{-6}$). The predefined CCR score combining CCP and CAPRA was highly predictive (HR = 2.17; 95% CI (1.8, 2.6), $\chi^2 = 89.0$, $P < 10^{-20}$) and captured all available prognostic information. The predictive value of the CCP score was maintained for 10 years, and there was no significant interaction with other prognostic factors. CAPRA identified 80 men (13.7%) in the low risk group (0-2) and they had a 10y prostate cancer mortality of 4.3%. CCR indicated 19 (3.2%) of these men had a higher risk, but identified a further 31 (5.3%) men with CAPRA $> 2$, but with a risk $<$ 4.3% using the combined score. **Conclusions:** The CCP score provides substantially more significant pre-treatment prognostic information than available from clinical variables and is useful for determining which patients can be safely managed by a conservative policy avoiding radical treatment.

**5060 General Poster Session (Board #189), Mon, 1:15 PM-5:00 PM**

**Phase I trial of docetaxel (D), prednisone, and pasireotide (P) (SOM230) in metastatic castrate-resistant prostate cancer (mCRPC).** *Presenting Author: Hema M. Vankayala, John D. Dingell VA Medical Center, Detroit, MI*

**Background:** Neuroendocrine (N) differentiation is a resistance mechanism to chemotherapy in mCRPC. Somatostatin (sst) receptor analogs demonstrate efficacy in N tumors. P is a multitargeted sst -receptor analog with affinity to sst 1, 2, 3 and 5, and the potential to overcome chemoresistance. A phase I trial of D+P was conducted to establish the maximum tolerated dose (MTD) and the recommended Phase II dose (RP2D). **Methods:** Chemotherapy naïve mCRPC patients (pts) with performance status (PS) 0-2 and adequate renal and hepatic function were enrolled. D was administered at a dose of 75 mg/m$^2$ intravenously every 21 days and P was administered intramuscularly (IM) every 28 days at escalating dose levels of 40, 60, and 80 mg. A 3 + 3 study design was utilized. Correlative studies included circulating tumor cell counts (CTC), IGF-1, neuron specific enolase (NSE), and chromogranin A (ChA) levels pre and post therapy. **Results:** Phase I portion of the study is complete. 12 pts were enrolled with a median age of 65 years (range 54-74) and PS of 1. Gleason score was $> 8$ in 8 pts. 4 pts had visceral metastases. Pre-study regimens included, enzalutamide (2pts); abiraterone (2 pts); and clinical trial agents (4 pts). Dose limiting toxicity noted at 80 mg of P were, grade 4 hyperglycemia unresponsive to therapy and 1 with grade 4 neutropenia lasting for $> 7$ days. The RP2D of P is 60 mg every 28 days in combination with D 75 mg/m$^2$ every 21 days. 4 of 6 pts at 60 mg of P had grade 3 hyperglycemia. No cholelithiasis, severe liver toxicity, or treatment related deaths were noted. 8 pts had grade 1-2 diarrhea, and 1 had grade 3 diarrhea. A median of 6.5 (range 2-14) cycles of D and 5 cycles (1-13) of P were administered. To date, 9 pts have progressed with median time to progression of 8.3 months (range 1.4 - 10.4) which compares favorably with docetaxel therapy alone (median 6.3 months). 3 of 6 pts with pretreatment CTC $> 5$ converted to CTC $< 5$ post therapy. Of the markers, only IGF-1 levels revealed a median 51% decrease with therapy. **Conclusions:** The addition of P to D is clinically feasible at a dose of 60 mg IM every 28 days. Clinical efficacy is encouraging and warrants study in the phase II setting. Supported in part by Novartis Inc. Clinical trial information: NCT01468532.

**5061 General Poster Session (Board #190), Mon, 1:15 PM-5:00 PM**

**Final analysis of a large, open-label global early access protocol (EAP) with abiraterone acetate (AA) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) progressing after chemotherapy.** *Presenting Author: Cora N. Sternberg, Hospital San Camillo-Forlanini, Rome, Italy*

**Background:** A global EAP was conducted to provide broader access to pts with mCRPC post-chemotherapy and to generate additional clinical efficacy and safety data for AA after registrational study COU-AA-301 had completed enrollment. In COU-AA-301, a phase 3 randomized trial of 1195 pts, AA + prednisone (P) significantly prolonged median overall survival by 4.6 months with a 26% reduction (HR = 0.74 [95% CI, 0.64-0.86]; $p < 0.0001$) in the risk of death vs placebo + P. **Methods:** 2314 pts with mCRPC who progressed after a taxane and possibly 1 additional chemotherapy entered an open-label EAP. Pts received AA (1000 mg po/d) + P (5 mg BID) in 28-day cycles. Ongoing pts were to be transitioned to marketed product upon regulatory and marketing approval in individual countries. Efficacy measures, collected to guide treatment decisions, were prostate-specific antigen progression (PSAP) and clinical progression (CP). Safety assessments included treatment-emergent adverse events (AEs). The final results are presented. **Results:** Pts were enrolled from 253 sites in 23 countries in Europe (51%), N. America (23%), Asia-Pacific (20%), and Latin America (6%). Baseline pt characteristics were similar to COU-AA-301, with median age 70 years (range 44-98) and bone metastases present in 91%. Median therapy duration was 4.9 months (74% received $\geq 4$ cycles). Median time to PSAP (683 events) and CP (721 events) was 8.5 months (95% CI, 8.3-9.7) and 12.7 months (95% CI, 11.8-13.8), respectively. Median time to PSAP was identical to the AA + P arm of COU-AA-301 (ie, 8.5 months; CP not measured). No new safety signals were detected. Grade 3/4 AEs of special interest were infrequent: any liver function test abnormalities (8.0%), hypertension (4.3%), cardiac disorders (2.2%), hypokalemia (1.2%), fluid retention/edema (1.0%). Discontinuations due to AEs or death were 7.4% each. **Conclusions:** These final EAP results demonstrate that the clinical safety and efficacy of AA + P are reproducible across a broader global distribution of sites than COU-AA-301, and reveal no additional safety concerns. Clinical trial information: NCT01217697.

**5062^ General Poster Session (Board #191), Mon, 1:15 PM-5:00 PM**

**Efficacy and quality of life (QoL) of cabazitaxel/prednisone (Cbz) in Canadian metastatic castration resistant prostate cancer (mCRPC) patients (pts) with or without prior abiraterone acetate (Abi).** *Presenting Author: Fred Saad, University of Montréal Hospital Center, CRCHUM, Montréal, QC, Canada*

**Background:** In the TROPIC study, Cbz was shown to improve overall survival in mCRPC pts post-docetaxel, however none of these pts had prior exposure to Abi. To better understand the impact of prior Abi treatment on Cbz efficacy and QoL, we evaluated Canadian pts enrolled in the International Phase IIIb/IV single arm Cbz study. **Methods:** In total 61 pts were enrolled from 9 centers (May 2011 to February 2012). Cbz efficacy (PSA Response Rate (RR, decline ≥50%)) and impact on QoL were analyzed as a function of prior Abi use. **Results:** Baseline and disease characteristics were similar between NoPriorAbi (n=35, 57%) and PriorAbi (n=26, 43%) groups, except for age and time between last docetaxel dose and progression (Table). Pts received a median of 9 cycles of prior docetaxel. 92% of pts were ECOG 0/1, with 88% having bone metastases and 25% visceral metastases. 31% of pts received prophylactic G-CSF. Median number of Cbz cycles received was similar between groups (NoPriorAbi= 6, PriorAbi= 7) as were PSA RR (NoPriorAbi= 42.4%, PriorAbi= 47.6%, p=0.78). QoL and pain were improved in Cbz pts with no significant difference observed based on prior Abi use (Table). Overall, treatment discontinuation was mainly due to progression (45.9%) and adverse events (32.8%). Most frequent grade 3/4 toxicities were anemia and fatigue (9.8%), with diarrhea, neutropenia and febrile neutropenia each observed in 8.2% of pts. **Conclusions:** Cbz efficacy and impact on QoL were not affected by prior Abi use. In routine clinical practice, toxicity rates observed were similar to the TROPIC study. Clinical trial information: NCT01254279.

| Variable | Unit | Total | No Prior Abi | Prior Abi | P |
|---|---|---|---|---|---|
| Median age | Yrs | 65 | 64 | 69 | 0.02 |
| Time between last docetaxel dose and progression | <0 mos | 11.7 | 17.1 | 4.0 | 0.05 |
| | 0-3 | 23.3 | 28.6 | 16.0 | |
| | 3-6 | 18.3 | 14.3 | 24.0 | |
| | ≥6 | 46.7 | 40.0 | 56.0 | |
| Pts with ≥10 cycles of Cbz | % | 26.7 | 28.6 | 24.0 | 0.70 |
| FACT-P ≥16 points ∔ | % | 14.8 | 12.1 | 19.1 | 0.70 |
| FACT-P ≥6 points ∔ | % | 44.4 | 39.4 | 52.4 | 0.41 |
| PCS subscale ≥2 points ∔ | % | 53.7 | 51.52 | 57.14 | 0.78 |
| PCS pain subscale ≥2 points ∔ | % | 27.8 | 24.24 | 33.33 | 0.54 |
| Pain response Rate * ∔ | % | 20.7 | 15.00 | 33.33 | 0.34 |

* as defined in TROPIC (de Bono 2010). ∔ Minimal clinically important difference observed on 2 consecutive cycles.

**5063 General Poster Session (Board #192), Mon, 1:15 PM-5:00 PM**

**A study of ERG, PTEN, and ki-67 in a phase III trial assessing docetaxel and estramustine in high-risk localized prostate cancer (GETUG 12).** *Presenting Author: Shanna Rajpar, Institut Gustave Roussy, Villejuif, France*

**Background:** High-risk localized prostate cancer (CaP) is a heterogeneous disease and only a minority of patients (pts) ultimately die of their cancer. GETUG 12 is a phase III trial assessing androgen deprivation therapy (ADT) with or without docetaxel-estramustine (DE) in pts with high-risk localized CaP (Eur J Cancer 2012; 48:209-17). Progression free survival (PFS) data will be reported at the ASCO 2014 meeting. The aim of this study was to investigate the prognostic and predictive value of Ki-67, PTEN, and ERG expression in GETUG 12. **Methods:** Pre-treatment prostate core biopsies were collected from 255 of the 413 pts (62%) who were enrolled in GETUG 12. Immunohistochemistry analysis was performed for Ki-67, PTEN and ERG. PTEN and ERG expression were defined as positive if there was a staining (1+ or 2+) in any core. Ki-67 was characterized as low and high according to the cut-off based on the observed median value (1%). PFS differences were compared using the Logrank test and multivariate analysis was conducted with established prognostic factors using the Cox model. **Results:** In the overall population, the median age was 63 (46-77) years. 72/174 pts (41%) had Ki-67 >1%, 106/178 pts (60%) were negative for PTEN and 103/191 pts (54%) were negative for ERG. ERG negative expression (p=0.03) and high Ki-67 (p=0.02) predicted for unfavorable PFS. In multivariate analysis, pN+ (p<0.0001), ERG negative expression (0.0003) and PTEN negative expression (p=0.05) were independent prognostic factors of poor PFS. DE improved PFS in pts with a ERG positive expression (HR=0.56 [0.28-1.15]) but not in pts without ERG expression (HR=1.12 [0.65-1.91]), interaction test: p=0.02. In contrast no PFS benefit was associated with DE in subgroups defined according to Ki-67 and PTEN expression. **Conclusions:** Docetaxel-estramustine is associated with an improved PFS in pts treated for a high-risk localized CaP with ERG expression.

**5064 General Poster Session (Board #193), Mon, 1:15 PM-5:00 PM**

**Phase I trial of docetaxel/prednisone plus fractionated dose radiolabeled anti-prostate-specific membrane antigen (PSMA) monoclonal antibody $^{177}$lu-J591 in patients with metastatic, castration-resistant prostate cancer (mCRPC).** *Presenting Author: Scott T. Tagawa, Weill Cornell Medical College, New York, NY*

**Background:** Docetaxel remains a standard agent for mCRPC and has radiosensitizing properties. $^{177}$Lu-J591 delivered with fractionated dosing leads to less myelosuppression while maintaining efficacy in mCRPC. This study was designed to determine the safety, dose limiting toxicity (DLT) and maximum tolerated dose (MTD) of fractionated $^{177}$Lu-J591 administered concurrently with standard docetaxel. **Methods:** Men with progressivem-CRPC received docetaxel 75 mg/m$^2$ every 3 weeks with escalating 2 fractionated doses of $^{177}$Lu-J591 (initial dose 20 mCi/m$^2$ x2 up to max of 40 mCi/m$^2$ x2) with cycle 3. Cycle 4 of docetaxel was planned 6 weeks after cycle 3 to allow for recovery from $^{177}$Lu-J591-associated hematologic toxicity. DLT was defined as delay in docetaxel >3 weeks, prolonged myelosuppression or need for >2 platelet (plt) transfusions, febrile neutropenia, or grade >2 non-heme toxicity following $^{177}$Lu-J591. PSA was assessed prior to each cycle and CTC count (CellSearch) was assessed at baseline and after $^{177}$Lu-J591. **Results:** 15 men with median age 67.3 (range 49.2-80.8), PSA 84.3 (17-776), 73.3% with elevated LDH, 71.4% unfavorable CTC counts received up to the highest anticipated dose (40 mCi/m$^2$ x2). No DLT was seen at any dose level. Significant toxicity was limited to reversible myelosuppression. Gr 4 neutropenia without fever occurred in 3 (20%) and Gr 4 plts in 2 (13.3%), with 2 receiving prophylactic plt transfusion. No Gr >2 non-heme toxicity was observed. 13 had PSA decline, with 11 (73.3%) and 12 (80%) having >50% and >30% PSA decline respectively. All 14 evaluable men had decline (85.7%) or persistently undetectable (14.3%) CTC counts, with 78.6% having CTC counts decline by >50% and 78.6% having favorable counts after $^{177}$Lu-J591. Of 10 analyzed to date, all had targeting of known sites of disease by planar $^{177}$Lu-J591 imaging. **Conclusions:** The combination offractionated dose $^{177}$Lu-J591 and docetaxel/prednisone is well tolerated in patients with mCRPC. Without pre-selection, accurate targeting of known sites of disease and a strong preliminary efficacy signal was observed. Clinical trial information: NCT00916123.

**5065 General Poster Session (Board #194), Mon, 1:15 PM-5:00 PM**

**Management trends in the United States for low-, intermediate-, and high-risk prostate cancer.** *Presenting Author: Kamran A. Ahmed, H. Lee Moffitt Cancer Center & Research Institute, Department of Radiation Oncology, Tampa, FL*

**Background:** The purpose of this study is to determine recent trends in the United States regarding management of clinically localized prostate cancer. **Methods:** A population-based analysis was conducted of 216,785 men with low (29%), intermediate (49%), or high (22%) recurrence risk prostate cancer, as defined by the National Comprehensive Cancer Network (NCCN). Annual rates of utilization of surgery, external beam radiation therapy, brachytherapy, external beam radiotherapy and brachytherapy, and no treatment between 2004 and 2010 were determined using the Surveillance, Epidemiology and End Results (SEER) database. **Results:** White patients were more likely than African American patients to undergo surgery (44.0% vs. 33.3%, respectively; p<.0001), and African American patients were more likely than White patients to undergo radiotherapy (28.1% vs. 22.6%, respectively; p<.0001) or no treatment (20.3% vs. 16.0%, respectively; p<.0001). There was an annual increase of 1.38% (95% confidence interval (CI) 1.06% to 1.70%) in surgery utilization corresponding to a 7.6% increase in utilization over the period of analysis. Using multivariate analysis, patients were more likely to receive no treatment if they were single (odds ratio (OR) 1.65; 95% CI 1.60-1.70), diagnosed in 2010 (vs. 2009 or earlier, OR = 1.18; 95% CI 1.14 -1.22), had low risk disease (vs. high risk, OR = 2.14; 95% CI 2.07-2.21), African American (vs. White, OR=1.42; 95% CI 1.37-1.47), resided in a county with a low education level (vs. high educational level, OR=1.30; 95% CI 1.26-1.35), or were >65 (vs. ≤ 65, OR = 2.25; 95% CI 2.19-2.31). For low risk prostate cancer, there was an annual decrease of 2.29% (95% CI -2.77% to -1.81%) in utilization of brachytherapy corresponding to a 14.3% decrease over the period of analysis and an annual increase of 2.57% (95% CI 1.79% to 3.36%) in patients receiving no treatment corresponding to a 15.7% increase. **Conclusions:** In patients with low risk prostate cancer, there was decreasing utilization of brachytherapy and increasing utilization of no treatment. Patients were less likely to receive treatment if they had low risk disease or were >65, African American, single, or resided in a county with a low educational level.

**5066 General Poster Session (Board #195), Mon, 1:15 PM-5:00 PM**

**Recent trends in the management of localized prostate cancer: Results from the National Cancer Data Base.** *Presenting Author: Phillip John Gray, Harvard Radiation Oncology Program, Boston, MA*

**Background:** The management of localized prostate cancer (PC) is evolving. Using a large national database, we sought to analyze recent trends in practice patterns for this common disease in the United States. **Methods:** Data on all patients presenting with a new diagnosis of PC between 2004 and 2011 were extracted from the National Cancer Data Base. Patients with nodal or distant metastases were excluded. Patients were categorized as low risk (LR), intermediate risk (IR) or high risk (HR) according to the National Comprehensive Cancer Network's (NCCN) guidelines. P-values correspond to trend tests for the described treatment modality. **Results:** 823,977 patients met the study criteria, with 38.5% of these patients classified as LR, 42.7% as IR and 18.9% as HR. For LR patients, rates of observation after diagnosis between 2004 and 2011 increased from 12.4% to 18.5% while receipt of prostatectomy increased from 40.3% to 54.4% (p both <.001). In contrast, receipt of brachytherapy fell from 24.4% to 11.4% and receipt of external beam radiation monotherapy fell from 18.2% to 13.4% (p both <.001). For IR patients, rates of observation increased from 6.1% to 7.3%, prostatectomy increased from 48.1% to 58.5% (p both <.001), brachytherapy fell from 12.1% to 6.4% (p <.001), receipt of external beam monotherapy remained relatively unchanged (~15%) while external beam radiation plus androgen deprivation therapy (ADT) fell from 14.7% to 8.7%. For HR patients, receipt of observation and external beam monotherapy were unchanged (~8% and ~10% respectively) while receipt of surgery increased from 30.6% to 41.3% (p< .001). In contrast, receipt of external beam therapy plus ADT fell from 30.4% to 28.0%, receipt of brachytherapy fell from 8.7% to 4.1% while receipt of ADT alone dropped from 7.2% to 5.8% (p all <.001). **Conclusions:** Utilization of prostatectomy for patients with localized PC increased significantly across risk groups from 2004 to 2011 while utilization of radiotherapy (especially brachytherapy) decreased. Rates of observation have increased in LR disease while rates of combined ADT and radiotherapy in IR and HR PC are declining. Further work is needed to elucidate the causes and appropriateness of these trends.

**5067 General Poster Session (Board #196), Mon, 1:15 PM-5:00 PM**

**Bone density in men receiving androgen deprivation therapy for prostate cancer: A randomized comparison between transdermal estrogen and luteinising hormone-releasing hormone agonists.** *Presenting Author: Ruth E Langley, Medical Research Council, Clinical Trials Unit at University College London, London, United Kingdom*

**Background:** Androgen deprivation therapy (ADT) for prostate cancer with luteinising hormone-releasing hormone agonists (LHRH) reduces bone mineral density (BMD), as testosterone suppression also causes estrogen deficiency in men. Transdermal estrogen is a compelling alternative to LHRH as it achieves similar castrate levels of testosterone but mitigates the cardiovascular toxicity associated with oral estrogen (Langley et al. Lancet Oncology 2013;14:306-16) and may avoid estrogen depletion related toxicities including osteoporosis. **Methods:** PATCH (Prostate Adenocarcinoma: TransCutaneous Hormones,PR09) is a randomised trial (n=686) comparing estrogen patches (EP; FemSeven 100 $\mu$g/24 hr, 4 patches changed twice-weekly reducing to 3 after 4 weeks) versus LHRH for locally advanced or metastatic prostate cancer (allocation ratio 2:1 before 21/2/2011, 1:1 after). In a bone-sub-study, dual-energy x-ray absorptiometry (DXA) scans were performed at baseline, 1 and 2 years. Primary outcome was change in lumbar spine (LS) BMD (mean L1-L4) at 1 year, compared between arms based on intention-to-treat using analysis of covariance, adjusting for baseline values. **Results:** 85 patients were enrolled from October 2007 to September 2012 from 7 centres (31 LHRH, 54 EP), of whom 8 were excluded (2 withdrew, 6 not eligible as they had osteoporosis on baseline scan). LS BMD data were available for 60 patients (21 LHRH, 39 EP). Median age was 77 years (IQR 73-80), 24 (40%) had bone metastases. At 1 year, mean LS BMD change was -0.03 g/cm$^3$ (95% CI -0.06, -0.003) in LHRH vs 0.08 g/cm$^3$(0.04, 0.11) EP arm (p<0.001); corresponding mean percentage change was -2.11% vs +6.43%, respectively. In patients without bone metastases, the difference was -3.74% LHRH vs +5.04% EP (p=0.001). At 2 years, LS BMD decreased further in LHRH patients (-6.09% from baseline, n=10) while the increase was maintained in those on EP (+4.58%, n=20); p<0.001 comparing arms. **Conclusions:** Transdermal estrogen, used for achieving androgen deprivation in prostate cancer, protects against bone mineral density loss, confirming the need to continue evaluation of its clinical efficacy. Clinical trial information: ISRCTN70406718.

**5068 General Poster Session (Board #197), Mon, 1:15 PM-5:00 PM**

**Enzalutamide monotherapy: One-year extended follow-up of a phase 2 study in hormone-naive prostate cancer patients.** *Presenting Author: Bertrand Tombal, Service d'Urologie, Cliniques Universitaires Saint-Luc, Brussels, Belgium*

**Background:** The efficacy and safety of enzalutamide monotherapy was assessed in men with any-stage hormone-naive prostate cancer eligible for androgen-deprivation therapy (ADT). The primary endpoint of PSA response rate (≥80% PSA decrease between baseline and week 25) was 92.5% (Smith M et al, ASCO 2013). The median (range) maximum PSA decline from baseline to week 25 was –99.6% (–100, –86.5). 1-year extended follow-up data are presented. **Methods:** In an open-label, single-arm Phase 2 study (NCT01302041), men ≥18 years with histologically confirmed prostate cancer requiring ADT, non-castrate testosterone (≥8 nmol/L), PSA ≥2 ng/mL at screening, and a life expectancy of ≥12 months, received 160 mg enzalutamide once daily until disease progression or unacceptable toxicity. Other endpoints included changes in hormone levels, metabolic parameters, BMD, safety, and quality of life (QoL). **Results:** 67 men were enrolled. Median (range) age was 73 years (48–86); 38.8% had metastases; 35.8% and 23.9% had undergone prior prostatectomy and radiotherapy, respectively. 54 men (80.6%) completed 1 year of treatment with a PSA response rate of 100% and 53 (98.1%) had ≥90% PSA decrease from baseline. The median (range) maximum decline in PSA was –100% (–100, –86.5) from baseline to 1 year. Luteinizing hormone and testosterone were increased from baseline by 215.2% and 101.7%, respectively. Mean changes from baseline for fasting metabolic variables were: +5.0% total cholesterol, +8.9% triglycerides, –3.5% HbA1c, and +19.7% insulin resistance (HOMA-IR). Total body BMD was maintained (–0.3% from baseline). The most frequently reported treatment-emergent AEs were gynecomastia (47.8%) and fatigue (38.8%). Seven non-drug-related serious AEs were reported. QoL scores at 1 year demonstrate maintenance of global health status and a decrease in sexual activity and sexual functioning. **Conclusions:** Extended follow-up of hormone-naive patients demonstrated sustained PSA reductions up to 1 year of enzalutamide monotherapy. Endocrine and metabolic changes, and AEs were consistent with potent AR inhibition and similar to results reported at 25 weeks. Clinical trial information: NCT01302041.

**5069 General Poster Session (Board #198), Mon, 1:15 PM-5:00 PM**

**Patient-reported quality of life (QOL) analysis of radium-223 dichloride (Ra-223) evaluating pain relief from the phase 3 ALSYMPCA study.** *Presenting Author: Sten Nilsson, Karolinska University Hospital, Stockholm, Sweden*

**Background:** Ra-223, a first-in-class $\alpha$-emitter, significantly improved overall survival vs placebo (pbo) and was well tolerated (Parker. *NEJM* 2013; ALSYMPCA). Ra-223 had a positive impact on pain, significantly delaying time to external beam radiotherapy and reducing pain and opioid use (Nilsson. ASCO GU 2013). This post hoc analysis assessed Ra-223 treatment (tx) effects on QOL Functional Assessment of Cancer Therapy-Prostate (FACT-P) pain-related score (PRS), with subgroup assessments by prior docetaxel use (pD) and baseline number of bone mets. **Methods:** Pain was assessed at baseline and wk 16 and 24 with FACT-P; PRS was derived from 4 pain-related questions. In responders, baseline PRS increased 2 points (improved pain). Nonresponders had neutral response (baseline PRS change -1, 0, +1) and failure (2-point baseline PRS decrease [worse pain], including pts starting opioids during tx). Chi-square tests calculated *P* values of responder rates between tx groups. Logistic regression determined odds ratios (ORs) (Ra-223 vs pbo) adjusted for stratification factors (pD, baseline total ALP, concurrent bisphosphonate) and baseline PRS as covariates. **Results:** Of 921 pts (Ra-223, n = 614; pbo, n = 307), analysis included pts with recorded PRS at each assessment visit (wk 16; Ra-223, n = 405; pbo, n = 175, wk 24, Ra-223, n = 305; pbo, n = 118, wk 16 and 24, Ra-223, n= 283; pbo, n = 109). Significantly more Ra-223 vs pbo pts were responders; pain improved at each visit (wk 16, $P = 0.028$; wk 24, $P = 0.007$) and across visits (improved for wk 16 and 24, $P = 0.013$). Ra-223 tx significantly increased odds of improved pain vs pbo at wk 16 (OR, 1.70; 95% CI, 1.08-2.70; $P = 0.023$) and wk 24 (OR, 2.18; 95% CI, 1.17-4.06; $P$= 0.014); Table shows increased odds for wk 16 and 24. For all assessed subgroups and time points, a nominally higher % of Ra-223 pts had improved pain vs pbo pts. **Conclusions:** Ra-223 was associated with greater odds of pain relief vs pbo based on FACT-P PRS. Clinical trial information: NCT00699751.

| | OR for continued pain improvement, wk 16 and 24 | | | |
|---|---|---|---|---|
| Group | Ra-223 (n) | Pbo (n) | OR | 95% CI |
| All pts | 283 | 109 | 2.58 | 1.18-5.62 |
| < 6 mets | 54 | 21 | 1.65 | 0.27-10.19 |
| 6-20 mets | 123 | 52 | 2.57 | 0.79-8.39 |
| > 20 mets/superscan | 106 | 36 | 2.80 | 0.74-10.60 |
| No pD | 116 | 51 | 1.75 | 0.65-4.68 |
| pD | 167 | 61 | 5.20 | 1.17-23.09 |

**5070 General Poster Session (Board #199), Mon, 1:15 PM-5:00 PM**

**1.5-year post-treatment follow-up of radium-223 dichloride (Ra-223) safety in patients with castration-resistant prostate cancer (CRPC) and symptomatic bone metastases from the phase 3 ALSYMPCA study.** *Presenting Author: Chris Parker, The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, Sutton, United Kingdom*

**Background:** Ra-223, an alpha-emitting pharmaceutical, significantly improved overall survival and was well tolerated in ALSYMPCA (Parker, *NEJM*2013). Long-term safety monitoring of Ra-223 is essential to build a complete safety profile and identify any association with secondary malignancies. Here we report adverse events (AEs) from ALSYMPCA patients (pts) ~1.5 y after last pt's final injection (inj). **Methods:** All ALSYMPCA pts were to enter designated follow-up starting 4 wk after each pt's last inj to 3 y after first inj. Only treatment (tx)-related AEs and specific diseases (acute myelogenous leukemia [AML], myelodysplastic syndrome [MDS], aplastic anemia [AA], primary bone cancer, primary cancer in other organs) were reported. **Results:** Of 921 pts (Ra-223, n = 614; pbo, n = 307), 574 entered designated ALSYMPCA follow-up (Ra-223, n = 406; pbo, n = 168). 335/406 (83%) Ra-223 pts and 119/168 (71%) pbo pts had 6 inj. Median follow-up time was 10.4 mo for Ra-223 pts and 7.6 mo for pbo pts. In the safety population, 25/404 (6%) Ra-223 pts and 8/167 (5%) pbo pts had 37 tx-related AEs (Table). Overall, myelosuppression incidence was ≤3%. No pts had AML, MDS, or primary bone cancer; 1 Ra-223 pt had AA, and 2 Ra-223 pts and 3 pbo pts had primary cancer in other organs (Table). **Conclusions:** Long-term follow-up of ~1.5 y after last pt's final inj showed no new safety concerns or secondary malignancies related to Ra-223. Clinical trial information: NCT00699751.

| | Ra-223 n = 404* | | Pbo n = 167* | |
|---|---|---|---|---|
| **ALSYMPCA Follow-up, n (%)** | **All Gr** | **Gr 3/4** | **All Gr** | **Gr 3/4** |
| **Hematologic AEs** | | | | |
| Anemia | 11 (3) | 5 (1) | 5 (3) | 1 (1) |
| Aplastic anemia | 1 (< 1) | 1 (< 1) | 0 | 0 |
| Leukopenia | 2 (< 1) | 2 (< 1) | 0 | 0 |
| Neutropenia | 2 (1) | 2 (1) | 0 | 0 |
| Thrombocytopenia | 4 (1) | 0 | 0 | 0 |
| **Nonhematologic AEs** | | | | |
| Cardiopulmonary failure | 0 | 0 | 1 (1)† | 0 |
| Nausea | 0 | 0 | 1 (1) | 0 |
| Fatigue | 0 | 0 | 1 (1) | 0 |
| General physical health deterioration | 1 (< 1) | 0 | 0 | 0 |
| Multiorgan failure | 1 (< 1)† | 0 | 0 | 0 |
| Pneumonia | 1 (< 1)† | 0 | 0 | 0 |
| Weight decrease | 1 (< 1) | 0 | 0 | 0 |
| Anorexia | 1 (< 1) | 0 | 0 | 0 |
| Musculoskeletal pain | 1 (< 1) | 0 | 0 | 0 |
| Pathologic fracture | 2 (< 1) | 1 (< 1) | 0 | 0 |
| Dizziness | 1 (< 1) | 0 | 0 | 0 |
| Primary cancers not tx related | · Bladder<br>· Lymph node mets not originating from prostate | | · Squamous cell carcinoma<br>· Adenocarcinoma rectosigmoid<br>· Skin | |

* Safety population. †Gr 5.

**5071 General Poster Session (Board #200), Mon, 1:15 PM-5:00 PM**

**Evaluation of the prostate health index (PHI) as a novel biomarker in active surveillance of prostate cancer.** *Presenting Author: Andrew Eichholz, University College London Hospitals NHS Foundation Trust, London, United Kingdom*

**Background:** PHI is calculated from serum PSA, free/total (f/t) PSA and [-2]proPSA using the Beckman Coulter assay kit, and has been approved for use in patient selection for diagnostic prostate biopsy. We hypothesized that phi might also predict outcome of active surveillance. **Methods:** From 2002, we have done a prospective cohort study of active surveillance for men with T1/2, Gleason <= 3+4, PSA < 15ng/ml prostate cancer. Serum was banked at baseline. Monitoring included 6 monthly PSA and 2-yearly repeat biopsy. Treatment was indicated for PSA velocity > 1ng/ml/yr or Gleason >= 4+3 on repeat biopsy. We analyzed baseline phi with respect to time to treatment. A multivariate model was fitted using total PSA, PSA velocity, PSA density, Gleason score, % biopsy cores positive, T stage, and maximum % cancer in any biopsy core. The fit of this model was then compared with the addition of % f/t PSA and PHI. **Results:** 370 patients were evaluable with a median follow-up of 5 years. The table shows the association between baseline PHI and time to treatment. On multivariate analysis, the model with % f/t PSA was a significant improvement over base model (change in fit 41.1, p<0.001), and the model with % f/t PSA and phi was a significantly better fit than % f/t PSA alone (change in fit 11.1, p=0.001). **Conclusions:** In men with favorable risk prostate cancer, PHI at diagnosis was a significant predictor of the outcome of active surveillance. The data require validation, but suggest that active surveillance is particularly attractive to men with a low PHI.

| PHI value | N | Events | Median time to treatment, years (95% CI) | Patients free from treatment at 5 years, % (95% CI) |
|---|---|---|---|---|
| **Up to 31.4 (quartile 1)** | 94 | 6 | Not estimable | 95.1 (90.3, 99.9) |
| **31.5 to 42.9 (quartile 2)** | 91 | 17 | 11.4 (not estimable) | 81.6 (72.8, 90.5) |
| **43.0 to 58.5 (quartile 3)** | 93 | 40 | 6.4 (4.1, 8.7) | 58.9 (48.1, 69.7) |
| **Over 58.5 (quartile 4)** | 93 | 52 | 5.1 (3.2, 7.1) | 54.1 (43.7, 64.5) |

**5072 General Poster Session (Board #201), Mon, 1:15 PM-5:00 PM**

**A safety study of cabozantinib (C) plus docetaxel (D) and prednisone (P) in metastatic castrate-resistant prostate cancer (mCRPC).** *Presenting Author: Fatima Karzai, National Cancer Institute, Bethesda, MD*

**Background:** Two landmark trials demonstrate docetaxel improves overall survival in metastatic castrate-resistant prostate cancer (mCRPC). Benefits remain short-lived requiring evaluation of other treatment options, including docetaxel (D) combinations. Combining D with other agents, such as cabozantinib (C) could target different cellular signaling pathways producing either additive or synergistic activities without overlapping toxicities. C is a multikinase inhibitor of c-Met, vascular endothelial growth factor receptor 2, and RET, which has shown activity in mCRPC. **Methods:** Patients (pts) with no prior history of D, receive D at 75 mg/m2 IV on day 1 of a 21 day cycle, and prednisone (P) at 5 mg po q12 hours, with C at three dose levels: 20 mg, 40 mg, or 60 mg po daily. Three-six pts are treated at each dose level until the maximum tolerated dose (MTD) has been defined. **Results:** Fifteen pts have been accrued; 4 at 20 mg C, 6 at 40 mg C, and 5 at 60 mg C. Median age is 67 (45-84 yrs). Median baseline PSA is 69.46 (0.01-521.5 ng/mL). Median Gleason score is 9 (7-10). Four pts have ECOG PS of 0 and 11 pts have a PS of 1. Six pts have bone only disease and 8 pts have bone and soft tissue/visceral disease (STD). Median number of cycles is 9 (1-23). Most common Grade 2 and 3 adverse events (AE's), possibly related to C are: anemia (2/14), diarrhea (2/14), hand/foot syndrome (3/14), fatigue (3/14), hypophosphatemia (4/14), and oral mucositis (4/14). Of 13 evaluable pts, PSA declines are seen in 7 pts (4 declines at 40 mg C, 3 declines at 60 mg C). Two pts with bone only disease have resolution of some lesions on bone scan (BS) and both pts had PSA declines >30%. 4 pts with bone only disease have stable BS, and of these, 2 pts had PSA declines >20%. Two pts with bone and STD have PSA declines >30% and stable imaging results. Of 15 pts, six month PFS is 83.9% (95% CI: 56.3% to 95.5%) and 9 month PFS is 59.9%. **Conclusions:** The addition of C to D and P has shown to have a tolerable side effect profile. An expansion cohort will be enrolled at the MTD to further characterize safety, toxicity, and to obtain additional information on the efficacy of the combination treatment. Clinical trial information: NCT01683994.

**5073 General Poster Session (Board #202), Mon, 1:15 PM-5:00 PM**

**An open-label phase II clinical trial of the RXR agonist IRX4204 in taxane-resistant, castration-resistant metastatic prostate cancer (CRPC).** *Presenting Author: Fairooz F. Kabbinavar, University of California, Los Angeles, Los Angeles, CA*

**Background:** IRX4204 is a potent, selective, oral small compound agonist of RXR nuclear receptor pathways. In preclinical studies IRX4204 synergizes with insulin-like growth factor binding protein-3, to induce apoptosis in human prostate cancer cells and was effective in reducing human prostate tumor burden in a murine xenograft model. The only prostate cancer patient in a phase I trial of IRX4204 trial manifested a sustained >90% PSA reduction and a PR lasting over 7 months. These findings led to the current open label phase II trial of IRX4204 to evaluate safety and activity or futility, for treatment of advanced CRPC. **Methods:** The trial enrolled 23 men with metastatic CRPC, who had failed a taxane or declined chemotherapy, with ECOG 0-2 with evidence of biochemical or radiographic progression on bone scan, CT and/or MRI. Patients continued with androgen blockade and had to have adequate organ function. Patients were deemed to have demonstrated benefit of IRX4204 treatment if they had PFS >56 days, and/or a 50% PSA decrease, and/or PR or CR by RECIST. Futility defined as 4 or fewer patients demonstrating benefit in the planned enrollment of 37 patients. Patients received IRX4204 (20 mg/orally daily) . PSA was checked Q 4 weeks & radiographic assessments Q8 weeks. Radiographic not PSA progression was used to determine progression. **Results:** IRX4204 was well tolerated for up to 11 months. No drug related SAE have occurred. Manageable decreases in TSH and increases in triglycerides, both known adverse effects of RXR agonists, have been observed. Protocoldefined patient benefit was observed in 13/23 (57%) patients. PFS >56 days observed in 13/23 (57%). PFS >112 days observed in 9/23 (39%), range 113 to 330 days. PSA 50% response occurred in 3/23 (13%), including one additional PSA 90% response. No objective responses have occurred. **Conclusions:** This study demonstrates that IRX4204 treatment of taxane-resistant CRPC is well tolerated, & provides an activity signal warranting further evaluation of IRX4204as a treatment for chemo-refractory CRPC. Funding: Supported by Io Therapeutics, Inc. 1805 East Garry Ave., Suite 110, Santa Ana, 92705. Clinical trial information: NCT01540071.

**5074 General Poster Session (Board #203), Mon, 1:15 PM-5:00 PM**

**A safety study of trebananib (AMG 386) and abiraterone in metastatic castration-resistant prostate cancer (mCRPC).** *Presenting Author: Michelle A. Ojemuyiwa, Walter Reed National Military Medical Center, Bethesda, MD*

**Background:** Trebananib is an angiopeptide angiopoietin1/2 peptibody antagonist . Androgens stimulate expression of VEGF via activation of hypoxia inducible factor-a (HIFa). Androgen deprivation therapy (ADT) is associated with lower HIF1a gene expression in prostate cancer tissue. Dual targeting of the androgen and angiogenic axis represents a potential synergistic anti-angiogenic therapeutic approach in mCRPC. In this preliminary safety study we hypothesize that trebananib in combination with abiraterone will have a favorable tolerability and efficacy profile. **Methods:** Patients(pts) with mCRPC were treated with abiraterone 1000mg daily and prednisone 5 mg twice daily. Trebananib was administered intravenously every week, in escalating doses from 15mg/kg to 30mg/kg on days 1, 8, 15 and 22 every 28-days. **Results:** A total of 9 pts were enrolled. Three of nine pts had prior chemotherapy. The median age was 63.8 (63-71yrs). No dose limiting toxicities were observed. The most common grade ≥2 toxicities included limb edema (3/9), hyperglycemia (1/9), gastrointestinal (2/9), fatigue (2/9), hypertension (1/9), confusion (1/9), weight gain (1/9) and insomnia (2/9). 5/9 of pts had an overall PSA decline of >30%. 8/9 pts were evaluable for response. Pts previously treated with chemotherapy were on study for 1and 3 months, respectively. Chemotherapy-naïve pts were treated for 1, 6, 9, 10, 10, and 21 months, respectively. **Conclusions:** Trebananib in combination with abiraterone is well tolerated and displayed an acceptable safety profile in pts with mCRPC. Based on this safety data a randomized phase II study randomizing chemotherapy-naïve mCRPC pts to either abiraterone/prednisone plus AMG 386 at 30mg/kg or abiraterone/prednisone is currently accruing at the NCI. Clinical trial information: NCT01553188.

**5075 General Poster Session (Board #204), Mon, 1:15 PM-5:00 PM**

**Symptomatic skeletal events (SSE) in patients with advanced prostate cancer: Results from a phase III trial of denosumab for the prevention of skeletal-related events.** *Presenting Author: Laurence Klotz, University of Toronto, Toronto, ON, Canada*

**Background:** In a randomized controlled trial of men with castration-resistant prostate cancer (CRPC) and bone metastases, denosumab was superior to zoledronic acid (ZA) for reducing skeletal-related events (SRE, defined as pathological fracture, surgery or radiation to bone [including the use of radioisotopes], or spinal cord compression) (Fizazi, et al. Lancet 2011;377:813-822.). Recently, the composite endpoint of symptomatic skeletal event (SSE, defined as symptomatic fracture, surgery or radiation to bone, or spinal cord compression) was introduced as an alternative term/clinical trial endpoint to describe skeletal morbidity. **Methods:** Men with CRPC, ≥ 1 bone metastasis, and no prior IV bisphosphonate use received either SC denosumab 120 mg or IV ZA 4 mg (adjusted for creatinine clearance) in a blinded fashion every 4 weeks. Oral calcium and vitamin D supplements were recommended. SSEs included pathologic fractures considered symptomatic by the investigator, spinal cord compression and surgery and radiation to bone. **Results:** As previously reported, fewer men who received denosumab than ZA had confirmed first SREs, and experienced multiple SREs (Table). Similarly, fewer patients in the denosumab group than the ZA group had confirmed first SSE and multiple SSEs. The median (95% CI) estimate of time to first SSE (superiority analysis) for denosumab was not reached (28.8 mo, not estimable), and for ZA it was 24.2 (20.7, 30.2) mo (HR = 0.78 [0.66, 0.93], $P < 0.01$). **Conclusions:** Denosumab reduced the risk of skeletal events in men with CRPC regardless of endpoint definition as SRE or SSE. The risk of developing SSEs was reduced by up to 22% when comparing denosumab with ZA. Clinical trial information: NCT00321620.

| Number of confirmed skeletal events, n (%) | Denosumab (N = 950) | ZA (N = 951) | Hazard or rate ratio (95% CI) |
|---|---|---|---|
| First SSE | 241 (25.4%) | 289 (30.4%) | HR = 0.78 (0.66, 0.93) $P < 0.01$ |
| First SRE | 341 (35.9%) | 386 (40.6%) | HR = 0.82 (0.71, 0.95) $P < 0.01$ |
| Multiple SSEs | 329 | 409 | RR = 0.78 (0.65, 0.92) $P < 0.01$ |
| Multiple SREs | 494 | 584 | RR =0.82 (0.71, 0.94) $P < 0.01$ |

**5076 General Poster Session (Board #205), Mon, 1:15 PM-5:00 PM**

**Genetic variant in fragile histidine triad gene (*FHIT*) and mortality in prostate and breast cancers: Results from the Prostate, Lung, Colon, Ovarian Cancer Screening Trial (PLCO) and Women's Health Initiative (WHI).** *Presenting Author: Yan Ding, City of Hope, Duarte, CA*

**Background:** Prostate and breast cancers combined account for over 10% of all cancer deaths each year in the U.S. Previous studies detected familial concordance in prostate and breast cancer-specific mortality, suggesting shared genetic component associated with poor survival in the two cancers. We previously identified a genetic locus associated with prostate cancer in a 28.5 kb intronic region of *FHIT*, a triphosphatase that promotes apoptosis in response to DNA damage in epithelial cell.To evaluate its association with mortality, a prostate cancer cohort nested in the PLCO (n=1239) and a breast cancer cohort nested in the WHI (n = 682) were studied. **Methods:** We obtained data on genotypes, tumor characteristics, and outcomes from dbGaP and PLCO, and imputed genotypes for genetic variants within the 28.5 kb region. Multivariable-adjusted Cox proportional hazard regression was used to calculate hazard ratio (HR) of genotypes on mortality due to prostate cancer, breast cancer, or due to all causes, with 95% confidence intervals (CI). Other variables included in the models were age at diagnosis, PSA, Gleason score, stage, and primary treatment for prostate cancer and age at diagnosis for breast cancer. **Results:** We identified a common genetic variant in the *FHIT* locus associated with mortality due to prostate cancer (GG or AG vs. AA, HR = 2.96, 95% CI, 1.05 – 8.27, p = 0.04) or due to breast cancer (HR = 3.76, 95% CI, 1.4 – 10.2, p = 0.01). Furthermore, the variant was associated with all cause mortality in patients who had prostate (HR = 1.98, 95% CI, 1.3 – 3.1, p = 0.003) or breast (HR = 2.00, 95% CI, 1.00 – 1.05, p = 0.017) cancer. The association was stronger in patients who were diagnosed at younger ages or had family history in first degree relatives. We also detected interaction between the *FHIT* variant and treatments with radical prostatectomy or radiation therapy on prostate-cancer specific mortality ($P_{interaction}$ = 0.0045). **Conclusions:** The significant effect of the *FHIT* variant on mortality in both prostate and breast cancers suggests a role for the *FHIT* region on cancer outcomes, justifying further investigation.

**5077 General Poster Session (Board #206), Mon, 1:15 PM-5:00 PM**

**Low-dose abiraterone (abi) with food in men with metastatic castration-resistant prostate cancer (mCRPC): The Princess Margaret Cancer Centre experience.** *Presenting Author: Raya Leibowitz-Amit, Division of Medical Oncology, Princess Margaret Hospital/University of Toronto, Toronto, ON, Canada*

**Background:** Abiraterone (abi) prolongs survival in men with mCRPC [de Bono et al. NEJM 2011; 364:1995.]. Initial studies showed that abi plasma concentrations are higher when administered with a high-fat meal vs the fasting state, and similar maximal plasma drug concentrations and areas under the curve were reported after administration of 250 or 500 mg of abi in the fed-state ('low dose') as after 1000 mg in the fasting state ('full dose') [Attard. JCO 2008; 26:4563. Ryan. JCO 2010; 28:1481.]. Two phase III trials assessed full-dose abi [de Bono et al. NEJM 2011; 364:1995., Ryan. NEJM 2012; 368:138.], and this dose was approved for both pre- and post-chemotherapy. At the Princess Margaret (PM) Cancer Centre, low-dose abi in the fed-state is sometimes prescribed to men who otherwise cannot access the drug due to funding constraints, particularly in the pre-chemotherapy setting. **Methods:** All men treated with abi at PM until Mar-2013 were reviewed. Associations between dose (full vs. low) and PSA response rate (PSA-RR), progression free survival (PFS), and overall survival (OS) were assessed using chi-square and log rank tests, respectively. PSA-RR was defined as a confirmed PSA decrease ≥50%, PFS was from start of abi to PSA progression, clinical progression, drug cessation, or death, and OS from start of treatment to death. **Results:** 90 and 21 men were treated with full or low dose abi, respectively. PSA-RR was non-significantly lower in chemo-naive men treated with low doses compared to full doses (p=0.09), but there were no significant differences in PFS or OS for both the entire cohort and the chemo-naïve cohort (table). **Conclusions:** Administration of low dose abi after a high-fat meal is not associated with shorter PFS or OS despite a trend to lower PSA-RR. These results may be relevant in resource-limited settings and warrant further prospective clinical research.

| | Dose | N | PSA-RR % (95% CI) | *P* value | median PFS, months (95% CI) | *P* value | Median OS, months (95% CI) | *P* value |
|---|---|---|---|---|---|---|---|---|
| All men | Full | 90 | 43 (32-54) | 0.36 | 4.4 (2.8-5.7) | 0.3 | 18.7 (14.8-22.1) | 0.25 |
| | Low | 21 | 32 (13-57) | | 5.6 (2.1-8.0) | | 16.6 (13.4- nr) | |
| Chemo-naive | Full | 34 | 53 (35-71) | 0.09 | 5.5 (4.4-6.5) | 0.9 | 18.8 (14.8-32.1) | 0.49 |
| | Low | 16 | 27 (8-55) | | 4.6 (2.0-8.0) | | nr (15.3-nr) | |

**5078 General Poster Session (Board #207), Mon, 1:15 PM-5:00 PM**

**Population-based analysis of a novel prognostic model for metastatic castration-resistant prostate cancer (mCRPC) patients (pts) treated with abiraterone acetate (AA).** *Presenting Author: Arun Azad, British Columbia Cancer Agency, Vancouver, BC, Canada*

**Background:** A prognostic model for predicting overall survival (OS) in mCRPC pts commencing AA was recently developed from a post-hoc analysis of the COU-AA-301 trial. The model consists of 6 pre-treatment risk factors (RF): ECOG performance status (PS) ≥2, presence of visceral metastases, time from start of androgen deprivation therapy (ADT) to start of AA ≤36 months (mos), low albumin (≤40g/L), high ALP (>160 IU/L) and high LDH (>250 IU/L). Our aim was to evaluate this model in a population-based cohort. **Methods:** Three Canadian cancer registries were used to identify mCRPC pts treated with AA. OS was estimated by the Kaplan-Meier method and compared by log-rank. Multivariate analysis was performed with the Cox proportional hazard regression model. **Results:** In post-docetaxel pts (n=286), 21%, 50% and 28% were classified into good (0-1 RF), intermediate (2-3 RF) and poor (4-6 RF) prognosis (prog) groups respectively based on the COU-AA-301 model. Median OS was significantly longer for good prog pts (23.9 mos) compared to intermediate (16.2 mos) and poor prog pts (8.0 mos) (Table). ECOG PS (p<0.001), LDH (p=0.040), albumin (p=0.003), visceral metastases (p<0.001) and time from start of ADT to start of AA (p=0.037) were confirmed as independent prognostic factors. In docetaxel-naïve pts (n=138), 31%, 50% and 19% were classified into good, intermediate and poor prog groups respectively. Median OS was significantly longer for good prog pts (36.9 mos) compared to intermediate (13.3 mos) and poor prog pts (7.3 mos) (Table). **Conclusions:** In a population-based setting, our data validate the COU-AA-301 model as a tool for prognostic stratification of both docetaxel-experienced and –naïve mCRPC pts treated with AA. This model can be used to predict outcomes for individual pts and to assist in selection of pts for clinical trials based on expected prognosis.

| | Post-docetaxel pts | | Docetaxel-naïve pts | |
|---|---|---|---|---|
| **Prognostic group** | **HR (95% CI)** | ***P* (log-rank)** | **HR (95% CI)** | ***P* (log-rank)** |
| **Good (0-1 RF)** | Reference | - | Reference | - |
| **Intermediate (2-3 RF)** | 2.02* (1.30, 3.12) | 0.001 | 4.70* (2.06, 10.74) | <0.001 |
| **Poor (4-6 RF)** | 4.41* (2.79, 6.97) | <0.001 | 12.19* (4.77, 31.11) | <0.001 |

*Versus good prog group.

**5079^ General Poster Session (Board #208), Mon, 1:15 PM-5:00 PM**

**Long-term efficacy and safety of androgen receptor inhibitor ODM-201 in ARADES phase I/II trial.** *Presenting Author: Christophe Massard, Gustave Roussy, University Paris Sud, Villejuif, France*

**Background:** ODM-201, is an novel oral androgen receptor (AR) inhibitor that has shown good preclinical efficacy, and has high antitumor activity in metastatic CRPC (mCRPC) patients (pts) (Fizazi et al. 2013). **Methods:** We report the long-term data in CYP17i-naïve progressive mCRPC pts in the ARADES phase I/II trial and the phase II extension study, in which pts were enrolled into dose levels of 100mg bid, 200mg bid or 700mg bid. Radiographic progression was evaluated either according to RECIST 1.1 for soft tissue or defined by at least 2 new lesions in bone compared to a prior scan. **Results:** 69 pts had progressive mCRPC; 37 pts were chemotherapy-naïve and 32 chemotherapy-pretreated. The median age was 69 yrs (53-83 yrs). 59 pts (86%) had bone metastases and 12 (17%) had visceral metastases. The median PSA was 99 ng/mL (3-1294) and the CTC count was 5 or more CTCs per 7.5ml in 42% of the pts. Forty-six (67%) pts continued drug over 12 weeks (wks). With a median follow-up of 38 wks the median time to PSA progression was 36 (95% CI: 24–74) wks for chemotherapy-naïve pts, and 21 (95%CI: 16–28) wks for chemotherapy-pretreated pts. The median time to radiographic progression was not reached for chemotherapy-naïve (95% CI: 24–not reached), and was 32 (95% CI: 12–not reached) wks for chemotherapy-pretreated pts. Treatment related AEs occurred in 22/69 (32%) pts. Most commonly reported treatment related AEs in the trial were asthenia/fatigue 6 (9%), decreased appetite 4 (6%), arthralgia 2 (3%), back pain 2 (3%), diarrhea 2 (3%), headache 2 (3%), hot flushes 2 (3%), and myalgia 2(3%), mostly mild to moderate. **Conclusions:** These data are in line with 12-wk efficacy and safety data reported previously, and show high anticancer activity and favorable tolerability of ODM-201. Clinical trial information: NTC01317641; NTC01429064.

**5080 General Poster Session (Board #209), Mon, 1:15 PM-5:00 PM**

**Role of serum lipids and glucose as biomarkers of prostate cancer severity.** *Presenting Author: Alejo Rodriguez-Vida, Medical Oncology department, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom*

**Background:** We have previously shown in a Swedish cohort study that high levels of triglycerides (TG) and glucose and low levels of high density lipoprotein (HDL) cholesterol and apolipoprotein A-I (apoA-I) are related to increased prostate cancer (PC) risk. The current study investigates serum lipids and glucose in relation to severity of localized PC, at time of diagnosis and at metastatic progression. **Methods:** Between 2001-2004, 203 consecutive patients with localized PC were recruited. Levels of total cholesterol (TC), HDL and low density lipoprotein (LDL) cholesterol, TG, apoA-I, apolipoprotein B (apoB), and glucose were assessed at baseline, with a second measure for 74 patients after a median time of 10 years. Correlation coefficients and multivariate logistic and Cox proportional hazards regression was used to assess associations between metabolic components and PC severity at time of diagnosis and at metastatic progression. **Results:** Median age at diagnosis was 65 years (range: 40-76), with a median follow up of 8.1 years (0.4-13.9). 66 men underwent radical radiotherapy (33%), 57 radical prostatectomy (28%), 27 active surveillance (13%) and 17 watchful waiting (8%). At baseline, we found a statistically significant inverse correlation between PSA and the apoB/apoA-I, LDL/HDL, and TC/HDL ratios (r=-0.18, r=-0.17, r=-0.18 respectively; P<0.05). Gleason score was positively associated with HDL and inversely with TC/HDL (r=0.15, r=-0.14; P<0.05). There was no association between the second lipid measurements and baseline PSA, but HDL remained positively associated with baseline Gleason and TG inversely associated (r=0.24, r=-0.30; P<0.05). Age-adjusted multivariate model including TG, HDL, glucose, and hypertension showed a statistically significant association between glucose and Gleason ≥7 versus <7 (OR 1.14, 95%CI: 1.00-1.29). A similar model for PSA ≥15 versus <15 did not show any statistically significant results, whereas an equivalent Cox model for progression to metastasis also showed a weak positive association with glucose (HR 1.13, 95%CI: 0.95-1.35). **Conclusions:** Our study supports the hypothesis that metabolic markers such as serum lipids and glucose may be a biomarker of prostate cancer severity.

**5081 General Poster Session (Board #210), Mon, 1:15 PM-5:00 PM**

**Improving the specificity of prostate cancer screening for early detection of lethal disease.** *Presenting Author: Hans Lilja, Memorial Sloan-Kettering Cancer Center, New York, NY*

**Background:** PSA is used to detect prostate cancer, but many men need to be screened, biopsied, and diagnosed to prevent one cancer death. We sought to increase the specificity of screening for lethal prostate cancer. **Methods:** We conducted a nested case-control study to determine the relationship between four kallikrein markers (kallikrein related peptidase 2, total, free, and intact PSA) and long-term risk of metastasis. Of the 40,379 men providing blood at age 40, 50, and 60 during 1986-2009 for the Västerbotten Intervention Project, 12,561 were followed for over 15 years. Using the Swedish Cancer Registry, 1,423 incident prostate cancer cases and 235 men with evidence of distant metastases were identified. Kallikrein markers were measured in cryopreserved blood from cases and controls. **Results:** Risk of prostate cancer metastasis at 20 years was higher (16-fold at age 60, 7-fold at age 50, 3-fold at age 40) among men with PSA in top quartile than men with PSA below median. Most metastatic cases occurred in men with PSA in top quartile at age 50 (69%) or 60 (73%). Among men with PSA levels above median, a pre-specified model based on four kallikrein markers improved prediction of distant metastasis documented 10-20 years later compared to PSA alone. Among men with PSA ≥2 ng/ml at age 50, discrimination increased from 0.77 (PSA alone) to 0.88 (kallikrein panel); for men with PSA ≥2 ng/ml at age 60, discrimination increased from 0.81 to 0.87. We also conducted a decision analysis evaluating hypothetical outcomes had the panel been used to aid decisions about biopsy in this cohort. Using the biopsy cutoff used in the European randomized prostate cancer screening trial (PSA ≥3 ng/ml) would have resulted in biopsies performed on 15.5% of men with blood drawn at age 60. This rate would have been reduced by 38% if biopsy were restricted to those with ≥7.5% risk of high-grade cancer according to the panel. However, 10 to 15-year risk of distant metastases was only 0.18% to 1.16% in this group; a 15-year risk of metastases less than an eighth of that for those with PSA ≥3 ng/ml and ≥7.5% risk score. **Conclusions:** The specificity of PSA screening can be improved by focusing on men with modestly elevated PSA at age 50-60 and by reflex testing of four kallikrein markers.

**5082 General Poster Session (Board #211), Mon, 1:15 PM-5:00 PM**

**A biopsy-based molecular diagnostic test for prediction of aggressive prostate cancer despite variability in pathology assessment.** *Presenting Author: Jeffry P. Simko, University of California, San Francisco, San Francisco, CA*

**Background:** The 17-gene Genomic Prostate Score, GPS (Genomic Health, Inc., Redwood City, CA), has been analytically (Knezevic et al. BMC Genomics 2013) and clinically validated as a biopsy-based predictor of adverse pathology at radical prostatectomy (RP) (Cooperberg et al. AUA 2013). In the clinical study, central review of biopsy and RP pathology was performed by a single expert uropathologist (JS). Given inter-observer variability of pathologic interpretations, we assessed the ability of GPS to predict adverse pathology at RP based on the original diagnostic reads. **Methods:** RP patients treated at UCSF from 1997-2011 for clinical low or low-intermediate risk PCa (biopsy Gleason score [GS] 3+3, or 3+4 with ≤ 3 (or 33%) positive cores; PSA ≤ 20; clinical stage ≤ T2) were eligible for the study. The original biopsy GS, RP GS and pathologic T stage reflected diagnoses rendered by > 15 different UCSF pathologists. GPS, using a 100-unit scale, was assessed by qRT-PCR of mRNA from microdissected biopsy tumor tissue. Adverse pathology at RP was defined as major pattern 4 or any pattern 5 and/or pT3 stage. Univariate and multivariable logistic regression models were used. **Results:** Of 395 patients, 295 (75%) had biopsy GS 6 disease based on original pathology review and 301 (76%) based on central review with 24% discordance. GPS was predictive of adverse pathology defined by central RP review after adjusting for either central biopsy GS (GPS OR/20 units=1.93, 95% CI: 1.30-2.88, p=0.001, GS OR=1.94, 95% CI: 1.17-3.21, p=0.011) or original biopsy GS (GPS OR/20 units=1.98, 95% CI: 1.33-2.93, p <0.001, GS OR=1.82, 95% CI: 1.11-2.98, p=0.019). At RP, 123 (31%) and 66 (17%) patients had adverse pathology based on central review and original review, respectively. Discordance for RP GS was 26% and for pT stage 14%. In univariate models, GPS was a significant predictor of adverse pathology at RP as assessed by central ($p < 0.001$) or original ($p < 0.001$) pathology review. **Conclusions:** The observed discordances between separate pathology assessments of grade and stage are consistent with previous studies. GPS is a robust predictor of adverse pathology despite differences in Gleason scoring and pathologic stage assessment.

**5083 General Poster Session (Board #212), Mon, 1:15 PM-5:00 PM**

**Active surveillance in phenotypically heterogeneous early-stage prostate cancer.** *Presenting Author: John W. Davis, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Active surveillance (AS) in prostate cancer (PC) is predicated on slow, stepwise disease (Dz) progression. Patient (Pt) selection, although not standardized in prospective AS trials, is based on clinical stage, prostate-specific antigen (PSA), and phenotypic characteristics of tumors on biopsy (BX). Changes on repeat BXs often trigger intervention. In a single-institution prospective cohort study, pts with early stage PC were stratified to AS group (GR) I (favorable risk), II (pt's choice), or III (competing comorbidities prevent local therapy [TX]). We describe early results for GR II, use of confirmatory and subsequent BX, and reclassification and TX rates. **Methods:** Enrolled 2006-2012 were 191 men into GR I, 369 into GR II, and 14 into GR III. GR I required a single core of Gleason score (GS) 3+3 < 3mm, or 3+4 < 2mm, and a PSA < 4 ng/mL. Pts with a life expectancy >10 years (yr) selecting AS were considered GR II. Pts had mandatory confirmatory BX at registration or within 6 months (mo) of diagnostic BX, and then repeat BXs every 1-2 yr. PSA and digital rectal examination were done every 6 mo. Dz was reclassified based on increases in tumor volume (TV) or grade. **Results:** In 369 GR II pts, clinical stage cT1c was found in 86%; median PSA was 4.4 ng/mL; and GS was 3+2 in 0.3%, 3+3 in 77.2%, 3+4 in 19.2%, and 4+3 in 3.3%. After a median 3 yr follow-up, 119 (32%) had been treated with curative modalities—surgery (43%), radiation (53%), and cryotherapy (3%). One pt (PSADT, <2 yrs; GS, 6 to 7) had an anterior tumor and a positive pelvic lymph node at 1.5 yrs. One pt with pT3b N0 at surgery at 9 mo had persistently elevated PSA. Time on study pre-TX was <6 mo in 53%, 6-<12 mo in 8%, 12-<24 mo in 24%, 24-<36 mo in 9%, and 36->48 mo in 5%. Dz was reclassified on BX that triggered TX in 106 pts based on increased BX TV and/or GS upgrading in 74 (70%) (6 to >7 in 61 [82%], 3+4 to 4+3 in 7 [10%], and Gleason 7 to >7 in 6 [8%]). **Conclusions:** In a prospective AS cohort with phenotypically heterogeneous tumors, one third were eventually treated for cure—mostly in the first yr, owing to BX variability. Biologically concerning TX triggers (GS 6/7 to 8/9) occurred in 12% of treated. Despite limitations of selection criteria and monitoring tools, AS is an important initial option in localized PC.

**5084 General Poster Session (Board #213), Mon, 1:15 PM-5:00 PM**

**Prognostic value of free testosterone (FT) levels during salvage chemotherapy with carboplatin plus weekly docetaxel in metastatic castration- and docetaxel-resistant prostate cancer (mDRPC).** *Presenting Author: Christoph W. Reuter, Department of Hematology, Hemostasis, Oncology, and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany*

**Background:** Recent data suggest that carboplatin plus weekly docetaxel (DC) may be effective in mDRPC. Platinum(II)-complexes have been shown to interfere with steroid biosynthesis lowering testosterone levels by inhibiting the cholesterol side chain cleavage enzyme (CYP11A1), 3$\beta$-hydroxysteroid dehydrogenase (HSD3B1,2) and 17$\alpha$ hydroxylase/C17,20-lyase (CYP17A1). **Methods:** Docetaxel failure/resistance was defined according to the Prostate Cancer Working Group (PCWG2 2007) criteria. Treatment consisted of at least two cycles of carboplatin AUC5 iv for 30 min on day 1 every 4 weeks (q4w), docetaxel at a dose of 35 mg/m2 iv for one hour on days 1, 8, (15) plus prednisone 2x5mg/day orally after receiving informed consent until disease progression or occurrence of intolerable adverse effects. Efficacy measures were done following PCWG2 recommendations. Free testosterone levels were measured before (n=59) and during DC chemotherapy (n=52). **Results:** Of the 84 pts. treated since February 2005, 95.2% had bone, 41.7% lymph node, 27.4% liver and 17.9% lung involvement. At the time of the current analysis, the median follow-up time was 15.1 months, 64 pts. had died and 75 had progressive disease. The objective response rate was 40.0% and the disease control rate 62.0% in the 50 pts. with measureable disease. Response of prostate-specific antigen (≥50%) was observed in 40/84 (47.6%) patients. Median progression-free survival (PFS) for all patients was 6.9 months (CI 95% 6.0, 7.8) and median OS was 17.9 months (CI 95% 12.6, 23.0). The most common reversible grade 3/4 toxicity was leukopenia/neutropenia (42.9/38.1%). Median free testosterone levels were 0.69 pg/ml before and <0.18 pg/ml during carboplatin/docetaxel treatment (p<0.001; detection limit <0.18 pg/ml). In multivariate analyses, LDH, number of radiation treatments, PSA response, free testosterone nadir levels, and total androgene nadir levels during DC treatment were associated with longer OS (p<0.05).**Conclusions:** These data suggest that DC may be an important second-line treatment option for DRPC patients by inhibiting the testosterone biosynthesis.

**5085 General Poster Session (Board #214), Mon, 1:15 PM-5:00 PM**

**Neuroendocrine differentiation patterns in metastases from advanced prostate cancer.** *Presenting Author: Rafael E. Jimenez, Mayo Clinic, Rochester, MN*

**Background:** Neuroendocrine differentiation (NED) in advanced prostate cancer (APC) is considered an aggressive phenotype with poor outcome and limited treatment options. Diagnosis depends on histological confirmation, which is not routinely performed during clinical care. Thus, information on NED in metastatic APC is rather limited. We evaluated an archival set of metastatic site biopsies (MSB) to determine NED expression patterns in APC. **Methods:** We searched medical and pathological databases for APC patients (pts) who underwent MSB during routine clinical care. Formalin-fixed, paraffin-embedded tissue sections were analyzed by immunohistochemistry (IHC) for expression of chromogranin-A (CGA) and synaptophysin (SYN), and graded as 0, 1+, 2+, or 3+, according to staining in none, <10%, 11-50%, or >50% of tumor cells, respectively. A score of 1+ or greater was considered positive. NED was considered present if positivity for either marker was observed **Results:** From 1994 to 2013, 237 MSB from 187 pts were identified (39, 9, and 2 pts had two, three and four MSB, respectively). MSB included bone (102), lung (40), liver (40), lymph node (20), bladder (14), soft tissue (11), brain (4), others (4). All tumors were adenocarcinomas or poorly differentiated carcinomas. No small cell carcinomas were identified. A total of 183 MSB from 157 pts were successfully stained for both markers, of which 92 MSB (50%) from 79 pts (50%) showed positive NED (72/142 1$^{st}$, 16/29 2$^{nd}$, 3/6 3$^{rd}$, and 1/1 4$^{th}$ MSB). In 7 of these patients the NED was demonstrated in a successive MSB, after a negative 1$^{st}$MSB. NED expression was positive in 41% bone sites, compared to 53% of non-bone sites (p=0.112). Clinical annotation was available for 72 pts, of which 47 underwent MSB during hormone sensitive stage (HSPC) and 25 during castrate resistant (CRPC) stage (median PSA 5.6 and 7.5 ng/ml, respectively). NED expression was observed in 21 (44%) HSPC cases, and 14 (56%) of CRPC cases (p=0.36). **Conclusions:** NED in APC was more common in this cohort than historically reported. This may have relevant prognostic or therapeutic implications. More than one MSB may be necessary to document NED in a patient with APC, as patterns of NED may vary within the same patient.

**5086 General Poster Session (Board #215), Mon, 1:15 PM-5:00 PM**

**Effect of abiraterone acetate and low-dose prednisone on PSA in patients with nonmetastatic castration-resistant prostate cancer: The results from IMAAGEN core study.** *Presenting Author: Charles J. Ryan, University of California San Francisco, San Francisco, CA*

**Background:** Abiraterone acetate (AA) is a prodrug of abiraterone, which is a selective, irreversible CYP17 inhibitor of androgen biosynthesis and significantly reduces testosterone production in the testes, adrenal glands and prostate cancer tissue. AA, 1000mg, in combination with prednisone (P), 10mg daily is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC). Patients with non-metastatic CRPC (nmCRPC) will eventually progress to mCRPC. Currently there is no approved therapy for nmCRPC. This phase II, multi-center study evaluated the ability of AA plus 5 mg of prednisone to decrease PSA levels in patients with nmCRPC and rising PSA. **Methods:** All patients had nmCRPC but with clinical features placing them at higher risk of developing mCRPC: PSA value $\geq$ 10ng/mL or PSA doubling time $\leq$ 10 months at screening. Patients received AA 1000mg with P 5mg (AA+P5) daily. The primary endpoint was PSA response rate at 6 months. Key secondary endpoints included change in testosterone levels, safety, time to PSA progression and time to radiographic disease progression. PSA assessment and imaging scans were conducted every 3 months. **Results:** From May 2011 to July 2013, 131 patients were enrolled at 38 sites in the US. Data cutoff for this analysis was December 31, 2013. Median age was 72 years (range 48-90). Median baseline PSA was 13.7ng/mL (range 1.6-167.8ng/mL). There were 122 patients evaluable for the analysis of PSA response. By the end of 6 cycles of treatment, 87% (106/122) of patients had $\geq$ 50% reduction in PSA and 60% (73/122) had $\geq$ 90% PSA reduction. To date, no patient has had his prednisone dose increased to greater than 5mg to manage symptoms of mineralocorticoid excess. Complete details of radiographic progression and other secondary endpoints including safety will be available by the time of the ASCO meeting. **Conclusions:** In men with high-risk nmCRPC, treatment using AA+P5 is very effective in lowering PSA. The rate and depth of PSA decline appear superior to men with mCRPC. Clinical trial information: NCT01314118.

**5087 General Poster Session (Board #216), Mon, 1:15 PM-5:00 PM**

**Dose escalation with high-dose-3D-conformal (HD-3D-CRT) or low-dose 3D-conformal radiotherapy PLUS HDR brachytherapy (LD-3D-CRT+HDR-B) for intermediate- or high-risk prostate cancer: Higher disease control and survival with lower toxicity.** *Presenting Author: Benjamin Guix, IMOR Foundation, Barcelona, Spain*

**Background:** To report early and late toxicity and biochemical outcome in a prospective series of 445 patients with intermediate- or high-risk clinically localized prostate cancer treated with either HD-3D-CRT or with LD-3D-CRT+HDR-B. **Methods:** Between 12/1999 and 10/2005, 445 patients (pts) with PSA›10, Gleason score›6 and/or T2b-T3 N0 M0 prostate cancer entered the study. Pts were prospectively assigned to one of the two treatment groups: 76 Gy HD-3D-CRT to the prostate in 38 fractions (group 1; 223 patients) or 46 Gy LD-3D-CRT+ 16 Gy HDR-B given in 2 fractions of 8 Gy (group 2, 222 patients), limiting the maximum rectal dose to 85% of the prescribed dose. Both groups were well balanced taking into account patient's as well as tumors' characteristics. Toxicities were scored by the EORTC /RTOG morbidity grading scales. Special attention to local, regional or distant recurrence, survival, late effects, PSA and testosterone levels and quality of life was done. **Results:** All pts completed treatment. None pts included in the group 1 or 2 experienced grade 3 or more rectal toxicity. 28 pts of group 1 (12.5%) and 6 pts of group 2 (2.7%) developed grade 2 rectal toxicity (rectal bleeding or urgency). 15 pts in group 1 (6.7%) and 3 pts in group 2 (1.3%) developed grade 1 rectal bleeding (less than 2 times/week). With a mean follow-up of 96 months, the 10-year free-from-failure survival was 90.7% and 98.3% ($p<0.002$) in group 1 and 2 respectively; free-from-metastases survival 96.9% and 97.9% ($p<0,008$)for group 1 and 2 respectively; and cause-specific survival 97.4% and 98.3% ($p<0.09$). **Conclusions:** High-dose 3D-EBRT + HDR brachytherapy was a safe and effective method of escalating the dose to the prostate without increasing the risk of late effects. Acute as well as late rectal complications were significantly reduced with the combined treatment, compared with what was observed with high-dose conventional, 3D-conformal radiotherapy. Control rates were better with in the HDR-boosted patients as expected by higher effective-dose.

**5088 General Poster Session (Board #217), Mon, 1:15 PM-5:00 PM**

**Molecular profiling of metastatic castration-resistant prostate cancer (mCRPC): Preliminary results from the SU2C/PCF/AACR West Coast Prostate Cancer Dream Team (WCDT).** *Presenting Author: George Thomas, Oregon Health & Science University, OHSU Knight Cancer Institute, Portland, OR*

**Background:** The molecular basis of mCRPC has not been well characterized because of its bone tropism and difficulties in obtaining adequate tissue to evaluate. Bringing next-gen sequencing into clinical (CLIA-licensed) laboratories is an important step in the advancement of personalized cancer care in these patients (pts). As part of the WCDT project, we are conducting next-gen, semiconductor-based sequencing using the GeneTrails®Solid Tumor Panel, which covers 37 commonly mutated cancer genes. **Methods:** mCRPC pts, both abiraterone and enzalutamide naive and resistant, underwent biopsy (bx) at one of 5 WCDT clinical sites. Oncogenic mutations or amplifications in 37 genes were detected in formalin-fixed, paraffin embedded (FFPE) bone and soft issue bx using amplicon + semiconductor-based sequencing within a CLIA-certified laboratory. PTEN status was also examined by immunohistochemistry. **Results:** 60 of 300 planned mCRPC pts have undergone a metastasis bx. FFPE tissue has been evaluated by sequencing in 26 of these bx. Bx sites were: bone (n=8), lymph node (n=9) liver (n=7) lung (n=1), and adrenal (n=1). Mutations were found in 16 (62%) of the samples, with a greater rate of mutations in soft tissue (13/18) vs. bone (3/8). The most frequent mutations were in *TP53* (N = 11, 42%), followed by *PTEN* (N = 4, 15%), *RB1* (N = 4, 15%), *PIK3CA* (N = 2, 7.6%). Single instances of mutations were observed for *AKT1, DDR2, EGFR, KIT, NOTCH1, TSC1, TSC2* and *HRAS* (3.2% each). Amplification of *EGFR* and *FGFR1* were also noted. 90% of these alterations are known to result in either gain or loss of function. PTEN loss by IHC and/or mutation was seen in 12 of 26 (46%) of pts. Overall, 13 pts (50%) demonstrated at least one alteration in the PTEN/PI3K/AKT axis. **Conclusions:** Bx from mCRPC pts, including bone, can be used for prospective molecular profiling of tumor biopsy specimens. The most common alterations were found in the PTEN/PI3K/AKT pathway (50%), p53 (11%) and RB1 (15%). Combining amplicon + semiconductor-based next-gen sequencing provides a fast, cost-effective and reliable approach to potentially clinically actionable targeted sequencing data from mCRPC sites.

**5089 General Poster Session (Board #218), Mon, 1:15 PM-5:00 PM**

**Activity of subsequent new drugs (NDs) in post-docetaxel (DOC) failure for metastatic castration-resistant prostate cancer (mCRPC) patients (pts): A multicenter Italian experience.** *Presenting Author: Orazio Caffo, Santa Chiara Hospital, Trento, Italy*

**Background:** Abiraterone acetate (AA), cabazitaxel (CABA), and enzalutamide (ENZ) may prolong survival in mCRPC pts progressing after DOC, although it is not clear how to use NDs, to best exploit their efficacy and avoiding their possible cross resistances. We report a large series of pts, receiving 2 NDs (or 3 in a limited series), after DOC progression in routine clinical practice. **Methods:** All NDs were available in Italy through a compassionate use program, or after the regulatory authorities approval (only CABA in 2012 and AA in 2013). Based on a multi-institutional collaboration, we collected data of pts who received at least 2 NDs after DOC. **Results:** A consecutive series of 203 mCRPC pts, median age 70 yrs (46-91), with bone (87%), nodal (57%) or visceral (17%) mets, was identified. All received NDs as 2nd and 3rd line after DOC, but 31 also as 4th line. The biochemical response rate (bRR) ($PSA^- > 50\%$) was 37% in 2nd line, 17% in 3rd and 6% in 4thline, while the rate of objective response (oRR) was 17%, 16% and 6%, respectively and the median PFS was 6, 4 and 3 mos respectively. The table reports the outcomes of AA, CABA and ENZ according to the sequence adopted. **Conclusions:** At our knowledge this retrospective study reports the highest number of pts treated post-DOC with at least 2 NDs and it is the first to provide 4th line data. It appears from our findings that similar bRR and oRR are achieved by CABA and ENZ while AA seems less active in 3rd line and that responses in 4th line are rare (only with CABA).

| | 2nd line | | | | | 3rd line | | | | 4th line | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | eval pts | bRR (%) | oRR (%) | median PFS (mos) | Sequence | eval pts | bRR (%) | oRR (%) | median PFS (mos) | eval pts | bRR (%) | oRR (%) | median PFS (mos) |
| **AA** | 114 | 32 | 15 | 7 | AA post CABA | 44 | 23 | 20 | 4 | 3 | 0 | 0 | 1 |
| | | | | | **AA post ENZ** | 8 | 0 | 0 | 3 | 5 | 0 | 0 | 2 |
| **CABA** | 65 | 47 | 24 | 7 | CABA post AA | 67 | 27 | 16 | 5 | 0 | - | - | - |
| | | | | | **CABA post ENZ** | 16 | 37 | 19 | 4 | 9 | 11 | 11 | 4 |
| **ENZ** | 24 | 37 | 8 | 4 | ENZ post AA | 47 | 36 | 17 | 3 | 4 | 0 | 0 | 4 |
| | | | | | **ENZ post CABA** | 21 | 38 | 19 | 6 | 10 | 0 | 0 | 3 |

**5090 General Poster Session (Board #219), Mon, 1:15 PM-5:00 PM**

**Distinguishing aggressive versus nonaggressive prostate cancer using a novel prognostic proteomics biopsy test, ProMark.** *Presenting Author: Fred Saad, University of Montréal Hospital Center, CRCHUM, Montréal, QC, Canada*

**Background:** Current clinical and pathological parameters are insufficient for accurate prediction of progression risk for patients with biopsy Gleason grades 3+3 or 3+4. Reasons for this include biopsy sampling error and pathologist grading discordance, resulting in inaccurate prostate pathology assessment. Consequently, a majority of these patients are over-treated. We have established a novel proteomics-based test, ProMark for automated quantitative measurements of biomarkers from tumor epithelium of intact FFPE biopsy tissue. The test generates a personalized risk score predictive of prostate tumor pathology at the time of biopsy. **Methods:** A clinical biopsy simulation study using prostatectomy tissue (N=380) was designed to identify 12 biomarkers that can predict surgical Gleason score and lethal disease despite sampling error. Next, a clinical study of 381 biopsies with matched prostatectomy annotation was done to select the best marker subset predictive of prostate pathology. Subsequently, the locked model was validated in a separate blinded clinical study with centralized Gleason grading (N=274). **Results:** The Promark risk scores were strongly predictive of prostate tumor pathology, the primary study objective. The test was able to separate 'favorable' cases [surgical Gleason score 3+3 or 3+4; organ-confined (<=pT2)] from 'non-favorable' cases [non-organ-confined disease (≥T3a, N, or M) or surgical Gleason >=4+3] with an AUC of 0.68 (0.61-0.74;p<0.0001). At risk score <0.33 the specificity for prediction of favorable disease is 90% with a predictive value of 81%. At a risk score > 0.8, the predictive value for non-favorable disease is 77%. Importantly, ProMark provides improved personalized disease prediction relative to standard risk stratification systems, including NCCN and D'Amico. **Conclusions:** We have established a novel prognostic test, ProMark, for prostate cancer biopsies. The risk scores are generated independent of clinical and pathological parameters and correlate strongly with pathological outcome. The test could be useful as an aid in clinical decision making for stratification of patients into good and poor candidates for active surveillance.

**5091 General Poster Session (Board #220), Mon, 1:15 PM-5:00 PM**

**The influence of insurance status on racial disparities in the treatment of African American men with high-risk prostate cancer.** *Presenting Author: Brandon A. Mahal, Harvard Medical School, Boston, MA*

**Background:** Treating high-risk prostate cancer (CaP) definitively improves survival. We evaluated whether having health insurance reduces racial disparities in the use of definitive therapy for high risk CaP. **Methods:** The Surveillance, Epidemiology and End Results Program was used to identify 70,006 men with localized high-risk CaP (PSA > 20 or Gleason 8-10 or stage > cT3a) diagnosed from 2007 – 2010. We used multivariable logistic regression to analyze the 64,277 patients with complete data to determine the factors associated with receipt of definitive therapy. **Results:** Compared to white men, African American (AA) men were significantly less likely to receive definitive treatment (adjusted odds ratio [OR] 0.60; 95% CI 0.56 – 0.64; $P < 0.001$) after adjusting for sociodemographics and known CaP prognostic factors. There was a significant interaction between race and insurance status ($P_{interaction} = 0.01$) such that among uninsured men, the adjusted OR for definitive treatment for AA vs. white was 0.38 (95% CI 0.27 – 0.54; P < 0.001), but among insured men, the adjusted OR was 0.62 (95% CI 0.57 – 0.66; P<0.001), suggesting that among insured men, there was a reduction in racial disparity between AA and white patients with regards to receipt of definitive therapy. **Conclusions:** AA men with high-risk CaP were significantly less likely to receive potentially life-saving definitive treatment when compared to white men. Having health insurance was associated with a reduction in this racial treatment disparity, suggesting that expansion of health insurance coverage may help reduce racial disparities in the management of aggressive cancers.

**Assessment of effect modification between insurance status and race for the outcome of employment of definitive therapy. All men were diagnosed with high-risk prostate cancer from 2007 – 2010 (N = 64,277).**

| | *Multivariable analysis | |
|---|---|---|
| **Characteristic** | **Adjusted OR (95% CI)** | ***P*-value** |
| **Interaction for employment of definitive therapy** | | 0.01 |
| **Race** | | |
| **White** | 1.47 (1.15 – 1.89) | 0.002 |
| **African American** | 2.23 (1.72 – 2.88) | < 0.001 |

*Multivariable analyses are adjusted for age, income, education, residence, cancer stage, and Gleason score.

**5092 General Poster Session (Board #221), Mon, 1:15 PM-5:00 PM**

**Identifying biomarkers specific to bone metastases in castrate-resistant prostate cancer.** *Presenting Author: Maahum Ali Haider, University of Washington, Seattle, WA*

**Background:** Castrate-resistant prostate cancer (CRPC) has a propensity to metastasize to bone. There is evidence to suggest a differential response to treatment in bone versus visceral metastases. We sought to identify molecular targets specific to CRPC bone metastases. **Methods:** Liver (n=19), lymph node (n=68), and bone metastases (n=20) from 54 CRPC patients were laser capture microdissected to identify biomarkers using Agilent Expression Arrays. Tissue microarrays (TMAs) were used to validate the differential expression of proteins of interest in bone (n=117) and visceral (n=65) metastases. Prosaposin (PSAP) was evaluated in serial serum samples from men who presented with localized, recurrent, and metastatic disease. **Results:** Gene Set Enrichment and Ingenuity Pathway Analyses identified pathways that were altered between bone and visceral metastases (q<0.05): 1) Epithelial mesenchymal transition (ZEB1/2, SNAI1/2, TGFB1, VIM), 2) Survival (BAD, BAX), 3) Innate immune response (CNN2, COL4A1, CCL14, FPR1, TLR4, MMP9, SERPINF1) and 4) Osteomimetic (POSTN, SPP1, RUNX2, DKK1, DMP1, IBSP, THBS3). Based on TMAs, both nuclear and cytoplasmic Twist were higher in bone than in visceral metastases ($p<0.01$). Nuclear Twist and SLUG were associated with fibroblast-like epithelial cells, suggesting that a subset of nuclear-Twist positive CRPC cells in the bone have high metastatic potential. BCL-2 and MCL-1 survival proteins have been shown to be decreased in CRPC bone metastases. Here we show that BAX and BAD are overexpressed. Moreover, we validated the increased expression of osteomimetic proteins and determined that serum PSAP (which has been associated with disease progression) is elevated in patients who developed bone metastases. **Conclusions:** Heterogeneity of CRPC metastases both within and between patients is an obstacle in determining the appropriate treatment regimen for each patient. However, our data highlight that differential response to therapy could also be based on the site of metastasis. We have identified biomarkers that differentiate bone from visceral metastases that may represent new therapeutic targets for CRPC bone metastases.

**5093 General Poster Session (Board #222), Mon, 1:15 PM-5:00 PM**

**Incidence of second primary malignancies in veterans after prostate cancer diagnosis.** *Presenting Author: Narjust Perez-Florez, Department of Internal Medicine, Rutgers University-New Jersey Medical School, Newark, NJ*

**Background:** With the advancement of diagnostic and treatment modalities in prostate cancer (PC) over the past 20 years, PC specific survival rates have improved. The aim of this study was to evaluate the incidence of second primary malignancies in our veteran population after diagnosis of PC. **Methods:** We reviewed the records of 548 patients (pts) diagnosed with PC between 1999 and 2011. Data including demographics, veteran status (Vietnam vs. non-Vietnam), Gleason score, PSA, PC stage, treatment, incidence of second primary malignancy and survival were studied. Cox regression analysis was performed using SAS v 9.2. **Results:** There were 548 pts with a median (M) age of 71 years (45-98). 265 pts (48%) were Caucasian, 256 pts (47%) African American and 28 pts (5%) of other races; 158 pts (31%) were Vietnam veterans. The M Gleason score was 7 (4-10) and PSA 9.3 (0.7-7870). 153 pts (28%) had one or more second primary malignancies after PC diagnosis. The incidence of second malignancy was significantly higher among Vietnam veterans (OR: 2.08, p<0.0003) and pts with localized PC (OR: 5.53, p<0.0001) in univariate analysis. Sites for second malignancy were lung 42 (28%), hematologic 21 (14%), bladder 19 (12%), colorectal 11 (7%) and liver 10 (6.5%). Of the 95 pts who received radiotherapy for PC and later developed a second malignancy, 28 (29%) developed the second malignancy in the radiotherapy field (bladder, colon and rectal cancer) and 12 (11%) developed a hematologic malignancy. In 72 (47%) pts the second malignancy was diagnosed ≥4 years after the diagnosis of PC, 62 (41%) between 1-3 years and 18 (12%) within 12 months of the diagnosis of PC. Age (OR: 0.95, 95% CI: 0.93-0.97, p<0.0001), PC stage (OR: 0.18, 95% CI: 0.08-0.38, p<0.0001) and veteran status (Vietnam vs. non-Vietnam; OR: 1.65, 95% CI: 1.07-2.55, p<0.02) were independent and significant predictors of a second primary malignancy by multivariate analysis. **Conclusions:** In this cohort, 28% of veterans with prior PC developed a second primary malignancy. Vietnam veterans had 1.7 times greater risk to develop a second primary malignancy and patients with localized PC had 18% higher risk of developing a second primary malignancy compared to patients with metastatic PC.

**TPS5094 General Poster Session (Board #223A), Mon, 1:15 PM-5:00 PM**

**PROSPER: A phase 3 study of enzalutamide in nonmetastatic (M0) castration-resistant prostate cancer (CRPC) patients.** *Presenting Author: Maha Hussain, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI*

**Background:** There is no standard of care for patients with M0 CRPC. In a recent study, patients with a PSA ≥8 ng/mL or PSA doubling time of ≤10 months had a median time to bone metastasis of only 2 years (Smith et al. Lancet 2012; 379: 39–46). Prostate cancer growth is dependent on androgen receptor (AR) signaling. Enzalutamide (formerly MDV3100) is a novel oral AR inhibitor that targets multiple steps in the AR signaling pathway. In two large Phase 3 studies, enzalutamide was shown to prolong overall survival and radiographic progression-free survival in patients with metastatic CRPC. The objective of the PROSPER trial is to evaluate the efficacy and safety of enzalutamide in M0 CRPC patients. **Methods:** PROSPER is a randomized, double-blind, placebo-controlled, international Phase 3 study (NCT02003924) initiated in December 2013 and involving more than 200 sites globally. Eligibility criteria include: asymptomatic M0 CRPC; PSA doubling time ≤10 months; screening PSA ≥2 ng/mL; and adequate hematologic, hepatic, and renal function. Approximately 1560 patients will have continued androgen deprivation therapy and will be randomized 2:1 to enzalutamide 160 mg/day or placebo. Patients will be stratified by PSA doubling time (<6 vs 6-10 months) and baseline use of bone-targeting agent (yes vs no).The primary endpoint is metastasis-free survival (MFS) based on central independent review of whole-body radionuclide bone scans for bone disease assessment and CT or MRI scans for soft tissue disease assessment. Imaging will be undertaken at screening and every 16 weeks post randomization till radiographic progression. The study has 90% power to detect a target hazard ratio of 0.75 based on a 2-sided log-rank test at an overall significance level of 0.05. Secondary endpoints include: overall survival; time to pain progression; time to opiate use for prostate cancer pain; time to first use of cytotoxic chemotherapy; time to first use of new antineoplastic therapy; time to PSA progression; PSA response; time to functional status deterioration as assessed by the FACT-P global score; and quality of life as assessed by EQ-5D-5L and QLQ-PR25. Clinical trial information: NCT02003924.

**TPS5095 General Poster Session (Board #223B), Mon, 1:15 PM-5:00 PM**

**Prevention of symptomatic skeletal events with denosumab administered every 4 weeks versus every 12 weeks: A noninferiority phase III trial (SAKK 96/12, REDUSE).** *Presenting Author: Arnoud J. Templeton, Kantonsspital St. Gallen, St. Gallen, Switzerland*

**Background:** Denosumab, a monoclonal antibody against RANK-Ligand has been shown to be superior to zoledronic acid in delaying time to a first on-study skeletal-related event (SRE) in patients with solid tumors, with no effects on disease progression or survival (Stopeck et al. JCO 2010, Fizazi et al. Lancet 2011). Many SREs were silent compression fractures found only because of scheduled imaging. The approved dose of denosumab is 120mg sc every 4 weeks (q4w). Although generally well tolerated, there is a dose-dependent increase in osteonecrosis of the jaw in up to 8% of patients (Fizazi et al, ESMO 2012, 937P). Cases of fatal hypocalcaemia were observed during post marketing surveillance. In a study of 255 women with breast cancer and bone metastases randomized to 1 of 5 blinded denosumab cohorts (30mg q4w, 120 mg q4w, 180 mg q4w, 60mg q12w, 180mg q12w) or an open-label iv bisphosphonate, a similar degree of creatinine-corrected urinary N-telopeptide (uNTx/Cr) suppression at weeks 13 and 25 was observed in all cohorts (Lipton et al. CCR 2008). The optimal dose and schedule of denosumab is unknown. Denosumab is associated with considerable costs and adds toxicity; thus a study of de-escalation is warranted. **Methods:** The aim of the present trial is to test the hypothesis that the benefit of denosumab is maintained if administered 120mg q12w as compared to 120mg q4w. The primary endpoint of this open-label randomized phase III non-inferiority trial is time to first on-trial symptomatic skeletal events (SSE; clinically significant pathological fracture, radiation therapy to bone, surgery to bone or spinal cord compression). With a non-inferiority margin of 1.2 for the hazard ratio, power 80% and type I error 5%, the total sample size is 1380. Secondary endpoints include safety, time to subsequent on-trial SSE, quality of life, health economic outcomes, and change in bone turnover markers. Patients with breast or prostate cancer with bone metastases and adequate organ function are eligible. This trial is open for international collaboration. Clinical trial information: NCT02051218.

**TPS5096 General Poster Session (Board #224A), Mon, 1:15 PM-5:00 PM**

**Randomized phase II study of abiraterone acetate maintenance in combination with docetaxel after disease progression to abiraterone acetate in metastatic castration-resistant prostate cancer (mCRPC): ABIDO SOGUG trial.** *Presenting Author: Miguel Angel Climent, Fundación Instituto Valenciano de Oncología, Valencia, Spain*

**Background:** Docetaxel (D) is the standard treatment for symptomatic or aggressive disease in mCRPC patients. Abiraterone acetate (AA), a specific inhibitor of CYP17, blocks persistent extragonadal and testicular androgen biosynthesis in mCRPC (Massard C, 2011). AA in combination with prednisone improves OS and rPFS in mCRPC patients after D-failure and for pts with asymptomatic or minimally symptomatic CT naïve (Fizazi K, 2012; Ryan CJ, 2013; ZYTIGA Janssen Biotech, Inc., 2012). This study aims to evaluate efficacy and safety of AA maintenance in combination with D after disease progression to first line AA in mCRPC. **Methods:** This is a randomized phase II open-label study conducted in chemotherapy naïve mCRPC patients progressing after AA treatment. Primarily, patients will be included for AA treatment (1000 mg/d plus prednisone 10 mg/d) if histologically or cytologically adenocarcinoma of the prostate is confirmed, metastatic disease other than visceral, prostate cancer progression to previous castration treatment documented by PSA (PCWG2), radiographic progression (modified RECIST) or bone scan progression; ECOG PS 0-1, testosterone < 50 ng/dL and adequate, hematologic, hepatic, and renal function. Patients will receive AA until clinical and/or radiographic disease progression. In a second phase patients will be randomized to receive D 75 mg/m$^2$ plus prednisone 10 mg/d combined with AA 1000 mg/d (arm A) or D 75 mg/m$^2$ plus prednisone 10 mg/d (arm B) alone in 21 day cycles. Primary objective is 1 year radiographic PFS. Secondary objectives include OS, PFS (radiographic and PSA), Response Rate (radiographic and PSA), pain, skeletal events, QoL, TTP and safety profile. At least fifty four pts are planned to be included in each arm to assess the treatment efficacy in terms of rPFS. Sample size has been calculated using the Fleming method with $\alpha$=0.05 and $\beta$=80%. This study is planned include 119 pts in 17 sites in Spain and is expected to start in February 2014. Clinical trial information: NCT02036060.

**TPS5097 General Poster Session (Board #224B), Mon, 1:15 PM-5:00 PM**

**A phase 1-2 study of the type I progesterone receptor (PR) antagonist onapristone (ONA) in patients (pts) with advanced castration-resistant prostate cancer (CRPC).** *Presenting Author: Joaquin Mateo, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*

**Background:** PR expression in prostate cancer increases with resistance to castration [Bonkhoff 2001]. The transcriptional, activated PR (APR), offers a potential target in advanced CRPC. ONA stops PR dimerization, inhibits ligand-induced PR phosphorylation and prevents PR association with co-activators, blocking PR-induced DNA transcription. ONA was active in preclinical models, with responses reported in pts with other PR+ cancers. An extended-release (ER) tablet formulation of ONA has been developed to achieve continuous exposure and to address the liver function abnormalities seen with an earlier formulation. Parallel development of an APR companion diagnostic allows for stratification of advanced CRPC pts. **Methods:** This is an open-label, phase 1-2 study with 2 stages: dose-selection and expansion (n~60). Main inclusion criteria are: metastatic/recurrent CRPC, good organ function, prior progression on abiraterone (AA) or enzalutamide (ENZ) and 1-2 lines of chemotherapy. Tumor biopsies are acquired from all pts at baseline to determine PR status. Paired biopsies at day 8-28 and upon progression are collected if possible. Primary endpoints are: determination of recommended phase 2 dose (RP2D) and response rate based on RECIST, circulating tumor cell (CTC) count conversion and/or >50% PSA decline. Secondary endpoints include safety and PK. Exploratory analyses of multiparametric MRI as a response biomarker in bone, circulating nucleic acids and hormone metabolism are included. Stage 1: Pts are randomized to 10 or 20 mg of ONA ER tablets BID (3-6 pts/cohort). Upon confirmation of safety, based on a dose-limiting toxicity (DLT) observation period of 8 weeks, a data review committee (DRC) will open randomization in parallel to the 30-40-50 mg cohorts (6pts/cohort). RP2D will be selected based on tolerability and PK. Stage 2: 36 pts will be treated at RP2D with an interim analysis after 21 pts. The DRC can permit continued AA/ENZ during ONA treatment at this stage. The adaptive design for biomarker-driven pt selection guarantees that >75% pts at RP2D will be APR+. The dose-selection stage of the study is open for accrual. Clinical trial information: NCT02049190.

**TPS5098 General Poster Session (Board #225A), Mon, 1:15 PM-5:00 PM**

**A randomized phase III, factorial design, of cabazitaxel and pelvic radiotherapy in patients with localized prostate cancer and high-risk features of relapse.** *Presenting Author: Karim Fizazi, Institut Gustave Roussy, Villejuif, France*

**Background:** Most patients (pts) with PC are currently diagnosed with localized disease and most of PC-related deaths occur in high risk (HR) pts due to metastatic dissemination. Combining androgen deprivation therapy (ADT) with radiotherapy (RT) improves the survival of pts with HR localized PC, but the risk of relapse in the HR population warrants investigation. In other epithelial neoplasms, chemotherapy (CT) regimens with proved activity in the metastatic setting often yielded a survival benefit when used in the localized setting. Cabazitaxel (Cbz) has demonstrated survival benefit in metastatic castrate-resistant PC post-docetaxel. One of the objectives is to evaluate the benefit of neoadjuvant Cbz in pts with HR localized PC. Dose-escalated RT benefits have been demonstrated in intermediate and HR PC. Randomized trials failed to demonstrate the superiority of pelvic over prostate only RT. In this trial involving HR PC pts the risk of occult pelvic lymph node metastases might be as high as 30%. With neoadjuvant CT, pelvic RT could help eradicate microscopic pelvic disease and improve PFS. As elective pelvic RT is still controversial, practices might vary between centers and potentially pts receiving Cbz or not. Therefore a second randomization is used to answer this major question concerning RT of the pelvis. **Methods**: This factorial design international trial started in December 2013 and aims to recruit 1048 pts with at least 2 HR criteria among Gleason score $\geq$ 8, T3 (MRI accepted)-T4 and PSA $\geq$ 20 ng/mL; localized disease (including pelvic lymph nodes $>$ 1 cm) and no prior treatment for PC. Pts are randomized between ADT + prostate-only RT +/- Cbz and ADT + pelvic RT +/- Cbz. Primary endpoint is clinical PFS (cPFS). 262 pts are needed in each of the four arms to detect an absolute difference in cPFS at 6 years of 7.5% (5% 2-sided test, power=80%) between ADT and ADT+CT arms and prostate only RT and pelvic RT arms. Planned accrual duration is 4 years. An interim analysis is planned at 50% of the events. **Conclusion**: The aim is to evaluate the benefits of neoadjuvant Cbz and pelvic IMRT in HR localized PC. This is a unique opportunity to study this paradigm in a largely powered trial. Clinical trial information: NCT01952223.

**TPS5099 General Poster Session (Board #225B), Mon, 1:15 PM-5:00 PM**

**Prostate Adenocarcinoma: TransCutaneous Hormones, PR09 (PATCH): A randomized controlled trial of transdermal estrogen patches versus luteinising hormone releasing hormone agonists in locally advanced and metastatic prostate cancer.** *Presenting Author: Ruth E Langley, Medical Research Council, Clinical Trials Unit at University College London, London, United Kingdom*

**Background:** Contemporary androgen deprivation therapy (ADT) with luteinising hormone releasing hormone agonists (LHRH) suppresses androgen to castrate levels but also depletes estrogen (synthesised from aromatised testosterone). Sex hormone depletion results in serious long term toxicities including osteoporosis and adverse metabolic changes potentially associated with increased cardiovascular (CVS) risk. Transdermal estrogen is a compelling alternative to LHRH for achieving castrate levels of testosterone, and should avoid the CVS toxicity associated with oral estrogen by circumventing first-pass hepatic metabolism, as well as mitigating estrogen depletion related toxicities. **Methods:** PATCHis a multi-centre, randomised, non-inferiority trial comparing the efficacy and safety of transdermal estrogen patches (FemSeven 100 $\mu$g/24 hour, 4 patches changed twice-weekly reducing to 3 after 4 weeks) against LHRH. Men (without significant CVS disease) with advanced prostate cancer (newly diagnosed or previous radical treatment and rising prostate specific antigen) are eligible. The trial was designed for evaluation in stages. Stage 1 (n=254) showed the patches produced castrate levels of testosterone similar to LHRH without additional CVS toxicity (Langley et al. Lancet Oncology 2013;14:306-16), and had more favourable blood glucose and lipid profiles. In stage 2, a pre-planned interim analysis (n=638) reviewed by the Independent Data Monitoring Committee (June 2013) led to the decision to extend the trial, with the aim of recruiting a total of 2,150 patients, to enable the evaluation of the patch efficacy to progress seamlessly from phase II to III. The design for the extension is based on the multi-stage, multi-arm (MAMS) approach and incorporates an interim analysis before continuing to the final stage. Primary outcome measures are overall and progression-free survival. The possibility of adding a new treatment arm for a phase II evaluation of an estrogen gel is being considered. Other international groups have been approached for potential collaboration. Clinical trial information: ISRCTN70406718.

**TPS5100 General Poster Session (Board #226A), Mon, 1:15 PM-5:00 PM**

**A randomized double-blind, comparative study of ARN-509 plus androgen deprivation therapy (ADT) versus ADT alone in nonmetastatic castration-resistant prostate cancer (M0-CRPC): The SPARTAN trial.** *Presenting Author: Matthew Raymond Smith, Harvard Medical School and Massachusetts General Hospital, Boston, MA*

**Background:** ADT is the standard of care for patients (pts) with metastatic prostate cancer and is frequently used in pts with non-metastatic prostate cancer. Initial ADT achieves responses in nearly all pts, but most progress to castration-resistant disease within a few years. Among men with M0-CRPC, a rising prostate-specific antigen (PSA) heralds the development of metastases and associated morbidity and mortality. Prevention of metastases is a major unmet medical need in M0-CRPC. ARN-509 (ARN) is a potent and selective androgen receptor (AR) antagonist that inhibits AR nuclear translocation and DNA binding without significant AR agonist properties (Clegg N et al. Cancer Res.2012). ARN demonstrates a 12- and 24-week PSA response rate of 91% in M0-CRPC pts and an excellent safety profile (Smith MR et al. ASCO GU 2013; Smith MR et al. ESMO 2013). **Methods:** This is a multicenter, double-blind, placebo-controlled, phase 3 trial evaluating the efficacy and safety of ARN in pts with M0-CRPC at high risk for progression (PSA doubling time [PSADT] $\leq$ 10 months). Continuous ADT is mandatory in order to maintain castrate concentrations of testosterone ($<$ 50 ng/dL). Pts are stratified based on PSADT ($\leq$ 6 vs $>$ 6 months), baseline use of bone-sparing agents for osteoporosis, and presence of locoregional disease, and randomized (2:1) to ARN + ADT or placebo + ADT. The absence of distant metastasis at screening is documented by central radiographic review. The primary end point is metastasis-free survival. Secondary end points include overall survival and other clinically relevant end points. Approximately 1200 pts will be randomized to provide appropriate statistical rigor to detect the hypothesized risk reduction in metastasis or death. This study uses group sequential design, including an interim analysis. The stratified log rank test will be used for the analysis. An independent data monitoring committee is commissioned to conduct reviews of the safety and efficacy data. Approximately 300 sites in 24 countries will participate. Pts are being screened and enrolled as of September 2013. Clinical trial information: NCT01946204.

**TPS5101 General Poster Session (Board #226B), Mon, 1:15 PM-5:00 PM**

**Carfilzomib for metastatic castration-resistant prostate cancer (mCRPC) following chemotherapy and androgen pathway inhibitors.** *Presenting Author: Guru Sonpavde, The University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL*

**Background:** mCRPC is an incurable disease despite increments in outcomes with new agents. Proteasome inhibitors are promising agents for the therapy of mCRPC. In a phase I trial of bortezomib in 47 men with mCRPC, 4% had $>$ 50% PSA decline, 25% had stable PSA; 9.5% had objective partial responses among 21 men with measurable disease. Dose-dependent inhibition of whole-blood 20S proteasome activity was seen. Carfilzomib is a second-generation epoxyketone proteasome inhibitor that binds selectively and irreversibly with its target. In vitro studies demonstrated potent pro-apoptotic activity across a broad panel of bortezomib-resistant tumor cell lines. The pharmacodynamic half-life of carfilzomib activity was $\geq$ 24 hours and doses of 15 to 36 mg/m$^2$ lead to 77% to 86% proteasome inhibition in whole blood 1 hour after dosing. The dose-limiting toxicity (DLT) in clinical trials was hematologic. Fatigue, nausea and diarrhea and neurotoxicity were manageable. Carfilzomib is approved for relapsed/refractory myeloma where the starting dose is 20 mg/m$^2$ over 2-10 minutes on days 1,2, 8,9,15,16 over 28 days in cycle 1, and the target dose is 27 mg/m$^2$ in subsequent cycles. With 30-minute infusions of carfilzomib, the MTD was 56 mg/m$^2$. **Methods:** A non-randomized proof-of-concept phase II trial (NCT02047253) was designed to evaluate carfilzomib for mCRPC following docetaxel and abiraterone acetate and/or enzalutamide. A 6-month PFS $\geq$30% is considered important, while PFS$<$10% is not; 28 patients are accrued to account for 10% inevaluable patients. Carfilzomib is administered on days 1,2,8,9,15,16 every 28 days. The starting dose is 20 mg/m$^2$ over 30 minutes during the first week followed by a target dose of 56 mg/m$^2$ if no DLTs occur. Daily oral acyclovir is administered for herpes zoster prophylaxis. Therapy will continue until progression or severe toxicities. PFS is the primary endpoint based on radiographic and symptomatic criteria (not PSA). Secondary endpoints are PSA declines, present pain index change, measurable tumor response, CTC (circulating tumor cell) declines and overall survival. Whole blood is collected at baseline for 20S proteasome activity. Clinical trial information: NCT02047253.

**TPS5102 General Poster Session (Board #227A), Mon, 1:15 PM-5:00 PM**

**SWOG S1216: A phase III randomized trial comparing androgen deprivation therapy (ADT) plus TAK-700 with ADT plus bicalutamide in patients with newly diagnosed metastatic hormone-sensitive prostate cancer (HSPC) (NCT01809691).** *Presenting Author: Neeraj Agarwal, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

**Background:** Responses to ADT in new HSPC are not durable and the disease progresses with in a median of ~ 18 months. Median overall survival (OS) is 48 months. Despite the failure of ADT, tumor progression may be driven by CYP17 mediated intratumoral androgen production and/or androgen receptor (AR) signaling. TAK-700 (orteronel) is a CYP17 inhibitor with a potentially greater 17,20 lyase selectivity (ie, for androgen as opposed to corticosteroid synthesis), and has shown activity in castrate resistant tumors. Based on data from > 1000 men with new HSPC in the SWOG-9346 study, a failure to achieve a prostate-specific antigen (PSA) of ≤4 ng/ml (or to be experiencing a rise in PSA) after 7 months of undergoing ADT + bicalutamide, is a powerful negative predictor of survival (JCO 2006; 24:3984). These data provide the rationale for optimizing androgen blockade in new HSPC. **Methods:** In S1216, an intergroup study, men with new HSPC, a performance status (PS) of 0-2, and a PSA of ≥ 2 ng/ml are randomized to ADT+TAK-700 vs ADT+ bicalutamide, and stratified according to PS, extent of disease (minimal or extensive) , and if they have started ADT prior to registration. OS is the primary end point. Secondary endpoints are: progression free survival, PSA response at 7 months (<0.2 vs 0.2-4 vs. >4 ng/ml), adverse effect profile, and long term survival after 10 years of follow up. It is assumed that the median OS of those randomized to ADT+ bicalutamide is conservatively 54 months (48 months based on results from SWOG-9346 + an additional 6 months from novel agents). The experimental regimen with TAK-700 would be of interest if median OS were improved by 25% (i.e., median=68 months). With 4.5 years of accrual and 4 more years of follow-up, and assuming a one-sided alpha=0.025 and 90% statistical power, study needs 1486 eligible men to be randomized. Planned correlatives include serum androgens, bone markers, and circulating tumor cells. Current rate of accrual is ~28 men per month with 220 men accrued so far. Support: NIH/NCI CA32102, CA38926, CA31946 and CA21115, and Millennium: The Takeda Oncology Company. Clinical trial information: NCT01809691.

**TPS5103 General Poster Session (Board #227B), Mon, 1:15 PM-5:00 PM**

**A randomized open-label phase 2a study evaluating the efficacy and safety of radium-223 dichloride (Ra-223) in combination with abiraterone acetate or enzalutamide in patients with castration-resistant prostate cancer (CRPC) and bone metastases.** *Presenting Author: Daniel Peter Petrylak, Yale Cancer Center, New Haven, CT*

**Background:** Ra-223, a first-in-class alpha-pharmaceutical targeting bone metastases (mets), reduced risk of death by 30% versus placebo in patients (pts) with CRPC and symptomatic bone mets in the phase 3 ALSYMPCA trial (Parker et al. NEJM 2013). Ra-223 has a favorable safety profile, and the absence of significant toxicity supports combining Ra-223 with other agents for additional beneficial effect. Hormonal agents abiraterone acetate (AA) and enzalutamide (Enz) improved overall survival (OS) in CRPC pts with bone mets (de Bono et al. NEJM 2011; Scher et al. NEJM 2012), and their safety profiles indicate nonoverlapping toxicity with Ra-223. This study evaluates efficacy and safety of Ra-223 + AA or Enz in CRPC pts with bone mets. **Methods:** In this open-label, multicenter, phase 2a study (NCT02034552), ~66 pts with CRPC and bone mets, no visceral mets, and treatment (tx) naïve to Ra-223, other radiotherapy, AA, or Enz will be randomized to tx group (Grp) 1 (n = 22), 2 (n = 22), or 3 (n = 22). All pts will receive Ra-223 (50 kBq/kg IV) every 4 wk for up to 6 doses (d 1, wk 4, 8, 12, 16, 20). Grp 1 will receive only Ra-223. Grp 2 will receive concurrent AA 1000 mg daily and prednisone 5 mg twice daily. Grp 3 will receive concurrent Enz 160 mg daily. The primary end point is radiologic progression-free survival. Secondary end points include safety, symptomatic skeletal event–free survival, OS, and time to bone progression. Pts will be assessed at screening; wk 8, 16, and 24; then every 12 wk with MRI/CT of the chest, abdomen, and pelvis and whole-body technetium-99 bone scanning, until radiologic progression (bone or soft tissue). A subset of pts will have diffusion-weighted MRI and $^{18}$F-NaF PET/CT. Automated computer-based quantitation of bone scan imaging and associated response will be evaluated. Pts will be followed up to 2 y after last Ra-223 tx; late toxicities will be assessed up to 7 y. An interim analysis will be done 30 days after last pt's Ra-223 tx. Statistical analyses will be descriptive, with event variables summarized using Kaplan-Meier estimates. This trial is currently recruiting pts. Clinical trial information: NCT02034552.

**TPS5104 General Poster Session (Board #228A), Mon, 1:15 PM-5:00 PM**

**Identifying enzalutamide resistance mechanisms in men with castration-resistant prostate cancer.** *Presenting Author: Joshi J. Alumkal, Oregon Health & Science University, OHSU Knight Cancer Institute, Portland, OR*

**Background:** Multiple lines of evidence demonstrate that castration-resistant prostate cancers (CRPCs) remain reliant on androgens that activate the androgen receptor (AR). Treatment with the novel anti-androgen enzalutamide improves progression-free survival (PFS) and overall survival (OS) in CRPC patients (Scher 2012, Beer 2014). However, nearly 50% of patients never respond, and progression is universal. Mechanisms of enzalutamide resistance in CRPC patient tumors are largely unknown, and few treatments exist for enzalutamide-resistant CRPC. Recent work demonstrates that CRPC tumors carry countless genomic aberrations that control many hallmarks of cancer (Grasso 2012, Hanahan 2011). Based on our work (Heiser 2012), we hypothesize that these aberrations work in concert to drive enzalutamide resistance and influence specific cancer hallmarks. **Methods:** We are enrolling men with metastatic CRPC who are eligible to receive enzalutamide (N=65). Through a DOD Synergistic Idea Award and a West Coast Prostate Cancer Dream Team Award, we perform a CT-guided metastatic tumor biopsy prior to treatment and at the time of PSAWG2-defined disease progression (Scher 2008). We perform RNA-seq and array CGH followed by an integrative genomic analysis with the PARADIGM algorithm to identify deregulated gene networks in each tumor sample (Heiser 2012). Then, we use logistic regression and Random Forests classification analysis to determine the association of these deregulated gene networks and our outcome measures. The primary endpoint is: Identify molecular features/pathways associated with enzalutamide response (>50% PSA decline at 12 weeks). Secondary endpoints include: Identify molecular features/pathways associated with PFS, OS, objective response, and acquired enzalutamide resistance (by comparing each subject's pre-treatment and progression biopsies). We anticipate that this trial will identify distinct subsets of CRPC patients with specific enzalutamide resistance mechanisms. Identifying these mechanisms will lead to rationally designed clinical trials of specific enzalutamide drug combinations in distinct molecular subsets of CRPC patients in the near-term.

**TPS5105 General Poster Session (Board #228B), Mon, 1:15 PM-5:00 PM**

**Establishing a neoadjuvant platform for developing targeted agents: Degarelix prior to prostatectomy for patients with intermediate- and high-risk prostate cancer.** *Presenting Author: Karim A. Touijer, Memorial Sloan-Kettering Cancer Center, New York, NY*

**Background:** We hypothesize that the unmet drug development needs in prostate cancer can be addressed using a standardized short exposure neoadjuvant clinical trial framework that ensures tumor tissue is available for profiling, the biomarker assays used are validated, and that trials are designed to address specific questions. This ongoing pilot study explores the response to short exposure androgen deprivation therapy (ADT) with degarelix prior to prostatectomy. The aims of the trial are to assess: (1) two time intervals to determine the maximal change in PC proliferation (Ki-67) and apoptosis rates (caspase-3) following ADT; (2) the association between PTEN status and maximal changes in proliferation and apoptosis rates in patients treated with ADT; and (3) the association between PI3K pathway (pAKT and pS6) and proliferation and apoptosis rates after treatment with ADT in relation to other markers of PC (ERG, AR and NCOA2). **Methods:** Thirty intermediate and high risk patients planning to undergo prostatectomy will be accrued. Two or more cores of the diagnostic biopsy must involve at least 3 mm of tissue with adenocarcinoma. Patients are randomized to receive degarelix (240 mg SC) either 4 or 7 days prior to radical prostatectomy based on the proliferation and apoptotic indexes in malignant human prostate biopsies taken 1-10 days after surgical castration which have demonstrated that maximal changes occur by day 7. (Ohlson, N., et al. Prostate 2005) Patients undergo open, laparoscopic, or robotic radical prostatectomy and are followed 6 weeks post-operatively. The first 20 patients have been successfully treated. Supported by funds from NCI P50-CA92629 SPORE in Prostate Cancer and PCF. Drug supplied by Ferring Pharmaceuticals. Clinical trial information: NCT01542021.

**TPS5106 General Poster Session (Board #229A), Mon, 1:15 PM-5:00 PM**

**Targeting reciprocal feedback inhibition in the clinic: ARN509 and PI3K pathway inhibition in patients with metastatic castration-resistant prostate cancer (mCRPC).** *Presenting Author: Dana E. Rathkopf, Memorial Sloan Kettering Cancer Center, Brooklyn, NY*

**Background:** Next-generation androgen receptor (AR) targeted agents provide dramatic benefit to patients with mCRPC, but the durability of response can be limited by intrinsic and acquired resistance to these drugs. (Rathkopf D et al., Cancer J 2013) Studies in xenograft CRPC and PTEN-deficient prostate cancer models have shown synergistic anti-tumor activity of next-generation anti-androgens such as ARN509 when combined with mTOR or PI3K/mTOR inhibitors such as everolimus. (Carver B et al., Cancer Cell 2011) This hypothesis has been validated in breast cancer in the Phase III BOLERO-2 study in which the addition of everolimus to exemestane was able to overcome hormonal resistance in patients with metastatic breast cancer previously treated with tamoxifen and a non-steroidal aromatase inhibitor. (Baselga J et al., New Engl J Med, 2012) The primary hypothesis of this study is that the combination of ARN509 with everolimus in mCRPC will overcome resistance to prior hormonal therapy with abiraterone acetate (AA). We believe that this strategy will effect a major change in the natural history of the disease, with potential to overcome primary resistance and/or delay the development of secondary resistance to AR targeted therapies through inhibition of reciprocal feedback. **Methods:** The primary endpoint is to determine the safety, pharmacokinetics, and the recommended phase 2 dose (RP2D) of the combination. Approximately 12 patients with progressive mCRPC will be treated with 240 mg/day of ARN509 (RP2D) and 5-10 mg/day of everolimus depending on the safety seen during dose escalation. Dose expansion will include 40 patients with prior AA: 20 with intrinsic resistance ($<$3 months treatment) and 20 patients with acquired resistance ($>$6 months treatment). Mechanisms of sensitivity and resistance will be evaluated through exploratory correlative studies such as FDG and FDHT PET imaging, AR allelic status, circulating tumor cells, and tumor biopsies. Supported by Prostate Cancer Foundation Young Investigator Award, Janssen Pharmaceuticals, Novartis (Drug only), and The Experimental Therapeutics Center of MSKCC.

**TPS5107 General Poster Session (Board #229B), Mon, 1:15 PM-5:00 PM**

**A phase I/II study of the investigational drug alisertib in combination with abiraterone and prednisone (AP) for patients with metastatic castration-resistant prostate cancer (mCRPC) progressing on abiraterone.** *Presenting Author: Jianqing Lin, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA*

**Background:** Aurora A kinase (AK) over-expression is found in 98% prostate cancer (PCa) lesions. Its level is associated with Gleason score, Ki-67 expression, preoperative PSA and pathological staging. AK phosphorylates and interacts with androgen receptor (AR) and enhances AR DNA binding activity and potentiates androgen action in AR. Targeting AK could suppress tumour growth and enhances chemosensitivity in both AR positive and negative in vitro. We hypothesized that AK contributes to castration resistance in PCa and targeting AK can inhibit AR function and re-sensitize PCa cell to castration. **Methods:** This is a phase I/II, open label, single institution trial to determine the safe dose of the investigational AK inhibitor alisertib when given in combination with AP. Patients with mCRPC and disease progression by PCWG 2 criteria while on AP will be eligible. AP will be continued during the study and alisertib will be added to AP regimen. In phase I, standard 3+3 design with 3 dose cohorts (alisertib 30, 40, 50 mg PO BID days 1-7 every 21 days) will be carried out to determine RP2D of alisertib when given in combination with AP. The safety and toxicity profile will be examined. Data analysis of phase I studies is descriptive. Cohort 2 is currently enrolling. The primary endpoint of the phase II expansion is to determine the proportion of patients without disease progression after alisertib is added to AP, using Minimax Simon two-stage design. The study will analyze the effects of alisertib on PSA kinetics; changes in circulating tumor cells (CTCs) and serum neuroendocrine marker (chromogranin A and NSE) levels. CTCs will also be isolated to determine AK amplification. Clinical trial information: NCT01848067.

**TPS5108 General Poster Session (Board #230A), Mon, 1:15 PM-5:00 PM**

**Abiraterone plus prednisone alone or with dasatinib in chemotherapy-naive metastatic castrate-resistant prostate cancer (mCRPC).** *Presenting Author: Tanya B. Dorff, USC Norris Comprehensive Cancer Center, Los Angeles, CA*

**Background:** Skeletal complications dominate the morbidity of disease progression for men with mCRPC and resistance eventually emerges to all known androgen suppression therapies. Abiraterone acetate (AA) was approved by the FDA for mCRPC based on a survival advantage as well as delay in skeletal-related events, however resistance ultimately develops. Src kinases are involved in androgen receptor phosphorylation, and may represent one resistance pathway. Src kinases also mediate osteoclast-osteoblast interactions, and inhibition has been associated with reduction in bone metastasis formation. Dasatinib is an oral multi-targeted kinase inhibitor with strong Src inhibition. Based on these properties, we hypothesized that the combination of abiraterone plus dasatinib would delay the time to disease progression in mCRPC. The two agents have been combined at full doses in a phase I trial without dose-limiting toxicity. **Methods:** Design: randomized, phase II. Treatment: Arm A=AA 1000 mg PO daily, prednisone 5mg PO bid. Arm B=same plus dasatinib 100 mg PO daily. Eligibility criteria: mCRPC without prior chemotherapy treatment. Endpoint: disease progression. Assessment, including PSA, will be defined by PCWG2 criteria but patients will be encouraged to stay on study therapy until radiographic progression. Statistics: Rather than binomial testing, we will compare the probability of remaining progression-free at 12 and 24 weeks in Arm A vs Arm B using actual follow-up on a continuous scale. Correlatives: circulating tumor cells will be captured and analyzed using the hi-definition technology (Kuhn laboratory, Scripps) and protein changes will be evaluated in the samples (Gross laboratory, USC) at baseline, 4 weeks, and at progression. Biomarkers examined will be chosen to reflect acquired/somatic changes associated with therapeutic response to androgen or Src-kinase directed therapies. Progress: 21 of 96 planned subjects have been accrued. Clinical trial information: NCT01685125.

**TPS5109 General Poster Session (Board #230B), Mon, 1:15 PM-5:00 PM**

**Presurgical axitinib and androgen deprivation therapy (ADT) in prostate cancer (PCa) patients (pts) presenting with lymph node (LN) metastasis.** *Presenting Author: Amado J. Zurita, MD Anderson Cancer Center, Houston, TX*

**Background:** Strategies that integrate systemic therapy and curative-intent surgery/radiation are being considered for men presenting with PCa with regional spread. In our previous phase II study of pre-surgical chemotherapy and ADT followed by radical prostatectomy (RP) in LN metastatic pts (Pagliaro et al., ASCO 2011), we found no apparently better pathologic or survival outcomes than might be seen with ADT alone and surgery. To improve effectiveness of the pre-surgical therapy and characterize tumor changes associated with potent anti-angiogenic treatment response, we designed a trial testing the combination of the VEGF receptor inhibitor axitinib and ADT before consideration of consolidative RP. **Methods:** In this randomized phase II clinical trial, eligible pts either have biopsy-proven PCa and evidence of LN metastasis (TxN1M0 or TxNxM1a) on imaging (LN size $\geq$2 cm) or pathology (nodal biopsy or resection), or suspected LN extension based on the presence of any of the following: stage T3 (and Gleason score [GS] $\geq$7), stage T4 (any GS), or serum PSA concentration $\geq$25 ng/mL (and GS $\geq$8). Pts with bone or visceral involvement are excluded. After 2 months of ADT, pts are randomized to receive 4 more months of ADT in combination with open label axitinib (5 mg PO bid daily) vs. continuation of ADT until surgery in a 2:1 fashion (2 ADT + Axitinib to 1 ADT alone), for a total duration of pre-surgical therapy of 6 months. At that time, clinically responding pts are offered RP and extended pelvic LN dissection. Systemic therapy is discontinued postoperative and PSA measured every 3 months until 1 year. Pts are stratified based on LN metastatic status (present vs. suspected). The primary objective is to define the proportion of pts progression-free 12 months after surgery, defined as PSA $\leq$1.0 ng/mL and no radiation or ADT. Fifty-four pts are being accrued. This sample size ensures that, if the trial continues to completion, we will have an 80% power to detect a 35% difference in the proportions of pts progression-free between the two treatment arms. Early stopping rules for lack of efficacy and toxicity are included. Status: 35 pts have so far consented for participation, and accrual is ongoing. Clinical trial information: NCT01409200.

**TPS5110 General Poster Session (Board #231A), Mon, 1:15 PM-5:00 PM**

**A phase II randomized, open label study of sipuleucel-T versus sipuleucel-T and tasquinimod in patients with metastatic castrate-resistant prostate cancer (CRPC).** *Presenting Author: Roberto Pili, Roswell Park Cancer Institute, Buffalo, NY*

**Background:** A barrier for cancer immunotherapy is the presence of suppressive cells including myeloid-derived suppressor cells (MDSCs) and tumor associated macrophages (TAMs). Tasquinimod is a novel anti-tumor agent that has shown clinical activity in patients with CRPC (Pili R et al JCO 2011). A potential target of tasquinimod is the inflammatory protein S100A9, which is associated with the accumulation and function of tumor suppressive myeloid cells. Our preclinical studies showed that combination of tasquinimod with a tumor vaccine in a prostate cancer model significantly enhanced the anti-tumor effects in mice. Compared to single treatment, tasquinimod inhibited MDSC and M2 polarized macrophages. T cell effector functions, including cell-mediated cytotoxicity and IFN-γ production, were potentiated. Taken together, these data suggest that pharmacological targeting of suppressive myeloid cells by tasquinimod induces therapeutic benefit in combination with cancer immunotherapies. **Methods:** This is a Phase II, open-label, randomized study to assess the immunomodulation of tasquinimod in combination with sipuleucel-T in patients with metastatic, castrate-refractory prostate cancer. 60 subjects will be randomized in a 1:2 ratio to either sipuleucel-T or sipuleucel-T + tasquinimod, respectively. The primary endpoint is change from baseline in immune response, which will be evaluated over time (Weeks 0, 2, 6, 26 and 52) with an IFN-γ ELISPOT assay specific for PA2024. Descriptive summaries of safety assessments and immune response parameters will be generated on a periodic basis. Key secondary endpoints include progression free survival and overall survival. Correlative studies will include assessment of immune response to sipuleucel-T and effects of tasquinimod on the inhibition MDSCs and other immune cells at defined time points post treatment. Blood samples will be analyzed for immune cell sub populations. CD4+, CD4+/Foxp3, CD8+ cells, NK cells will be quantitated by FACS analysis. Additional studies will include assessment of clinical efficacy based on PSA response, response on imaging, and change in circulating tumor cells.

**TPS5111 General Poster Session (Board #231B), Mon, 1:15 PM-5:00 PM**

**A randomized, double-blind phase 2 study of sipuleucel-T followed by indoximod or placebo in the treatment of patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer.** *Presenting Author: Gautam Gopalji Jha, University of Minnesota, Minneapolis, MN*

**Background:** Vaccine development is complicated by tumor induced immune tolerance, a phenomenon in which the immune system identifies tumor antigens as "self" and allows immune evasion and subsequent sparing of the tumor to occur. This local and possibly systemic immunesuppression is primarily mediated by the inhibitory regulatory T cells (Tregs), which dominantly inhibit other T cells. Vaccine therapy is limited by this anergy and immunosuppressive microenvironment. Although sipuleucel-T has overcome this in part by its ex-vivo sensitization, Treg depletion or interfering with Treg function will likely potentiate its activity. Indoleamine 2,3-dioxygenase (IDO) is a key immune-modulatory enzyme within the IDO pathway that degrades tryptophan and promotes peripheral immune tolerance by T cell inhibition and conversion of naïve T cells to Tregs. We hypothesize that targeting the IDO pathway by indoximod (1-methyl tryptophan; 1-MT) will inhibit Treg and abrogate tumor-mediated immunosuppression permitting a robust and possibly more sustained immune response to sipuleucel-T. Primary Objective: To assess the augmentation of immune response to sipuleucel-T measured at 14 weeks from first leukapheresis, in response to indoximod or placebo therapy. Secondary Objectives: To assess safety, clinical efficacy (PFS, OS) and HR-QOL. **Methods:** Phase 2 investigator initiated multi-center, randomized, double-blind, placebo-controlled trial. Patients will be treated with indoximod or placebo for a period up to 6 months starting a day after completion sipuleucel-T therapy. Research-related correlatives will include serial blood sampling for immune monitoring and an optional prostate or metastatic site biopsy at enrollment and at week 14. Immune monitoring will include measurements of T cell subsets, Tregs, NK cell function, PA2024-specific response, and IDO pathway inhibition. Major eligibility: Patients will be eligible for sipuleucel-T therapy as per phase III IMPACT trial inclusion criteria (Kantoff PW, NEJM 2010). Sample size and accrual: Study is open and actively recruiting, n=50 patients. Clinical trial information: NCT01560923.

**LBA5500 Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**A randomized phase 2 trial comparing efficacy of the combination of the PARP inhibitor olaparib and the antiangiogenic cediranib against olaparib alone in recurrent platinum-sensitive ovarian cancer.** *Presenting Author: Joyce Liu, Dana-Farber Cancer Institute, Boston, MA*

**The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, May 31, 2014, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2014, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Saturday edition of *ASCO Daily News*.**

**5501 Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**Genomic alterations in paired pretreatment (pre) and progression (prog) tumor samples from ovarian cancer patients (pts) treated with pazopanib (pazo) or placebo (plb).** *Presenting Author: Florian Heitz, Department of Gynecology and Gynecologic Oncology, Klinken-Essen-Mitte, Essen, Germany*

**Background:** BRCA mutational status, in combination with the accumulation of somatic mutations, has been associated with ovarian cancer prog and response to chemotherapy. AGO-OVAR16/VEG110655 is a randomized study to evaluate pazo vs plb in women with advanced ovarian cancer that have not progressed after first line chemotherapy. Paired pre and prog tumor samples were examined by next generation sequencing (NGS) to evaluate differences in tumor genomics, and to identify potential biomarkers for, and mechanisms of, resistance to pazo. **Methods:** Samples (n=22 pairs) were collected from consenting pts. DNA was isolated, followed by PCR. NGS was run on the Ion Torrent Proton Platform with 2 gene panels (409 comprehensive cancer gene panel [CCP] and BRCA1/2; AltheaDx). Data were aligned to hg19 and processed using ANNOVAR1, SIFT, PolyPhen programs, and COSMIC, 1000g and BIC databases. Mutation changes in paired samples were identified by allele frequency (AF) differences (prog minus pre) greater than 3xIQR (interquartile range) of differences from all markers determined to be damaging by both SIFT and PolyPhen. **Results:** CCP: after QC, N=15 pairs (8 pazo, 7 plb) were available for analysis. Synonymous (syn) alterations (67% of total) were removed; remaining alterations (n=11,587) were primarily non-syn (92%) and stopgain (4%). The AF cutoff was determined to be ±32. Changes in damaging mutations were observed in 47 markers across 40 genes. Pts in plb arm had greater number of changes compared to pazo arm (average 7/pt in plb arm vs 1.3/pt in pazo arm). Potential driver genes were FLT3 and ITGA9. BRCA1/2: N=20 pairs (10 pazo, 10 plb). After removing syn alterations (28% of total), remaining were primarily non-syn SNV (93%) and stopgain SNV (6%). The AF cutoff was ±17.5; 5 and 10 markers (BRCA1/2) had changes, of which 14/15 were in plb arm. Additional results will be presented. **Conclusions:** Changes in the genetic composition of tumors can be detected using NGS. In pre and prog matched tumor pairs, pts in plb arm had 6 fold higher number of genetic alterations per pt compared to pts in pazo arm. Potential driver genes have been identified.

**5502 Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**Molecular subgroup of high-grade serous ovarian cancer (HGSOC) as a predictor of outcome following bevacizumab.** *Presenting Author: Charlie Gourley, Edinburgh Cancer Research UK Centre, Edinburgh, United Kingdom*

**Background:** HGSOC is a histopathological diagnosis and may represent multiple diseases at a molecular level. We investigated whether distinct molecular subgroups may influence treatment choice. **Methods:** mRNA was extracted from 265 macrodissected formalin fixed paraffin embedded HGSOCs from Scottish patients (pts) treated with primary debulking then platinum based chemotherapy. Transcriptional analysis was performed using the Ovarian DSA microarray. This was repeated using 283 UK samples from the ICON7 study [first line paclitaxel/carboplatin +/- concomitant and maintenance bevacizumab (bev) for 12 months]. **Results:** Unsupervised hierarchical clustering (Scottish tumours) identified three major subgroups, two with angiogenic gene upregulation and one with angiogenic gene repression and immune gene upregulation. This latter 'immune' subgroup had a superior overall survival (OS) compared to the other two subgroups combined [HR = 0.66 (0.46-0.94)]. A 63-gene expression signature to prospectively identify this subgroup was generated and validated as prognostic for OS in an independent dataset [HR = 0.32 (0.19-0.54)]. As the immune subgroup had repressed angiogenesis-related gene expression we hypothesised that these pts would benefit less from bev [power to detect interaction > 2 in predicted direction for progression free survival (PFS) in ICON7 was 88% ($\alpha$=0.1, one-tail)]. In ICON7 the gene signature showed a difference in impact of bev on PFS between the immune and proangiogenic subgroups (1-sided test for interaction, p=0.016). For the immune group (41% of cases), the addition of bev conferred a worse PFS [HR = 1.73 (1.12-2.68)] and OS [HR = 2.00 (1.11-3.61)] compared to chemotherapy alone. In the proangiogenic group there was a non-significant trend to improved PFS for the addition of bev (median 17.4 vs 12.3 months in controls). **Conclusions:** An immune molecular subgroup of HGSOC has superior survival to other HGSOC. The addition of bev appears to significantly reduce PFS and OS in this subgroup. Patients in the proangiogenic subgroups have a trend towards a PFS benefit from bev. These data suggest a mechanism for stratification of bev therapy and should be validated in additional datasets.

**5503^ Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**MITO-11: A randomized multicenter phase II trial testing the addition of pazopanib to weekly paclitaxel in platinum-resistant or -refractory advanced ovarian cancer (AOC).** *Presenting Author: Sandro Pignata, National Cancer Institute of Naples, Naples, Italy*

**Background:** few drugs are available for patients (pts) with platinum resistant or refractory AOC; their efficacy is scanty. Evidence on antiangiogenic drugs efficacy in AOC is increasing. Pazopanib is an oral multi-kinase inhibitor of VEGFR-1, -2, -3, PDGFR-$\alpha$ and -$\beta$ and c-Kit with antiangiogenic properties. **Methods:** AOC pts with disease progressing during or within 6 months from the last platinum-based chemotherapy, aged≤75, ECOG PS 0-1 were eligible for a multicenter comparative randomized phase 2 trial of weekly paclitaxel (wP, 80 mg/m$^2$ dd 1, 8, 15 q 28) vs wPP (wP + pazopanib 800 mg/day); both treatments could continue until progression. Primary endpoint was progression-free survival (PFS). With 61 events, the trial would have 80% power to detect a 0.65 hazard ratio (HR), prolonging median PFS from 3 to 4.6 months with one-tail alfa = 0.20; 72 pts were planned. Partially supported by GSK. Clinicaltrials.gov NCT 01644825. **Results:** 74 pts (37 in each arm) were enrolled by 11 centers. Median age 57; 46% had received only one prior platinum based treatment; 24% were platinum-refractory; no pt had received prior bevacizumab. As of Jan 24, 2014, with median follow-up 12.5 months (95% CI 11.6-16.3), 66 PFS events and 34 deaths were recorded. Median PFS was 3.5 months (95% CI 2.0-5.7) with wP and 6.3 months (95% CI 5.4-11.0) with wPP; log-rank test one-tail p=0.0008; HR 0.45 (95% CI 0.27-0.75). Median overall survival was 14.8 months (95% CI 9.1-NA) with wP and 18.7 months (95% CI 11.5-NA) with wPP; p=0.07; HR 0.60 (95% CI 0.30-1.21). There was no toxic death. Neutropenia (Wilcoxon-Mann-Whitney exact test p=0.0007), hypertension (p<0.0001), diarrhoea (p=0.0002), mucositis (p=0.0007), AST/ALT (0.019), sensory neuropathy (p=0.025), and other neurologic events (p= 0.023) were more frequent and severe with pazopanib. Any grade 3-4 toxicity occurred in 8 (22%) pts with wP and 20 (54%) with wPP (Chi-square p=0.0052). **Conclusions:** The addition of pazopanib to wP in the treatment of pts with platinum-resistant or refractory advanced ovarian cancer might produce a significant prolongation of PFS and OS. A phase 3 trial is strongly supported. Clinical trial information: NCT 01644825.

**5504 Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**Progression-free survival in ovarian cancer patients in second remission with mucin-1 autologous dendritic cell therapy.** *Presenting Author: Heidi J. Gray, Department of Obstetrics and Gynecology, University of Washington, Seattle, WA*

**Background:** CVac is an autologous cellular therapy made by culturing autologous dendritic cells with a mucin 1 fusion protein and is intended to elicit a killer T cell response that is specific to mucin 1 over-expressing ovarian cancer cells. CAN-003 is an open label phase 2 study evaluating Cvac as compared to standard of care (SOC) with the efficacy endpoints of progression free (PFS) and overall survival (OS), as well as safety and immune monitoring. **Methods:** Eligible patients were stage III or IV epithelial ovarian cancer (EOC) who obtained a complete response to standard first (CR1) or second line chemotherapy (CR2).The first 7 patients were non-randomized and received Cvac (NR Cvac) for manufacturing comparison. Thereafter patients were randomized to either Cvac (10 doses over 52 weeks) or to SOC. **Results:** 63 patients were enrolled into the trial; 7 NR Cvac, and 29 Cvac and 27 SOC randomized. 42 patients were CR1 and 21 CR2. Overall CR1 and CR2 demographics were similar regarding tissue histology, optimal debulking and staging. 9 SAEs were reported in total. None were unexpected and only one (small bowel obstruction) was classified as unlikely-related to Cvac. PFS was not improved in CR1 with Cvac over SOC (HR=1.18, p=0.69) where as in CR2, CVac demonstrated a significant improvement in PFS; median PFS for SOC was 4.94 months; the median PFS for Cvac was not reached but is greater than 12.91 months (p=0.04). Patient blood was assessed for antibodies to mucin 1; as anticipated, none were detected. Peripheral PBMC were assessed for T cell responses to mucin 1. Mucin 1 specific CD4 and CD8 T cell responses were observed, though without a significant correlation with PFS. **Conclusions:** Cvac treatment was safe and showed a significant improvement in PFS in 20 EOC patients in CR2. This strong efficacy signal in the CR2 population warrants further investigation in a larger trial. Clinical trial information: NCT01068509.

**5505 Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**Lurbinectedin (PM01183), an active compound in platinum-resistant/refractory ovarian cancer (PRROC) patients: Results of a two-stage, controlled phase II study.** *Presenting Author: Andres Poveda, Instituto Valenciano de Oncologia, Valencia, Spain*

**Background:** PM01183 is a new anticancer agent that blocks the trans-activated transcription and induces the formation of double-strand breaks in a wide range of cancer cell lines, including platinum-resistant (Pt-res). **Methods:** PRROC patients (pts) with less than 3 prior chemotherapy (CT) containing lines, adequate organ function and performance status (PS) 0-2 were included. The primary endpoint was overall response rate (ORR) (by RECIST v1.1 and/or Rustin criteria). Secondary endpoints were progression free survival (PFS), overall survival (OS) and safety. Pts were treated with i.v. PM01183 (P1), 7 mg flat dose, q3wk in the first stage. In the second stage, pts were randomized (1:1) to PM01183 (P2) or topotecan (T) (standard or weekly regimen). Cross-over to the P2 arm was allowed after progression to T. **Results:** 81 pts were included (P1/P2/T: 22/30/29). Global median characteristics of pts were balanced: age 61 years; PS 1; Pt-res (P1/P2/T: 16/17/16 pts); prior bevacizumab: 18.5% of pts, median prior advanced chemotherapy lines: 1 in each arm. Efficacy results are summarized in the Table. The most common PM01183 related AEs were neutropenia (Gr 3-4, 85%), febrile neutropenia (23%), thrombocytopenia (Gr 3-4, 29%), nausea/vomiting (Gr 3, 16%) and fatigue (Gr 3, 37%) **Conclusions:** PM01183 is an active drug in Pt-res/Pt-ref ovarian cancer. The study has met the primary endpoint, showing statistically significant superiority over T in terms of ORR, PFS and OS. The safety profile is predictable and manageable; prophylactic G CSF is recommended. A phase III study in Pt-res ovarian cancer is planned.

| | PM01183 (n=51) | | | |
|---|---|---|---|---|
| | First stage (P1) (n=22) | Second stage (P2) (n=29) | Topotecan (T) (n=29) | p-value |
| **OR [n (%)]** | | | | |
| **CR** | 0 (0) | 1 (3) | 0 (0) | - |
| **PR** | §6 (27) | 4 (14) | 0 (0) | |
| **SD** | 12 (55) | 13 (45) | 15 (52) | |
| **PD** | 4 (18) | 10 (34) | 14 (48) | |
| **Treatment failure** | 0 (0) | 1 (3) | 0 (0) | |
| **ORR (%) (95% CI)** | 22 (11-35) | | - | 0.006 |
| **Pt-res** | 30 (16-49) | | - | 0.002 |
| **Pt-ref** | 6 (0-27) | | - | 1 |
| **DCR (%)** | 71 | | 52 | - |
| **PFS (months)** * | 3.9 | | 2.0 | 0.003 |
| **Pt-res** | 4.5 | 7.1 | 1.7 | 0.002 |
| **Pt-ref** | 2.9 | 1.4 | 2.7 | 0.809 |
| **OS (months)** + | 10.6 | | 5.7 | 0.029 |
| **Pt-res** | 12.6 | Not reached | 7.0 | 0.053 |
| **Pt-ref** | 12.6 | 8.7 | 5.4 | 0.253 |

Abbreviations: Pt-ref, platinum-refractory; DCR, disease control rate. §2 PRs by Rustin criteria, *events: 81%; +events: 64%.

**5506 Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**Genotype matched treatment for patients with advanced type I epithelial ovarian cancer (EOC).** *Presenting Author: Anna Spreafico, Princess Margaret Cancer Centre, Toronto, ON, Canada*

**Background:** Type I EOCs are uncommon, genetically stable tumors that are often resistant to chemotherapy. Genomic alterations that activate the Mitogen-Activated Protein-Kinase (MAPK) signaling pathway frequently occur in Type I EOCs that may sensitize to downstream MEK inhibition. **Methods:** Formalin fixed paraffin embedded tumor tissues from patients (pts) with Type I EOC were prospectively screened for genomic alterations in a CLIA-certified laboratory using Sequenom MassArray genotyping or targeted sequencing using the Illumina MiSeq TruSeq Amplicon Cancer Panel. The outcomes of pts receiving treatment at Princess Margaret Cancer Centre were retrospectively reviewed. **Results:** From Mar/11 to Jan/14, 49 pts with type I EOC underwent molecular testing, including 80% low grade serous (LGS), 10% clear cell (CC), and 10% mucinous (MC) histologies. Thirty-two pts (65%) were found to have ≥1 somatic mutations: 23 *KRAS*, 6 *NRAS*, 2 *PIK3CA*, 1 *BRAF*, 1 *AKT*, 1 *PTEN*, 1 *TP53*, 1 *CTNNB1*. Fifteen pts (47%) with a median of 2 (range 0-4) prior systemic therapies were treated on genotype-matched phase I or II trials with targeted inhibitors. Fourteen pts (93%) with *KRAS/NRAS* mutations (12 LGS, 1 CC, 1 MC) were treated with targeted combinations that include a MEK inhibitor. Best RECIST 1.1 response for the 14 evaluable pts included: 5 PR (4 confirmed), 8 SD and 1 PD. In pts with PR/SD as best response, the median % of target-lesions shrinkage was 27% (range 12.5-62.5%). Gynecological Cancer Intergroup CA125 related-response was observed in 8/8 *KRAS* and/or *NRAS* mutant pts treated with MEK inhibitor combination treatments. Of 9 pts who had received prior systemic therapy for recurrent disease, the median duration of genotype-matched treatment was 19 weeks (range 6.5-58), compared with 9 weeks (range 4-53) for the immediate prior line of therapy. **Conclusions:** Genotyping and targeted sequencing of Type I EOCs frequently identifies actionable mutations. Matched treatment with MEK inhibitors in *KRAS* and/or *NRAS* mutant type I EOC pts is an active therapeutic strategy.

**5507 Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**Randomized phase III trial of paclitaxel/carboplatin (PC) versus cisplatin/irinotecan (CPT-P) as first-line chemotherapy in patients with clear cell carcinoma (CCC) of the ovary: A Japanese Gynecologic Oncology Group (JGOG)/GCIG study.** *Presenting Author: Aikou Okamoto, Jikei University School of Medicine, Tokyo, Japan*

**Background:** CCC is a histologic subtype of epithelial ovarian cancer showing different clinical and biological characteristics. CCC has become well known for its resistance to current standard chemotherapy (PC). Our previous trial demonstrated the potential benefit of CPT-P regimen on CCC. **Methods:** Patients (pts) with Stage I-IV CCC were randomized to receive paclitaxel 175mg/m$^2$ plus carboplatin AUC6 IV q3wk or irinotecan 60mg/m$^2$ IV (days 1, 8, 15) plus cisplatin 60mg/m$^2$ IV (day 1) q4wk for 6 cycles. International central pathologic review was performed for all cases. The primary endpoint was progression-free survival (PFS). Secondary endpoints were overall survival (OS), response rate per RECIST, and adverse events. Adverse events were graded according to NCI-CTCAE, version 3.0. **Results:** From November 2006 to March 2011, 667 patients were registered, and 619 pts were clinically and pathologically eligible for evaluation (305 pts in PC arm and 314 pts in CPT-P arm). Median age was 53 years. Baseline pt characteristics were not significantly different. Following 44.3 months median follow-up, 2-years PFS was 73.0% (95% CI:67.7-77.5) in the CPT-P arm vs. 77.6% (95% CI:72.4-81.9) in the PC arm, which was not significantly different (HR:1.171, 95% CI:0.867-1.581, p=0.303). Two-years OS was 85.5% in CPT-P arm (95% CI:81.1-89.0) and 87.4% in PC arm (95% CI:83.1-90.7), respectively (HR:1.133, 95% CI:0.796-1.613, p=0.486). Grade 3/4 leukopenia, neutropenia, thrombocytopenia, peripheral sensory neuropathy and joint pain occurred more frequently in the PC arm, whilst grade 3/4 anorexia, diarrhea, nausea, vomiting and febrile neutropenia occurred more frequently in the CPT-P arm. **Conclusions**: In this first CCC-specific international clinical trial, survival benefit was not observed by CPT-P. Since both regimens were well tolerated and the toxicity profiles were different, CPT-P can be an alternative regimen for CCC.

**5508 Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

**Comparison of treatment invasiveness between upfront debulking surgery versus interval debulking surgery following neoadjuvant chemotherapy for stage III/IV ovarian, tubal, and peritoneal cancers in phase III randomized trial: JCOG0602.** *Presenting Author: Takashi Onda, Department of Gynecology, Kitasato University School of Medicine, Sagamihara, Japan*

**Background:** We conducted a phase III trial comparing upfront primary debulking surgery (PDS) and NAC for stage III/IV ovarian, tubal and peritoneal cancers (JCOG0602). Two preceding studies, EORTC55971 and CHORUS, successfully demonstrated non-inferior survival of patients treated with NAC. However, invasiveness of treatment (Tx) has not yet fully been analyzed. To prove efficacy of NAC compared to standard Tx, it is necessary to demonstrate apparently reduced invasiveness of Tx. (UMIN-CTR: UMIN000000523). **Methods:** JCOG0602 is now on-going and the primary analysis of OS is planned in 2016. Patients were randomized to standard arm (PDS followed by 8 cycles of paclitaxel and carboplatin, i.e. TC regimen) and NAC arm (4 cycles of TC, interval debulking surgery [IDS], 4 cycles of TC). In standard arm, IDS was optional for patients who underwent suboptimal or incomplete PDS. Surgical invasiveness and incidence of adverse events related to Tx were compared between two arms. **Results:** From Nov 2006 to Oct 2011, 301 patients (149 standard arm and 152 NAC arm) were randomized. In standard arm 147/149 underwent PDS and 46 of them and 132/152 in NAC arm underwent IDS. Though pelvic and paraaortic lymphadenectomy (PLA/PALA) were more frequently performed in NAC arm ($P<0.01$), frequency of bowel or organ resection was lower in NAC arm ($P<0.01$). In a comparison between PDS in standard arm and IDS in NAC arm, blood/ascites loss (<0.01), albumin transfusion (<0.01), and G3/4 adverse events after surgery in total were fewer in IDS. **Conclusions:** Tx with NAC is less invasive than standard Tx. When non-inferior survival will be confirmed in this trial and new staging system is established, Tx with NAC can become a new standard Tx for advanced ovarian cancer. Clinical trial information: UMIN000000523.

| | Standard arm (N=149) | NAC arm (N=152) | p value |
|---|---|---|---|
| **PLA** | 57 | 94 | <0.01 |
| **PALA** | 27 | 65 | <0.01 |
| **Bowel or organ resection** | 66 | 39 | <0.01 |
| **Treatment-related death** | 2 | 1 | 0.62 |
| **Comparison of surgery** | PDS (N=147) | IDS (N=132) | |
| **Blood/ascites loss (median)** | 3,235 ml | 795 ml | <0.01 |
| **Red cell transfusion** | 75 | 72 | 0.63 |
| **Alb transfusion** | 86 | 35 | <0.01 |
| **G3/4 adverse events** | | | |
| **During surgery** | 1 | 16 | 1.00 |
| **After surgery** | 22 | 6 | <0.01 |

**5509 Clinical Science Symposium, Sun, 8:00 AM-9:30 AM**

**Bevacizumab and improvement of progression-free survival (PFS) for patients with the mesenchymal molecular subtype of ovarian cancer.** *Presenting Author: Boris J. N. Winterhoff, Division of Gynecologic Surgery, Department of Obstetrics and Gynecology, Mayo Clinic Rochester, Rochester, MN*

**Background:** ICON7 demonstrated that the addition of bevacizumab to carboplatin and paclitaxel improves progression free survival (PFS), but not overall survival (OS) in first-line treatment of ovarian cancer. Our aim was to determine if response to bevacizumab was associated with the molecular classification as described by The Cancer Genome Atlas (TCGA) project. **Methods:** Core biopsies from formalin fixed paraffin embedded (FFPE) tissue blocks were examined to ensure >70% tumor nuclei from 425 of 455 ICON7 patients enrolled in Germany. Quality Illumina Whole-Genome DASL HT global gene expression data was generated to stratify 380 (89%) patients into four TCGA subclassifications. Median PFS with 95% confidence intervals (CI) and log rank tests were used to evaluate treatment effect on PFS in the presence of non-proportional hazards. **Results:** Molecular classification was as follows: 86 were differentiated (23%), 124 immunoreactive (33%), 73 mesenchymal (19%), and 97 proliferative (25%). The groups were balanced over treatment arms. 267 (70.3%) were of serous histology. Patients with serous carcinomas of mesenchymal subtype obtained the greatest benefit from bevacizumab with an improvement of median PFS of 9.5 months (25.5 [95%CI 21.1, NA] vs. 16 [95%CI 10.5, NA] months, p=0.053). In contrast, the differentiated, immunoreactive and proliferative subtypes demonstrated median PFS improvements of 5.8 (19.4 [18.6, NA] vs. 13.6 [9.7, 32.7], p=0.35), 3.4 (17.9 [15.9, NA] vs. 14.6 [12.4, NA], p=0.38) and 3.2 months (21.5 [19.8, 29] vs. 18.3 [13.8, NA], p=0.76), respectively. Patients with mesenchymal tumors or high risk clinical characteristics (suboptimal stage III, all stage IV) (46% of cohort) demonstrated a 7.3 month improvement in median PFS with bevacizumab (19.8 [18.3, 23.7] vs. 12.5 [10.1, 16.2] months, p<0.01). **Conclusions:** Assignment to molecular subclassifications based on gene expression signatures was feasible using FFPE tissue. Patients with mesenchymal subtype ovarian cancer may be most likely to obtain sustained benefit from treatment with bevacizumab.

**5510 Clinical Science Symposium, Sun, 8:00 AM-9:30 AM**

**Prospective evaluation of the molecular effects of metformin on the endometrium in women with newly diagnosed endometrial cancer: A window of opportunity study.** *Presenting Author: Pamela T. Soliman, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Metformin reduces cancer incidence and improves overall survival in diabetic patients. Preclinical studies have shown that metformin decreases endometrial cancer (EC) cell growth by activation of AMPK and mTOR inhibition. The purpose of this study was to determine the effects of short-term metformin on serum and tumor biomarkers in women diagnosed with EC. **Methods:** In this IRB approved, prospective trial, women with newly diagnosed EC underwent a pre-treatment blood draw/endometrial biopsy, were administered oral metformin 850 mg daily for a minimum of seven days, and then underwent post-treatment blood draw/definitive surgery. Pre- and post- serum analyses were performed. Immunohistochemical analyses on tumor tissue from the pre- and post-treatment samples were compared to evaluate molecular changes in the PI3K/AKT pathway, apoptosis, proliferation, and AMPK activity. **Results:** Twenty patients completed the study. Median age and BMI were 54 years (range 27-68) and 36.0 kg/m$^2$ (range 21.9-50.0), respectively. Median waist circumference was 113 cm (range 80-156). Median duration of metformin treatment was 10 days (range 7-24). A majority of women had endometrioid adenocarcinomas (86.7%) and were early stage (93%). Two patients were noted to have *KRAS* mutations. After treatment with metformin, there were significant decreases in serum IGF-1 (p=0.046), omentin (p=0.007), insulin (p=0.012), C-peptide (p=0.018), and leptin (p=0.0035). Comparison of pre- and post-treatment tissue samples showed decreased levels of phospho-AKT (90%, p=0.0002), phosphor-S6rp (70%, p=0.057), and phosphor-p44/42MAPK (83.3%, p=0.0038). There was no difference in Ki67, phosphor-ACC, or caspase 3 staining in pre- and post-treatment samples. These changes did not correlate with BMI. **Conclusions:** In this prospective phase 0 study we demonstrate that relevant serum and molecular changes occur in patients with newly diagnosed EC after a short course of low dose metformin. Decreased circulating insulin and down regulation of the PI3K/AKT pathway signaling at the tissue level likely results in mTOR inhibition and a decrease in cell growth. Clinical trial information: NCI-2012-01796.

**5511 Clinical Science Symposium, Sun, 8:00 AM-9:30 AM**

**Efficacy and safety of anti-PD-1 antibody (Nivolumab: BMS-936558, ONO-4538) in patients with platinum-resistant ovarian cancer.** *Presenting Author: Junzo Hamanishi, Kyoto University, Kyoto, Japan*

**Background:** Programmed death-1 (PD-1) is a co-inhibitory receptor expressed on activated T cells which regulates antitumor immunity. Nivolumab is a fully-humanized IgG4 that blocks the engagement of PD-1 by PD-1 ligands. Here we report the first trial for clinical application of nivolumab in ovarian cancer patients. **Methods**: Nivolumab was administered every 2 weeks to patients with advanced or relapsed, platinum–resistant ovarian cancer, at the doses of 1 or 3 mg/kg during two cohort examination (10 patients each). The phase II efficacy trial defined 1$^{st}$ endpoint of response rate, and second endpoints of safety, and disease control rate. Patients receivednivolumab up to 6 cycles (4 doses/cycle) of treatment or until PD or disease progression. Response rate was assessed by RECIST **v**1.1, and adverse events were evaluated by CTCAE v4.0. The data were cut-off on January 1, 2014. **Results**: Fifteen patients were treated with nivolumab (1 mg/kg: n=10, 3mg/kg: n=5), and evaluated. Median duration of therapy was 14 wks. There was one patient who had severe adverse drug reaction with fever, disorientation and gait disturbance. Clinical response rates were shown in Table. At the time of data cut off, one of the three partial responders had responses for 5 months, and the other two were on study with response for 4 and 10 months. **Conclusions**: Nivolumab at 1 mg/kg cohort is well tolerated and has encouraging clinical efficacy for advanced or relapsed, platinum-resistant ovarian cancer patients. 3 mg/kg cohort is now under investigation. Clinical trial information: UMIN000005714.

| Dose | Total (n) | CR | PR | SD | PD | NE | RR | DCR |
|---|---|---|---|---|---|---|---|---|
| **1 (mg/kg)** | 10 | 0 | 2 | 3 | 4 | 1 | 2/10 (20%) | 5/10 (50%) |
| **3 (mg/kg)** | 3 | 0 | 1 | 1 | 1 | 0 | 1/3 (33%) | 2/3 (67%) |
| **Total** | 13 | 0 | 3 | 4 | 5 | 1 | 3/13 (23%) | 7/13 (54%) |

Abbreviations: RR: response rate; CR+PR; DCR: disease control rate; CR+PR+SD.

**5512 Poster Highlights Session (Board #1), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**A prospective evaluation of universal tumor testing strategies for Lynch syndrome in endometrial cancer.** *Presenting Author: Kari Lassen Ring, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Screening for Lynch Syndrome (LS) in endometrial cancer (EC) has traditionally been based on early age at diagnosis and family history. Universal tumor testing has been proposed given poor sensitivity of referral criteria and low referral rates. While immunohistochemistry (IHC) is cost effective and widely available, no prospective evaluation of concordance between screening strategies has been completed in EC to define the optimal approach. Our objective was to perform a prospective, population-based evaluation of universal tumor testing in EC to evaluate concordance between microsatellite instability (MSI) and IHC. **Methods:** MSI and IHC for expression of mismatch repair (MMR) proteins (MLH1, MSH2, MSH6, and PMS2) were performed prospectively on all EC undergoing surgical staging from August 2012 to August 2013 (n=184). PCR-based *MLH1* methylation analysis was performed on tumors with IHC loss of MLH1. **Results:** Forty-five tumors (24.9%) were MSI-H and 50 tumors (27.2%) had loss of ≥1 MMR protein on IHC. Overall concordance between MSI analysis and IHC was 93.9% (CI 89.4 – 96.9); however, 11 patients (6.1%) had discordant tumor studies. One of 45 MSI-H tumors (2.2%) had intact IHC for all 4 proteins and demonstrated MLH1 methylation. Five of 50 tumors (10.0%) with loss of ≥1 MMR protein on IHC were MS-stable (MSS). Three of these 5 tumors had heterogeneous loss of MLH1 and PMS2 and 1 tumor had complete loss of expression of MLH1 and PMS2. All 4 tumors had MLH1 methylation and presumed sporadic. One MSS tumor had isolated MSH6 loss and a confirmed germline mutation in MSH6. Five tumors (2.8%) were MSI-L, 4 of which had intact IHC. Of these 4, 2 had no germline mutation detected in MSH6, 1 had a variant of unknown significance (VUS) in MSH6, and one did not undergo germline testing. One MSI-L tumor had loss of MLH1 and PMS2, with MLH1 methylation. **Conclusions:** Overall concordance between MSI and IHC was high in this prospective EC population. However, 6.1% of patients had discordant tumor studies and 2 of 5 patients without MLH1 methylation had a confirmed germline mutation or VUS. Heterogeneous loss of expression on IHC and MSI-L tumors present clinical caveats that are not well defined in EC and warrant further evaluation.

**5513 Poster Highlights Session (Board #2), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Phase II trial of GDC-0980 (dual PI3K/mTOR inhibitor) in patients with advanced endometrial carcinoma: Final study results.** *Presenting Author: Vicky Makker, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background**: Treatment options for patients with recurrent or persistent endometrial cancer (EC) are limited. The PI3K/AKT/mTOR pathway has been implicated in the pathogenesis of EC. This single arm, open-label trial was designed to evaluate the activity of GDC-0980, a dual PI3K/mTOR inhibitor, in patients with advanced EC. NCT01455493. **Methods**: Patients with recurrent or persistent EC treated with 1 or 2 prior lines of chemotherapy but no prior PI3K/mTOR inhibitor received oral GDC-0980 40 mg daily on a 28-day cycle until progression or intolerable toxicity. Type I/II diabetics requiring insulin were excluded. The primary endpoints were progression-free survival (PFS) at 6 months and objective response rate (ORR). Archival tissue samples were collected for PI3K pathway biomarker analysis. **Results**: A total of 56 women were enrolled including 13 (23%) with well-controlled diabetes at study entry. Discontinuation reasons were disease progression, 24 (43%); adverse events, 13 (23%); withdrawal by subject, 12 (21%). Frequency of Grade 3/4 related adverse events in all patients were hyperglycemia (46%), rash (30%), colitis (5%), and pneumonitis (4%). At 6 months, 20% of patients were progression free (K-M estimate 95% CI: 7%-33%). ORR was 9% (unconfirmed). Median PFS was 3.5 months (95% CI: 2.7-3.7 months). Median time on study was 69 (12-226) days for non-diabetic and 27(4-84) days for diabetic patients. Discontinuation prior to first tumor assessment occurred in 19 patients, with 8/13 diabetics discontinued prior to Cycle 2, due to hyperglycemia. Dose reductions were required for 4 (31%) diabetics and 18 (42%) non-diabetics. Evaluable archival tumor samples were obtained from 44 (85%) patients, and 52% of patients had at least one alteration in PIK3CA, PTEN or AKT1. All 3 patients with a confirmed response had at least one alteration in a PI3K pathway gene. **Conclusions**: Evaluation of the anti-tumor activity of 40mg GDC-0980 daily was limited by tolerability, especially in diabetic patients. The trial provides data about the PI3K pathway mutation frequency in patients with recurrent EC and suggests that patients with a PI3K pathway mutation may have derived enhanced benefit from GDC-0980. Clinical trial information: NCT01455493.

**5514 Poster Highlights Session (Board #3), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Advanced or recurrent endometrial cancer (EC) and co-occurring mutations in multiple oncogenic pathways.** *Presenting Author: Alexandra Leary, Department of Medicine and INSERM U981, Gustave Roussy, Villejuif, France*

**Background:** The prognosis of EC is excellent and mainly driven by early stage type I EC. However, for type II or advanced EC, relapses are frequent. Genomic studies so far included mainly early stage good prognosis primary tumors. Here, we aimed to characterize genetic alterations in high risk advanced or recurrent EC, determine the rate of co-occurring mutations and evaluate concordance between primary and metastatic sites. **Methods:** High risk EC patients were identified from the IGR tumor bank and defined as stage III or IV, or any stage with subsequent relapse. Samples with >30% cellularity were subjected to Sanger sequencing on 79 exons from 13 genes (*KRAS, NRAS, HRAS, BRAF, AKT1, PIK3CA, PIK3R1, PIK3R2, PTEN, STK11, ESR1, TP53, FGFR2*). Mutation calls were confirmed by an independent analysis. **Results:** 75 samples from 57 patients (pts) representative of high risk EC were identified: 49% (28/57) were type II EC, 70% were stage III/IV and the remaining stage I/II pts had all relapsed. By comparison, the TCGA set included 75% stage I/II pts of which only 11% had relapsed. 69 samples from 54 pts qualified for DNA analysis including 13 pts with both primary and metastatic tumors. 80% (43/54) of pts harbored at least one mutation (M+). The most frequent mutation was *TP53* in 35% (19/54) of pts. Alterations of core components of the PI3K pathway (*AKT1, PIK3CA, PIK3R1, PIK3R2, PTEN, STK11*) were identified in 65% of pts (81% and 48% for type I vs. type II EC). *RAS* M+ were identified in 24%. 65% of pts had >1 M+ including concomitant *TP53* M+ and PI3K related M+ (18%), concomitant *TP53* M+ and *RAS* M+ (7%); concomitant PI3K-related M+ and *RAS* M+ (15%), concomitant *FGFR2* M+ and PI3K-related M+ (9%) or concomitant *FGFR2* M+ and *RAS* M+ (4%). Among 13 cases with available primary and metastatic tumor, discordant M+ were found in 5/13 (38%). **Conclusions:** Co-occurring actionable oncogenic mutations are frequent in high risk advanced or recurrent EC. This may explain disappointing results with single agent targeted therapies in EC, but provides the rationale for trials investigating combined inhibition of PI3K and MEK, PI3K and FGFR, or MEK and FGFR in molecularly selected EC. Supported by a research grant from Sanofi Oncology.

**5515 Poster Highlights Session (Board #4), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Phase II, single stage, cohort expansion study of MK-2206 in recurrent endometrial serous cancer.** *Presenting Author: Panagiotis Konstantinopoulos, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Although PTEN mutations or loss of PTEN expression are uncommon in endometrial serous carcinomas, approximately half of these tumors harbor PIK3CA mutations and/or amplification of PIK3CA. A Phase II, 2-stage, 2-arm PIK3CA mutation stratified trial of MK-2206 (an allosteric inhibitor of AKT) in recurrent or advanced endometrial cancer showed that all patients with 6 months progression free survival (PFS) had serous histology, leading to an expansion cohort in patients with endometrial serous tumors. **Methods:** Eligible patients had recurrent or advanced high grade endometrial carcinoma with a serous component. Up to 2 prior chemo lines were permitted; prior treatment with PI3K/MTOR inhibitors was not allowed. All patients were treated with MK-2206 135mg QW; dose was amended from 200mg QW to 135mg QW during the initial patient cohort because of skin toxicity. Primary objective was to evaluate the efficacy of MK-2206 using a composite endpoint of complete and partial response by RECIST 1.1 and PFS of ≥6 months. A target sample size of 14 patients was planned to allow greater than 80% power to reject a null rate of 10% if the true rate of clinical benefit is 36%, when using a binomial exact test with a one-sided alpha $< 0.05$. If 4 or more responses were seen among the 14 subjects, then the null hypothesis would be rejected to conclude sufficient efficacy for further investigation of MK-2206. **Results:** 14 patients were enrolled. There were no grade ≥4 toxicities. Potentially drug related grade 3 toxicities (rash, diarrhea, and anemia) were seen in 3 patients (21%). 10 (71%) patients developed disease progression without meeting any of the efficacy endpoints. The remaining 4 patients are currently on study; two (14%) have met the 6 month PFS endpoint with ongoing decrease in the sum of their target lesions of 27.5% and 21.8% from baseline respectively; the other 2 are on cycles 5 and 2 respectively. Updated results will be presented at the time of the meeting. **Conclusions:** MK-2206 activity has been detected in a fraction of uterine serous cancers. Translational studies including targeted exome sequencing and copy number analysis of PI3KCA are ongoing. We expect to know whether the goal of 4 responses is reached in the next 4 months. Clinical trial information: NCT01312753.

**5516 Poster Highlights Session (Board #5), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Molecular profiling of clear cell ovarian carcinoma.** *Presenting Author: Michael Friedlander, Prince of Wales Hospital, Sydney, Australia*

**Background:** Clear cell ovarian carcinomas (CCOCs) are a distinct histopathological subtype and account for 5-10% of epithelial ovarian cancers (EOCs). They have a poor prognosis in advanced stages and at recurrence. They are commonly resistant to platinum-based chemotherapy and treatment options are limited in patients with progressive disease. Molecular profiling may identify patient subsets who could benefit from targeted therapies when standard treatment has failed and also provide an insight into the genomic heterogeneity of CCOC's that share a similar phenotype. **Methods:** Over 435 CCOC's referred to Caris Life Sciences (from 2009 - 2014) were evaluated; diagnoses were based on reported pathology. Specific testing was performed per physician request and included a combination of sequencing (Sanger, NGS or pyrosequencing), protein expression (IHC), gene amplification (CISH or FISH), and/or RNA fragment analysis. **Results:** Patients were further grouped into pure CCOCs (n=363) and mixed CCOCs (n=72). The most common findings in CCOC's were overexpression of TOP2A (61%), TS (52%), TLE3 (48%), loss of TUBB3 (49%) and MGMT (56%). cMET was overexpressed in 19% of CCOCs tested and in 6% of mixed CCOCs. CCOCs had lower expression of AR, ER, and PR (7%, 9%, and 15%) than mixed CCOCs (21%, 39%, and 31%) and EOCs (24%, 45%, and 30%). In 69 CCOC's analyzed by NGS, PIK3CA was the most common mutation (52% - vs. 8% in all EOCs and 14% in mixed CCOCs) followed by TP53 (16%) and KRAS (11%). Mutations in FBXW7 (10%), APC (7%) and ATM (6%) were observed at a higher rate than in all EOCs. No BRAF mutations were seen. In the 33 CCOCs with PIK3CA mutations, 4 (12%) had co-existing mutations in KRAS and 2 (6%) had TP53 mutations while 70% (23/33) overexpressed cMET and 12% had a loss of PTEN. **Conclusions:** Molecular profiling of proteins, gene expression, and mutations underscores the heterogeneity of CCOC and the potential role in better selecting patients for clinical trials. Drugs, which target the mTOR pathway or cMET may have therapeutic potential in selected subsets. Mutations in FBXW7, APC and ATM may also help direct patients to trials of targeted therapies.

**5517 Poster Highlights Session (Board #6), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Combination chemotherapy with temsirolimus and trabectedin for recurrent clear cell carcinoma of the ovary: A phase II single arm clinical trial.** *Presenting Author: Masashi Takano, Department of Obstetrics and Gynecology, National Defense Medical College, Tokorozawa, Japan*

**Background:** Recurrent clear cell carcinoma (RCCC) of the ovary showed exceedingly chemo-resistant phenotype, especially in the case with recurrent or refractory to previous therapy. A phase II trial to evaluate the effect of combination therapy with temsirolimus and trabectedin for patients with RCCC was performed. **Methods:** Simon's two-stage design was used. In the first stage, 9 patients were accrued. If there were no responder in these patients, the study would be stopped. Otherwise, eight additional patients will be accrued for a total of 17. If three or more responder were observed in 17patients, this design yields a type I error rate of 0.05 and power of 0.81 when the true response rate were 25%. Patients with RCCC were treated with weekly regimen using two drugs: 15mg/m$^2$ of temsirolimus and 0.15mg/m$^2$ of trabectedin (3 weeks, one week rest) with written informed consents. Treatment was continued until development of progressive disease (PD) or unmanageable adverse effects. **Results:** Among 9 patients in the first stage, two responses were observed, and a total of 17 patients were analyzed in this study. There were no cases that discontinued the therapy due to toxicities. Median age was 60 years (range: 30-69), and median number of previous chemotherapy was 3 (range: 1-6). All cases were assessable by RECIST and CTCAE. One patient (6%) had a complete response (CR), and two cases (12%) achieved a partial response (PR), and 5 patients (29%) had a stable disease (SD) beyond three months, resulting in clinical benefit rate (CBR; CR+PR+SD>3month) of 47%. Median response duration in CBR case was 3.5 months (range: 3-24+). There were no cases that developed toxicities more than grade2. **Conclusions:** Combination therapy with temsirolimus and trabectedin was a candidate for salvage therapy for patients with RCCC. These results warrant further study in such clinical settings.

**5519 Poster Highlights Session (Board #8), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**A phase II randomized open-label study of MM-121, a fully human monoclonal antibody targeting ErbB3, in combination with weekly paclitaxel versus weekly paclitaxel in patients with platinum-resistant/refractory ovarian cancers.** *Presenting Author: Joyce Liu, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Heregulin induced activation of ErbB3 has been implicated as a mechanism of resistance to many targeted and cytotoxic therapies such as paclitaxel in preclinical models. MM-121 is a monoclonal antibody designed to interfere with this mechanism of resistance. **Methods:** This was a global, open-label, randomized Phase II study of MM-121 in patients with platinum resistant ovarian cancer. Patients were randomized (Ratio 2:1) to receive MM-121 plus paclitaxel (M+P) or paclitaxel alone (P). The primary objective was to compare progression-free survival (PFS) between the groups. Pretreatment fresh biopsies obtained from all patients were analyzed to assess a pre-specified set of mechanistically-linked biomarkers (BM): heregulin (HRG), betacellulin, EGFR, ErbB2, and ErbB3. **Results:** 223 patients (140 (M+P), 83 (P)) were included in the efficacy analyses. Baseline demographics and disease characteristics were balanced. Most patients (80.3%) had received 2 or more prior platinum-based regimens. Median PFS was analyzed after 171 events (115 (M+P), 56 (P)) and was 3.75 months (M+P) and 3.68 months (P) with a stratified hazard ratio (HR) of 1.027 [95% CI 0.741 - 1.425]. Two biomarkers based on pre-clinical predictions were used to identify a subset of BM positive patients (34%: 57/169 patients with BM available). In this BM positive group the HR for PFS was 0.37 [0.2 - 0.8] and the HR in the BM negative group was 1.54 [1.0 - 2.4]. The overall safety profile was consistent with expected adverse events (AEs), with the exception of an increase in the pulmonary embolism rate (5.0% (M+P) vs. 1.2% (P)). However, the overall rate of venous thromboembolic events was comparable (5.7% (M+P) vs. 7.5% (P)). Most AEs were reported as mild to moderate in severity and included diarrhea, vomiting, stomatitis, and mucosal inflammation. **Conclusions:** A signal of benefit was observed in a biomarker positive subpopulation, althoughthe study regimen was not effective at prolonging PFS in the overall study population. Any further development of MM-121 in ovarian cancer should focus on biomarker-selected patients. Clinical trial information: NCT01447706.

**5520 Poster Highlights Session (Board #9), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Clinical and genetic aspects of ovarian stromal tumors: A report from the International Ovarian and Testicular Stromal Tumor Registry.** *Presenting Author: Kris Ann Pinekenstein Schultz, Children's Hospitals and Clinics of Minnesota, Minneapolis, MN*

**Background:** Ovarian sex cord-stromal tumors are rare tumors that tend to occur in children, adolescents and young adults. The International Ovarian and Testicular Stromal Tumor (OTST) Registry was established in December 2011 to investigate the clinical and biologic aspects of these rare tumors. **Methods:** For each Registry participant, clinical data and biologic specimens including germline DNA and tumor tissue were collected. Pathology was centrally reviewed and germline *DICER1* testing was performed. **Results:** Overall, 52 patients with ovarian tumors have enrolled. Forty-one of these have SLCT (n=22), juvenile granulosa cell tumor (n=14), Sertoli cell tumor (n=4) or gynandroblastoma (n=1) and are presented here. Median overall survival is 25 months (range 3 to 223). Four patients have recurred and 2 have died from disease. Median age at diagnosis was 15 (range ≤1 to 51 years, 73% younger than 21 years). Eleven of 32 patients tested (34%) have a deleterious germline *DICER1* mutation. *DICER1* mutations were seen in 56% of patients with SLCT. Additional tumors, including carcinoid, pleuropulmonary blastoma, cystic nephroma and rhabdomyosarcoma, were seen in 18% of patients prior to or following the diagnosis of SLCT. **Conclusions:** Establishment of the International OTST Registry allowed rapid accrual of patients with these rare tumors. Although most patients are alive, recurrences and other tumors occurred, especially in SLCT. Germline *DICER1* mutations were seen in more than half of patients with SLCT as well as in one patient with juvenile granulosa cell tumor and one with gynandroblastoma. Further analysis of *DICER1* in tumor tissue is underway.

| Diagnosis | n | Age at diagnosis (yrs), median (range) | *DICER1*+ n (%) | Thyroid nodules n (%) | Other (non-thyroid) tumors n (%) | Recurrence n (%) | Overall survival n (%) | Overall survival (months) median (range) |
|---|---|---|---|---|---|---|---|---|
| SLCT | 22 | 17 (3-40) | 9/16 (56%) | 4 (18%) | 4 (18%) | 3 (14%) | 21 (95%) | 13 (3-202) |
| Juvenile granulosa cell tumor | 14 | 9 (<1-18) | 1/12 (8%) | 1 (7%) | 0 | 1 (7%) | 13 (93%) | 28 (15-223) |
| Sertoli cell tumor | 4 | 46 (34-51) | 0/3 | 2 (50%) | 1 (25%) | 0 | 4 (100%) | 27 (9-37) |
| Gynandroblastoma | 1 | 15 | 1/1 (100%) | 1 (100%) | 0 | 0 | 1 (100%) | 98 |
| Total | 41 | 15 (<1-51) | 11/32 (34%) | 8 (20%) | 5 (12%) | 4 (10%) | 39 (95%) | 25 (3-223) |

**5521 Poster Highlights Session (Board #10), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Phase 1/1b study of the FAK inhibitor defactinib (VS-6063) in combination with weekly paclitaxel for advanced ovarian cancer.** *Presenting Author: Manish R. Patel, Florida Cancer Specialists and Research Institute, Sarasota, FL*

**Background**: Defactinib (VS-6063) is an oral inhibitor of focal adhesion kinase (FAK). Blockade of FAK has been shown to reduce tumor growth and metastasis through inhibition of tumor cell survival, proliferation, invasion and tumor angiogenesis. FAK inhibitors also reduce the proportion of cancer stem cells (CSCs) while paclitaxel (PTX) treatment enriches for CSCs. This multicenter study investigated the safety/tolerability and activity of defactinib in combination with weekly PTX. **Methods:** Pts with advanced or refractory ovarian cancer were enrolled. In the Phase 1, defactinib was administered at either 200mg or 400mg BID with PTX 80 mg/m$^2$ on days 1, 8, and 15, every 28 days. In the Phase 1b, an additional 12 pts were enrolled at a dose of 400 mg BID defactinib with 80 mg/m$^2$ PTX. In pts with biopsiable disease, paired tumor biopsies were collected following a 10-day run-in with defactinib alone. **Results:** Eighteen pts were enrolled (6 in phase I and 12 in phase Ib): median age was 67.5 years (50-77); ECOG PS was 0 or 1. Pts received a median of 3 (1-9) prior regimens of therapy. All patients had prior taxane exposure and 15/18 (83%) were platinum resistant. The combination therapy was well tolerated with no DLT observed. The recommended dose was determined to be defactinib 400 mg BID with PTX 80 mg/m$^2$. Reported treatment related grade 3 toxicities included: neutropenia (n=5), hyperbilirubinemia (3), thrombocytopenia (1), anemia (1), leukopenia (1), nausea (1), vomiting (1), increased alanine aminotransferase (1). No grade 4/5 drug related toxicities were observed. Defactinib did not alter PTX exposure. A decrease of p-FAK was observed in all 3 patients who underwent paired biopsies. One pt had a CR by RECIST, 1 pt has an ongoing PR of >6 months and 1 pt has ongoing SD of >8 months. Nine of the 18 pts remain on study. **Conclusions:** Defactinib was generally well tolerated in combination with weekly PTX, and further analysis of PD and biomarkers is ongoing. Radiographic tumor changes, normalization of serum markers, and tumor reductions in pFAK support further development of this combination. Clinical trial information: NCT01778803.

**5522 Poster Highlights Session (Board #11), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Preclinical and early clinical activity of the oral selective inhibitor of nuclear export (SINE) exportin 1 (XPO1) antagonist KPT-330 (Selinexor) in patients (pts) with platinum-resistant/refractory ovarian cancer (OvCa).** *Presenting Author: John Martignetti, Mount Sinai School of Medicine, New York, NY*

**Background:** Increased XPO1 expression has been linked to progression of OvCa and is an independent poor prognostic for survival. Most tumor suppressor proteins (TSP) are transported out of the nucleus exclusively by XPO1 and thereby rendered non-functional. KPT-330 is a slowly reversible inhibitor of XPO1, and forces the nuclear retention and activation of over 10 TSP resulting in OvCa cell death while sparing normal cells. **Methods:** SINE compounds were tested for their ability to localize OvCa-relevant TSP to the nucleus and induce apoptosis in platinum sensitive and resistant cell lines *in vitro*. Combination with cisplatin was assessed *in vitro* and in patient-derived xenograft models (30 mg/m$^2$ po, 3 times/week). As part of an on-going Phase 1 (KCP-330-002) in pts with solid tumors, oral KPT-330 (8-10 doses/4-weeks cycle) was administered to pts with heavily pre-treated OvCa that were progressing on study entry. Pharmacokinetic (PK) analyses were performed. Response was evaluated every 2 cycles (RECIST 1.1). **Results:** SINE potently induced OvCa cell death in platinum sensitive and resistant cell lines ($IC_{50}$s $< 0.12$ $\mu$M). Nuclear accumulation and functional activation of p53 and other TSP was demonstrated. Synergy between SINE and cisplatin was shown *in vitro* and *in vivo* in OvCa models with diverse genetic backgrounds, and increased overall survival. Seven OvCa pts resistant/refractory to platinums and other agents (median age 55 yrs; ECOG PS 0/1: 3/4; median number of prior therapies 5) were treated with 30-35 mg/m$^2$ oral KPT-330 (300 mg/cycle or 280 mg/cycle). No grade 4 AEs were reported. The most common AEs were fatigue, nausea, diarrhea, and vomiting; manageable with supportive care. PK analysis showed $C_{max}$ of 0.5-1 mM and $AUC_{0\text{-}inf}$ 2800-4000 ng*h/mL, which exceed levels *in vitro* and in animal models. RECIST response was evaluable in 5 pts: 1 PR (5 months), 2 SD (4 and 7+ months) and 2 PD. **Conclusions:** KPT-330 treatment is generally well tolerated and shows preliminary antitumor activity in pts with platinum resistant or refractory OvCa. Additional single agent and combination studies are planned. Clinical trial information: NCT01607905.

**5523 Poster Highlights Session (Board #12), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Randomized phase II trial of NGR-hTNF with an anthracycline in platinum-refractory or -resistant ovarian cancer (OC).** *Presenting Author: Domenica Lorusso, Fondazione IRCCS National Cancer Institute, Milan, Italy*

**Background:** Low-dose NGR-hTNF induces in preclinical models an early tumor blood vessel stabilization that enhances T-lymphocyte infiltration and survival, an effect that is mediated by CD8$^+$ effector cells **Methods:** OC patients with disease progression while receiving or within 6 months after completion of $\leq$ 2 platinum/taxane lines were stratified by platinum resistance (refractory or resistant), PS (0 or 1/2) and anthracycline (doxorubicin, D or pegylated liposomal doxorubicin, PLD) and randomly assigned to receive D (60 mg/m$^2$ q3w) or PLD (50 mg/m$^2$ q4w) with (arm A) or without (arm B) NGR-hTNF (0.8 $\mu$g/m$^2$ q3w). Progression free survival (PFS) was primary endpoint ($\beta$=20%; $\alpha$=20%, hazard ratio, HR=0.62; n=100). Main secondary aims were overall survival (OS), response rate (RR, complete plus partial response) and adverse events (AE) **Results:** Baseline characteristics in arm A (n=58) vs B (n=51): median age, 60 vs 60 years; resistant, 71% vs 75%; PS of 0, 79% vs 82%; serous, 67% vs 71%; two prior lines, 48% vs 35%; D, 81% vs 84%; median baseline peripheral blood lymphocyte count (PBLC), 1.4/mL vs 1.6/mL. In all, 262 cycles were given in arm A (mean 4.5; range 1-20) and 227 in B (4.4; 1-8). Grade 3/4 AEs (arm A vs B): neutropenia, 29% vs 22%; anemia, 4% vs 6%. With median follow-up time of 16.1 months, there was no significant difference between the two arms in PFS (stratified HR=1.08; 95% CI, 0.70-1.65), RR (odds ratio=1.34; 0.21-8.33) and OS (HR=0.70; 0.42-1.17). Median and 18-month OS rates were 12.1 months (6.9-17.2) and 44% ($\pm$7) vs 9.4 months (8.4-10.4) and 22% ($\pm$7) for arm A vs B, respectively. In resistant disease (n=79), median OS was 14.2 months for arm A and 9.5 months for arm B (HR=0.66; 0.36-1.21). In patients with baseline PBLC above the median value (n=56), median OS was not reached yet for arm A compared with 9.5 months for arm B (HR=0.45; 0.22-0.91; p=0.02). Follow-up assessment for a next patient cohort (n=24) receiving a weekly schedule of NGR-hTNF is ongoing **Conclusions:** NGR-hTNF plus D/PLD was safely given, without increase in PFS over D/PLD in unselected population. Consistently with previous findings, significantly improved OS rates for the combination were noted in patients with high baseline lymphocyte counts Clinical trial information: NCT01358071.

**5524^ Poster Highlights Session (Board #14), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**A phase I study of the vascular-disrupting agent BNC105P in combination with gemcitabine-carboplatin in platinum-sensitive ovarian cancer patients in first or second relapse.** *Presenting Author: Danny Rischin, Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia*

**Background:** BNC105P is a tubulin polymerization inhibitor and a vascular disrupting agent (VDA) selectively active against tumor endothelium. Pre-clinical data has demonstrated greater than additive activity of BNC105P when combined with platinum or with gemcitabine. The primary objective of this study was to evaluate the safety and tolerability of BNC105P in combination with gemcitabine and carboplatin in patients with recurrent ovarian cancer, and to find a dose suitable for evaluation in a randomized trial. **Methods:** Patients with ovarian cancer who progressed > 4 months after first or second-line platinum based chemotherapy received carboplatin AUC4 at day 1 in combination with escalating doses of gemcitabine at day 1 and 8 and escalating doses of BNC105P at day 2 and 9 every 21 days for a maximum for 6 cycles. Maintenance treatment with 16 mg/m$^2$BNC105P treatment continued for a maximum of 6 additional cycles. Blood samples were collected at baseline and 4 hours post BNC105P to study potential pharmacodynamic biomarkers associated with BNC105P biological action in previous trials. **Results:** 15 patients were enrolled in the study. Adverse events were most commonly of haematological origin. Dose limiting toxicities occurred in 1 patient on dose level 1 and 2 patients on dose level 2a and consisted of thrombocytopenia and neutropenia. The recommended dose was gemcitabine 1,000 mg/m$^2$, carboplatin AUC 4 and BNC105P 12 mg/m$^2$. 10 patients achieved a response according to GCIG CA125 and/or RECIST 1.1 criteria. Increases in blood levels of ferritin, interleukin-8, interleukin-16 and macrophage inflammatory protein-1beta post 12 mg/m$^2$BNC105P were consistent with a pharmacodynamic response.. **Conclusions:** The combination of BNC105P with gemcitabine and carboplatin is safe and tolerable in patients with potentially platinum sensitive recurrent ovarian cancer. The data supports continued development of BNC105P in this setting. Clinical trial information: ACTRN12612000522819.

| | Dose level 1 | Dose level 2a | Dose Level 2b |
|---|---|---|---|
| **BNC105P** | 12 mg/m$^2$ | 16 mg/m$^2$ | 12 mg/m$^2$ |
| **Gemcitabine** | 800 mg/m$^2$ | 800 mg/m$^2$ | 1000 mg/m$^2$ |
| **Carboplatin** | AUC4 | AUC 4 | AUC 4 |
| **No. registered** | 6 | 3 | 6 |
| **No. DLTs** | 1 | 2 | 0 |

**5525 Poster Highlights Session (Board #15), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Adoption and impact of concurrent chemotherapy with radiation in the treatment of patients with vaginal cancer: A National Cancer Data Base (NCDB) study.** *Presenting Author: Malolan Sri Rajagopalan, University of Pittsburgh Cancer Institute, Pittsburgh, PA*

**Background:** Vaginal cancer is uncommon entity for which concurrent chemoradiation (CCRT) is increasingly used based on extrapolation from cervical cancer. However, studies supporting CCRT use are limited to single-institution reports. We sought to explore the adoption rate of CCRT and determine its impact on survival in vaginal cancer patients. **Methods:** We identified patients in the NCDB diagnosed with vaginal cancer from 1998-2011 who received definitive radiation therapy with or without chemotherapy. Univariate and multivariable exploratory analyses of factors associated with CCRT use were performed. Log-rank test and Cox proportional hazards modeling identified the overall and independent contribution of CCRT use on overall survival (OS) in the context of known/putative prognostic factors. **Results:** A total of 13,689 patients were identified of whom 8,086 (59.1%) received radiation therapy. Of these, 3,932 (48.6%) received CCRT, the use of which increased from 20.8% in 1998 to 59.1% in 2011. Of the 23 patient, disease, treating facility, and treatment factors explored, 13 were found to have significant associations in chi-square testing and were entered into a binary logistic regression model. Younger age, larger tumor size, later year of diagnosis, treatment at a higher volume facility, squamous histology, and higher stage (in order of increasing association) are independently associated with increased use of CCRT. Median OS of patients who received CCRT is significantly longer than those who did not (56.2 vs. 41.2 months, $p<0.0005$). On multivariable analysis, younger age, treatment at a facility with higher-volume, squamous histology, lower Charlson-Deyo comorbidity score, treatment with CCRT, treatment with brachytherapy and lower stage (in order of increasing association) are independently prognostic of improved survival. **Conclusions:** Use of concurrent chemotherapy with radiation therapy in the treatment of vaginal cancer has become increasingly adopted over the past decade and is associated with a significant improvement in OS in this large national cohort. CCRT should be integrated into treatment guidelines for vaginal cancer.

**5526 Poster Highlights Session (Board #16), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Cisplatin with dose-dense paclitaxel before and after radical hysterectomy for locally advanced cervical cancer: Final results of a multicenter phase II study (Sankai Gynecology Study Group 013).** *Presenting Author: Satoshi Yamaguchi, Gynecologic Oncology Division, Hyogo Cancer Center, Akashi, Hyogo, Japan*

**Background:** The primary objective of the study was to investigate survival after cisplatin plus dose-dense paclitaxel (ddTP) before and after radical hysterectomy (RH) without radiotherapy of patients for locally advanced cervical cancer. **Methods:** Patients with stage IB2, IIA2, or IIB cervical cancer received 3 cycles of cisplatin (75 mg/m$^2$, day 1) with paclitaxel (80 mg/m$^2$, days 1, 8, and 15) every 21 days, RH, and another 2 cycles of the same regimen. Primary endpoint was 2-year recurrence-free survival (RFS). Secondary endpoints were 2-year overall survival (OS), safety, response, and pathologic complete response (pCR), defined as no evidence of malignancy in all surgical specimens. **Results:** Fifty one patients were enrolled from 2010 to 2012 (41 with squamous cell carcinoma [SCC], 9 with adeno/adenosquamous carcinoma, and 1 with small cell carcinoma). Median age was 52 years (range 30-70). The FIGO stage was IB2 in 14 patients, IIA2 in 3, and IIB in 34. All but 1 non-responsive patient underwent RH. At the median follow-up time of 27 months, 2-year RFS and OS were 88.2% and 94.1%, respectively. Six recurrences occurred within 1 year from last treatment. Five patients died. Except 1 patient with grade 4 hypersensitivity during the first paclitaxel infusion, 18 patients achieved complete response and 29 achieved partial response, with response rate of 94% (47/50). Fourteen patients (28%; 13 with SCC, 1 with adenocarinoma) achieved pCR. Eight good responders refused to receive adjuvant ddTP, with no recurrence. Grade 3/4 adverse events were neutropenia (34%), nausea (12%), appetite loss (10%), fatigue (6%), and anemia (6%). Febrile neutropenia was uncommon (2%). No serious long-term adverse events occurred. **Conclusions:** Administering with ddTP before and after RH for locally advanced cervical cancer achieves good survival and is feasible, evidenced by the acceptable toxicity. Phase III studies should compare this with concurrent chemoradiation. Clinical trial information: UMIN000006440.

**5527 Poster Highlights Session (Board #17), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Phase Ib/II with expansion of patients at the MTD study of olaparib plus weekly (metronomic) carboplatin and paclitaxel in relapsed ovarian cancer patients.** *Presenting Author: Saul E. Rivkin, Marsha Rivkin Center for Ovarian Cancer Research, Seattle, WA*

**Background:** To establish the maximum-tolerated dose (MTD) and evaluate dose-limiting toxicities (DLTs) and response to therapy of combination therapy with carboplatin/paclitaxel and olaparib, an oral tablet inhibitor of poly ADP ribose polymerase (PARP) of BRCA 1 and 2, in advanced (Stage III or IV) relapsed ovarian cancer. **Methods:** Eligibility required measurable disease, adequate organ function and ECOG performance status of $\leq 2$. Subjects had to have failed first line platinum containing chemotherapy. All subjects were tested for BRCA 1 and 2. Subjects received the metronomic therapy of paclitaxel 60mg/m2 IV and carboplatin AUC 2 IV weekly, 3 weeks out of 4 and increasing doses of olaparib until the maximum tolerated dose was obtained. Olaparib started at 50 mg bid administered orally for 3 consecutive days (D1-D3), every week for each cycle. Subjects were assessed for toxicity and response according to the protocol. Subjects received combination therapy until DLT or disease progression. **Results:** The MTD was found to be olaparib 150 mg bid, three (D1-D3) consecutive days of each week of each cycle. Total number of patients enrolled in the phase 1b part of this study was 14. Median age was 58. Median number of prior therapeutic regimens was 4. Median number of cycles on study to date is 9.3. There have been no deaths due to study regimen or grade 4 toxicities. The most common grade 3 toxicities were neutropenia, lymphopenia, anemia, fatigue, and MDS (1pt.). There was no evidence of GI, cardiac, hepatic, pulmonary or dermatologic toxicities in any of these patients. 4 subjects had a complete remission (CR), 3 had partial remissions (PR), 3 had stable disease (SD), 2 had progressive disease (PD) and 2 were not evaluable. Of the 4 CR's three were BRCA positive Of the PR's two were BRCA positive and one was variant. Of the SD's there were 2 BRCA positive. Of the PD's one was BRCA positive. **Conclusions:** Olaparib, an oral tablet can be safely administered with a weekly regimen of carboplatin and paclitaxel in heavily pretreated, ovarian cancer patients. This is the first successful combination of olaparib with carboplatin and paclitaxel that has been well tolerated with minimal toxicity. Clinical trial information: NCT01650376.

**5528 Poster Highlights Session (Board #18), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Phase II trial of intraperitoneal (IP) administration of catumaxomab (C) as consolidation therapy for patients (pts) with relapsed epithelial ovarian cancer (OC) in second or third complete remission: GEICO 1001 study.** *Presenting Author: Ignacio Romero, Area Clinica Oncologia Ginecológica. Instituto Valenciano de Oncologia, Valencia, Spain*

**Background:** Treatment with the trifunctional anti-EpCAM x anti-CD3 antibody, Catumaxomab, has shown antitumor activity in patients with advanced OC and refractory ascites. We explored prospectively the potential activity of C as consolidation therapy in pts with clinical complete response (CCR) following treatment for relapse. **Methods:** Pts with 2nd or 3rd CCR (CA-125 $<$ 35 UI/ml and no evidence of disease in CT Scan), received IP C 10 $\mu$g day 0, 20 $\mu$g d3, 50 $\mu$g d7, 200 $\mu$g d10 . All pts received premedication with paracetamol and methylprednisolone 20 mg. Primary endpoint was progression-free survival (PFS) defined as time in months (m) from beginning of therapy for the most recent relapse until progression by RECIST criteria in the Intent to treat population (at least 1 dose of C). CA-125 was double-blinded during follow-up. Secondary end-points were safety, 2nd PFS (PFS of pts in 2nd CCR), 3rd PFS (PFS of pts in 3rd CCR) and PFS from first C dose. A median PFS $>$ 14 m would be considered clinically meaningful to assess a confirmatory randomized trial. **Results:** 46 pts were included, 39 received 1st dose (29 in 2nd and 10 in 3rd CR) and 32pts completed 4 doses. Catheter-related issues preclude 4 pts to receive 1st dose and 3 pts to complete the 4 doses. Median duration of C therapy was 13 d (1-22). Grade 3-4 AE were observed in 29 pts (74.4%) and lead to interruption of C in 4 pts (10.2%). Grade 3-4 AE in $>$ 5% of pts: GGT (35.9%), ALT/AST(20.5%), abdominal pain (12.8%), nausea (10.3%), asthenia (7.7%), Bilirubin (7.7%), diarrhea (5.1%), vomiting (5.1%) and non-neutropenic infection (5.1%). Additionally, pyrexia grade 2 in 33.3% of pts. Median PFS is 17.08 m (CI 95%: 12.9-21.5), 2nd PFS is 17.28 m (CI 95%: 12.9-21.5), 3rd PFS is 17.08 m (CI 95%: 9.26-25.5) and median PFS from first C dose is 8.71 m (CI 95%: 6.01-12.3). **Conclusions:** Intraperitoneal catumaxomab as consolidation therapy for pts with relapsed OC in 2nd or 3rd CCR is feasible. Median PFS of 17.08 m from most recent relapse and 8.71 m from C first dose may indicate an impact of C in relapsed OC with minimal residual disease after 2nd or 3rd CCR, and should be confirmed in a randomized trial. Clinical trial information: NCT01246440.

**5529 Poster Highlights Session (Board #19), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**A phase II, multicenter, randomized, double-blind, placebo-controlled trial of ganitumab or placebo in combination with carboplatin/paclitaxel as front-line therapy for optimally debulked primary ovarian cancer: The TRIO14 trial.** *Presenting Author: Gottfried E. Konecny, David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA*

**Background**: IGF signaling has been implicated in the pathogenesis and progression of ovarian cancer (OC). Ganitumab (GAN; AMG 479) is an investigational, fully human, monoclonal antibody inhibitor of IGF1R. We explored the efficacy and safety of adding GAN to carboplatin and paclitaxel (CP) front line chemotherapy in patients with optimally debulked (<1 cm) FIGO stage III and IV (positive pleural cytology only) ovarian epithelial (including fallopian tube and primary peritoneal) cancer. **Methods**: Patients were randomized in a 1:1 fashion to receive CP (C AUC6/ P 175 mg/m$^2$ q3w) plus GAN (18 mg/kg q3w) or placebo (PLB) for 6 cycles followed by 6 additional cycles of single agent GAN (18 mg/kg q3w) or PLB. The primary endpoint was PFS. Secondary objectives were: Overall survival (OS), safety, quality of life (QOL FACT-O), and to explore the relationship between PFS and molecular OC subtypes (gene expression) or IGFR1 signaling (phospho-proteins). **Results**: 170 patients were enrolled. Median age was 58 yrs (range 18-77); ECOG PS 0/1/2, 41%/53%/6%. 165 patients were assessable for toxicity; most frequent grade 3/4 adverse events for CP+GAN vs. CP+PLB were neutropenia (42% vs. 38%), thrombocytopenia (23% vs. 13%), hyperglycemia (3.4% vs. 1.3%) and skin rash (3.4% vs. 0%). The median PFS estimates were 15.7 mos (CP+GAN) vs. 16.7 mos (CP+PLB); HR (PFS): 1.22 (95% CI:0.81-1.82); median OS not yet reached. Self-reported QOL showed no difference between treatment arms. Correlative biomarker studies in 116 patients are ongoing and will be presented. **Conclusions**: PC+GAN was well tolerated in this population, however, the addition of GAN did not prolong PFS with respect to PC in unselected OC patients. Clinical trial information: NCT00718523.

**5530^ Poster Highlights Session (Board #20), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Phase II prospective study on trabectedin (T) in BRCA-mutated and BRCAness phenotype advanced ovarian cancer (AOC) patients (pts): The MITO 15 trial.** *Presenting Author: Domenica Lorusso, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy*

**Background:** T is a minor groove DNA binding agent with suggested activity in homologous recombinant defective (HRD) pts. This prospective phase II study was designed to evaluate activity of T in BRCA mutated and BRCAness phenotype AOC pts**. T**he trial was partially supported by Pharma-Mar. **Methods:** AOC pts with documented BRCA mutation or BRCAness phenotype defined as at least 2 previous response to platinum (P), were treated with T (1.3 mg/m$^2$q 21 i.v.) until disease progression. According to the number (N) of previous P responses, pts were stratified in moderately P sensitive (MPS, <3 P responses) and highly P sensitive (HPS, > 3 previous P responses). **Results:** 100 pts were enrolled and 88 were evaluable for response (52MPS, 46 HPS) after a median FU of 6 months (range: 1.5-20). Patient characteristics: median age 59 (range 49-73); 86% of tumours were serous and 60% were grade 3; median N of previous chemotherapy lines was 4 (range 2-14); median N of administered T cycles/pt was 6 (1-15), median cumulative T dose 11.0 mg/m$^2$(range 1.9-30). In the whole population ORR was 41%, media PFS 18 weeks and median OS was not reached (NR). Oncologic outcome according to P sensitivity is shown in the Table. Among 518 administered cycles the most frequent Grade 3-4 haematological toxicities (per cycle) were: neutropenia 17.3%, leukopenia 7.7%, anemia 2.7%, thrombocytopenia 2.3%; the most frequent non-haematological Grade 3 toxicity was transaminitis 5.2%. Evaluation of responses according to BRCA mutational status, expression profiling and DNA polymorphisms of genes involved in DNA repair is ongoing. **Conclusions:** T represents a valuable treatment option in the specific setting of AOC pts showing multiple platinum responses. Clinical trial information: 2011-001298-17.

| | MPS 46 pts (%) | HPS 42 pts (%) |
|---|---|---|
| **Complete responses** | 0 | 4 (9.5) |
| **Partial responses (PR)** | 15 (32.6) | 17 (40.5) |
| **Overall response rate (ORR)** | 15 (32.6) | 21 (50) |
| **Stabilizations of disease (SD)** | 12 (26.1) | 10 (23.8) |
| **Progression of disease** | 19 (41.3) | 11 (26.2) |
| **Progression-free survival (PFS, weeks)** | 11 | 24 |
| **Overall survival (OS, weeks)** | 40 | NR |

**5531 Poster Highlights Session (Board #21), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Meta-analysis of public microarray databases for prognostic and predictive gene signatures of late-stage ovarian cancer.** *Presenting Author: Michael J. Birrer, Massachusetts General Hospital/Dana-Farber Cancer Center/ Harvard Medical School, Boston, MA*

**Background:** Numerous gene signatures of patient prognosis for late-stage, high-grade ovarian cancer have been published, but diverse data and methods have made these difficult to compare objectively. However, the corresponding large volume of publicly available expression data creates an opportunity to validate previous findings and to develop more robust signatures. **Methods:** We built a database of uniformly processed and curated public ovarian cancer microarray data and clinical annotations, and re-implemented and validated 14 prognostic signatures published between 2007 and 2012. **Results:** For the microarray datasets investigated, twelve published models performed better than 97.5% of randomized risk scores, and six out-performed 97.5% of random signatures of the same size trained on the same data. The most accurate prognostic model was that of The Cancer Genome Atlas Consortium. By meta-analysis and "leave-one-dataset-out cross-validation" of 1,622 samples we generated and tested a prognostic signature that improved on all previously published signatures. In addition, we established a predictive signature for suboptimal surgical debulking which was 90% accurate and validated by immunohistochemistry. The debulking signature reveals activated TGF-beta pathway which promotes tumor migration, invasion and progression. **Conclusions:** The debulking signature, if further validated, has the potential to change clinical practice by identifying women for triage to alternative adjuvant therapy and interval debulking.

**5532 Poster Highlights Session (Board #22), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Molecular profiling of serous ovarian carcinoma to identify extreme response phenotypes and diagnostic discrepancies.** *Presenting Author: Douglas A. Levine, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Patients with serous ovarian cancer (SOC) generally require multiple lines of chemotherapy for the long-term management of disease. Clinical trials and standard care are increasingly stratified by histologic subtypes. Molecular profiling may help to select chemotherapy regimens and identify diagnostic discrepancies that influence treatment decisions and clinical trial stratification. We aimed to identify extreme resistance phenotypes and diagnostic discrepancies through commercial molecular profiling. **Methods:** Patients with a clinical diagnosis of SOC who underwent molecular profiling in a CLIA-certified laboratory were identified through database searches. Results from immunohistochemistry and target capture next-generation sequencing were reviewed. Extreme phenotypes were identified through a combination of putative resistance markers. Diagnostic discrepancies were identified when mutation profiles were inconsistent with reference frequencies defined by The Cancer Genome Atlas (TCGA) ovarian cancer project. Two-sided statistical tests were used, as appropriate, with significance at $P < 0.05$. **Results:** An extreme drug resistance phenotype was identified in 20 (3.4%) of 597 patients through a combination of ABCB1 overexpression and either high expression of TUBB3 or low expression of TOP2A, suggesting resistance to taxanes and anthracyclines, respectively. PTEN loss was identified in 60 (16.6%) of 361 patients with pathogenic *TP53* mutations, suggesting potential therapeutic utility for AKT/mTOR pathway inhibitors. *KRAS, NRAS* or *BRAF* mutations were identified in 41 (7.1%) of 578 patients sequenced. Most (82.9%) of these mutations were in patients without *TP53* mutations, suggesting a diagnostic discrepancy as SOCs typically have universal somatic *TP53* mutations and no RAS/RAF mutations. **Conclusions:** Molecular profiling can identify putative extreme resistance phenotypes and diagnostic discrepancies. As gynecologic oncology moves toward stratified treatments for SOC, accurate histologic subtyping is increasingly important. Future studies are needed to demonstrate the predictive accuracy of putative resistance phenotypes.

**5533 Poster Highlights Session (Board #23), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Real-time identification of tumor lesions and response to vintafolide treatment.** *Presenting Author: Wael A. Harb, Horizon Oncology Center, Lafayette, IN*

**Background:** In treating cancer, companion diagnostics are most useful when they can identify patients who cannot benefit from treatment. However, existing tests suffer from inaccuracy due to dependence on single specimens of a multifocal tumor or dependence on historically obtained specimens that may not represent the current tumor state. This analysis evaluates the performance characteristics of etarfolatide (EC20), a technetium-folate imaging diagnostic designed to provide real-time information on all patient tumor lesions that may respond to treatment with vintafolide (desacetylvinblastine-folate conjugate, EC145). **Methods:** 209 baseline lesions from 44 patients were evaluated in a phase 2 open-label, multicenter study of vintafolide in advanced ovarian cancer (EC-FV-02, NCT00507741). Data from 9 patients (52 lesions) without follow-up were excluded. 21 lesions were categorized as not evaluable, and 6 lesions were categorized as not imaged. 8 lesions that did not meet minimal size criteria were also excluded. The final analysis set included 107 lesions from 33 patients. **Results:** Etarfolatide correctly identified 24 of 26 lesions whose tumor size numerically decreased following vintafolide treatment (sensitivity for numerical decrease=92%). The corresponding negative predictive value (NPV=percent of EC20− lesions that did not numerically decrease) was 86% with a specificity of 15% and a positive predictive value (PPV=percent of EC20+ lesions that numerically decreased) of 26%. Among the etarfolatide negative lesions, 0 decreased by at least 30%. Among the etarfolatide positive lesions, 5 decreased by at least 30%. Therefore, among the 5 lesions that decreased by at least 30%, 5 were etarfolatide positive (sensitivity=100%). Among 102 lesions that did not decrease by at least 30%, 14 were etarfolatide negative (specificity=14%), corresponding to PPV and NPV of 5% and 100%, respectively. **Conclusions:** Etarfolatide identified nearly all tumor lesions that responded to vintafolide treatment in a phase 2 ovarian cancer study. Lesions that do not demonstrate etarfolatide uptake will not demonstrate major shrinkage (>30%) following vintafolide treatment. Clinical trial information: NCT00507741.

**5534 Poster Highlights Session (Board #24), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Characterization of ovarian cancer long-term responders on olaparib.** *Presenting Author: Stephanie Odile Lheureux, Princess Margaret Cancer Centre, Toronto, ON, Canada*

**Background:** *BRCA1/2* mutations (*BRCA*m) appear to predict benefit from PARP inhibition. However, non-mutation carriers also benefit and not all patients (pts) with *BRCAm* respond to PARP inhibitors. The objective of this study was to identify and clinically characterize pts remaining on durable olaparib therapy for further molecular analyses to determine the features underlying long-term response. **Methods:** A retrospective meta-analysis comprised pts with recurrent ovarian cancer (OC) from trials in the olaparib clinical program. Long- and short-term benefits were defined as olaparib treatment for > 2 years and < 6 months respectively, segregated by monotherapy or maintenance. **Results:** 372 OC pts, 323 with *BRCA*m have been already treated with olaparib 400 mg bid capsule as monotherapy at time of relapse (Studies D0810C000001-02-09-12-20-24-42). In these trials, 197 pts (53%) were treated < 6 months from which 169 pts (52.3%) had *BRCA*m. Conversely, there were pts with long-term benefit from olaparib, such as 6 pts in the D0810C000020 study, treated for > 4 years. The table shows the OC pts treated with maintenance olaparib (n=136) and also with olaparib in combination with chemotherapy followed by maintenance (n=81), separating out the pts with *BRCA*m. **Conclusions:** Although many long-term responders to olaparib have *BRCA*m, there are several with no known *BRCA*m. Response durability may be related to a number of factors including germline and somatic *BRCA*mutations. The clinical and molecular characterization of these pts and comparison with short- or median-term disease control will improve understanding of response and resistance to PARP inhibitors.

| Treatment duration | D0810C000019: Olaparib maintenance 400 mg bid capsule monotherapy* | | | | D0810C000041: Combination with carboplatin/paclitaxel followed by maintenance 400 mg bid capsule monotherapy* | | | |
|---|---|---|---|---|---|---|---|---|
| Pts | All (n=136) | *BRCA*m (n=74) | *BRCA* wt/vus (n=57) | *BRCA* missing (n=5) | All (n=81) | *BRCA*m OC subgroup (n=20) | *BRCA* wt/vus OC subgroup (n=34) | *BRCA* missing OC subgroup (n=27) |
| < 6 months | 49 (36%) | 21 (28.4%) | 25 (43.9%) | 3 (60%) | 19 (23.5%) | 0 | 11 (32.4%) | 8 (29.6%) |
| > 24 months | 32 (23.5%) | 21 (28.4%) | 11 (19.3%) | - | 17 (21%) | 11 (55%) | 3 (8.8%) | 3 (11.1%) |

Abbreviations: wt, wild type; vus, variant unknown significance. *Data cut off: November 2012.

**5535 Poster Highlights Session (Board #25), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Biomarker correlates from the randomized phase 2 trial of the PARP inhibitor olaparib (O) with or without the antiangiogenic TKI cediranib (C) in recurrent platinum-sensitive ovarian cancer (NCT01116648).** *Presenting Author: Jung-min Lee, National Cancer Institute, National Institutes of Health, Bethesda, MD*

**Background:** O and C have single agent activity in recurrent platinum-sensitive high-grade serous ovarian cancer (HGSOC). A multi-institutional phase 2 open label study evaluated the efficacy of O with or without C in HGSOC pts. We hypothesized O+C combination may yield greater inhibition in tumor vascularity and VEGF pathways than O alone and these changes may correlate with response rate (RR) and progression-free survival (PFS). **Methods:** A self-selected subset of eligible pts were randomized 1:1 to O (400mg capsules BID) or O+C (O 200 mg capsules BID; C 30 mg daily). No prior anti-angiogenic therapy in the recurrent setting or prior PARPi was allowed. Blood samples were collected at baseline and day 3 to measure circulating endothelial cells (CEC: nucleated CD133-CD146+CD31+CD45-), circulating endothelial progenitor cells (CPC: viable nucleated CD133+, CD146-, CD31+ CD45 - or dim), plasma for cytokine concentrations of IL-6, IL-8, VEGF, and sVEGFR-2. DCE-MRI obtained at baseline and day 3 on therapy were evaluated for changes of $K^{trans}$ and $K^{ep}$as a result of decreases in angiogenesis. **Results:** The clinical cohort and results of the full trial will be presented independently. 13 pts (median age 53 yr [32-70]; 7pts on O, 6pts on O+C) had paired correlative studies including DCE-MRI (10pts), CEC/CPC (10pts), and cytokine measurements (12pts). Median PFS with RR for O and O+C were 11mo, 57% and 14mo, 83%, respectively for this subset. Pts on O+C had a greater decrease in IL-8 and a median 3.5 fold increase in CEC compared to O alone ($p$=0.016 and 0.013, respectively). The increase of CEC pretreatment to day 3 was correlated with PFS>6mo in 6 pts on O+C ($p$=0.011, 95%CI 0.47-0.99, $R^2$=0.91). Pre-day3 $K^{trans}$ and $K^{ep}$ did not correlate with RR or PFS in either arm. **Conclusions:** Significant changes of IL-8 concentration and CEC number with O+C suggest greater inhibition in angiogenesis compared with O alone. Further studies of this combination with prospectively planned validation of these potential predictive biomarkers may yield information to focus therapy to HGSOC pts who may best respond. Clinical trial information: NCT01116648.

**5536 Poster Highlights Session (Board #26), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Analysis of candidate homologous repair deficiency genes in a clinical trial of olaparib in patients (pts) with platinum-sensitive, relapsed serous ovarian cancer (PSR SOC).** *Presenting Author: Brian Dougherty, AstraZeneca, Waltham, MA*

**Background:** In a randomized trial of 265 pts with PSR SOC, maintenance therapy with the PARP inhibitor olaparib led to a PFS benefit vs placebo in pts with *BRCA1/2* mutations (hazard ratio, 0.18; Study 19 [NCT00753545]; Ledermann *et al* ASCO 2013). A PFS hazard ratio of 0.54 (0.34–0.85; $P$=0.007) in BRCA wild type/VUS (variant of unknown significance) pts is consistent with preclinical and clinical evidence that homologous recombination repair-associated genes (HRR genes) in addition to *BRCA1/2* may contribute to PARP inhibitor response. **Objective:** Exploratory characterization of genetic changes in tumors from PSR SOC pts to determine the frequency and co-occurrence patterns of mutations in *BRCA1/2* and other HRR genes, and the presence of these mutations in pts with a long-term response (LTR; treatment duration >24 mo) (olaparib, 24%; placebo, 4%). **Methods:** Using Foundation Medicine's 287-gene, next-generation sequencing test, alterations were categorized based on loss-of-function mutations and *BRCA1/2* mutual exclusivity, and analyzed for loss of heterozygosity and tumor heterogeneity. **Results:** Compared with ovarian pts from The Cancer Genome Atlas (TCGA; n=316), Study 19 pts with sequenced tumors (n=209) had considerably higher mutation rates in *BRCA1* (36% vs 12%) and *BRCA2* (17% vs 9%). As with TCGA, most HRR genes had low mutation rates, but the proportion of Study 19 pts with *BRCA1/2*-mutually exclusive mutations was lower for *PTEN* (2% vs 6%) and higher for HRR genes (14% vs 9%). *BRCA1/2*-mutually exclusive HRR gene mutations in ≥1 pt were *BRIP1* (5 pts), *RAD54L* (3 pts), *CDK12* (3 pts), *RAD51B* (2 pts). Of 33 sequenced LTR pts, 7 (21%) had no candidate *BRCA1/2* loss-of-function mutation: 5 had candidate HRR gene mutations (*BRIP1*, *RAD51B*, *FANCL*, *PTEN*, *MSH2*) and 2 had no clear HRR mutation among the genes tested. **Conclusions:** Prior Study 19 analyses showed a greater clinical benefit in pts with *BRCA1/2* mutations. The proportion of pts with non-*BRCA1/2* HRR gene mutations is relatively small in Study 19, but could include candidate genes deserving further study for a potential role in prolonged treatment benefit and survival on platinum or PARP inhibitors. Clinical trial information: NCT00753545.

**5537 General Poster Session (Board #319), Sat, 8:00 AM-11:45 AM**

**Frequent use of complex surgeries and survival outcomes in ovarian cancer patients: A propensity score analysis from the Korean Gynecologic Oncology Group.** *Presenting Author: Sokbom Kang, National Cancer Center, Koyang, South Korea*

**Background:** To develop an indicator representing the quality of ovarian cancer surgery and to determine its predictive role in a prognostic model. **Methods:** From January 2002 to December 2008, the clinical records and computed tomography (CT) data of epithelial ovarian cancer patients were reviewed from the KGOG-3022 dataset. A propensity score was developed from a multivariable logistic model and used as a stratification factor or co-variable in Cox models to balance the differences between the high- and low/intermediate-complexity surgery group. **Results:** Data for 331 patients from six specialized teaching hospitals were reviewed. Complex surgery, defined as a surgery with a surgical complexity score $> 7$, was more frequently performed in patients with an 'upper abdominal extension' pattern, 'diffuse peritoneal spread' pattern, and grade III disease ($P <$ 0.001, 0.017, and 0.001, respectively). To balance the differences, a propensity score for complex surgery was developed. The use of complex surgery for greater than 25% of advanced cases at the institutional level was consistently associated with improved progression-free survival (PFS) when the score was used as a covariate (Hazard ratio [HR] = 0.69, $P =$ 0.038) or as a stratification factor (HR = 0.68, $P = 0.033$). In contrast, the complexity of individual surgery showed no significant association with PFS regardless of the adjustment methods ($P = 0.90$ and 0.76, respectively). **Conclusions:** The institutions that perform complex surgeries for greater than 25% of advanced ovarian cancer patients were associated with an approximately 30% reduction in recurrence risk after primary treatment.

**5538 General Poster Session (Board #320), Sat, 8:00 AM-11:45 AM**

**Carboplatin hypersensitivity reaction (HSR): Analysis of safety and success of a short outpatient platinum rechallenge protocol (PRP) in epithelial ovarian carcinoma (EOC).** *Presenting Author: Los Vincent Newton, Auckland City Hospital, Auckland, New Zealand*

**Background:** Platinum remains mainstay to EOC therapy, in first line and relapse. HSR to Carboplatin(Cb) is well reported and limits utility of further platinum therapy. Reported desensitisation regimes are lengthy, involving inpatient high dependency care. In 2005 our centre developed a standardised rapid 1.5 hour, 3 step outpatient PRP for patients(pts) who had HSR to Cb. We performed a retrospective review of the outcomes and safety of our PRP. **Methods:** All pts given Cb for stage I - IV EOC from 2005 to 2012 were identified. Data was obtained on baseline characteristics, all therapy, HSR, safety and efficacy of the PRP. HSR severity was graded consistent with published data. Our PRP consists of pre- and post-medication with antihistamine and steroids, a 15 minute infusion of diluted Cb or Cisplatin (Cis), then 15min of undiluted platinum at reduced rate, with the remainder administered thereafter over 1 hour. **Results:** 406 pts were identified. Median age 60.6 years (range 21-88). 64pts (15.8%) had an HSR to Cb. First HSR occurred at median cycle 8.5 (range 1-24) of Cb exposure. 67% of HSR occurred during second line Cb. 8/64 pts had a moderate-severe HSR to Cb. The incidence of pts having a Cb HSR during second line treatment at PFI of 6-12 months, 12-24 months and >24 months was 44%, 36% and 27% respectively. 51/64 pts (79.7%) were retreated with either the Cb PRP (29pts) or Cis PRP (22pts) at clinician discretion. 14/29 pts had a HSR on Cb PRP, 1/22pts on Cis PRP. The Cis PRP was significantly less likely to result in second HSR, OR=0.05 (p=0.006). Second HSR grade was a higher than initial HSR in 4pts but none graded severe. 9/14 pts having second HSR on Cb PRP were subsequently treated with Cis PRP. 7/9 pts had no further HSR. Using our PRP, patients received a median of 4 further cycles of platinum on the PRP (range 1-11). There were no deaths from HSR in our cohort **Conclusions:** Our rapid outpatient PRP is safe and allowed a significant proportion of patients to continue further platinum chemotherapy. Treatment with Cis PRP has significantly fewer reactions than Cb PRP and should be considered the preferred platinum for rechallenge in suitable patients.

**5539 General Poster Session (Board #321), Sat, 8:00 AM-11:45 AM**

**Female germ cell tumors (GCT): The Memorial Sloan Kettering Cancer Center (MSKCC) experience.** *Presenting Author: Jane Lowe Meisel, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background**: Due to their rarity, little is known about female GCT biology and response to therapy. Management is largely based on studies of male GCT and epithelial ovarian cancer. **Methods**: We identified 111 female patients (pts) treated at MSKCC for malignant GCT of gynecologic origin from 1990 to 2012 and reviewed their clinical characteristics and outcomes. Pts receiving chemotherapy (CT) were classified using a modification of the IGCCCG system for men. Kaplan-Meier methods were used to estimate progression-free (PFS) and overall survival (OS) and the log-rank test to assess differences. **Results**: Histologies in the 111 pts (107 ovarian) included immature teratoma (28), dysgerminoma (DG) (24), mixed GCT (20), yolk sac (18), mature cystic teratoma (MCT) (12), struma ovarii (SO) (6), and other (3). 72 (65%) were stage I, 5 (5%) stage II, 28 (25%) stage III, and 6 (5%) stage IV. All pts underwent primary surgery and 85 (77%) received CT; in 67 (79%), BEP was the 1st-line regimen. IGCCCG risk was good in 46 (54%), intermediate in 12 (14%), poor in 10 (12%) and unknown in 17 (serum tumor markers (STM) not drawn at CT start). AFP, HCG, and LDH were elevated in 36, 6, and 11 pts, respectively. Complete response (CR) to 1st-line CT was seen in 64 (75%), partial response in 1, and incomplete response (IR) in 20 (24%). 29 (26%) pts progressed after initial therapy (26 after CT), with 14/29 (52%) diagnosed by imaging, 6 by STM, 1 by exam, and 8 by multiple methods. 11/26 (42%) who progressed after CT received high-dose CT (HDCT) with ASCT resulting in 6 CRs and 5 IRs. 4/6 CRs had received only 1 prior CT regimen vs 2/5 IR pts. With median f/u of 4.9 years (y), 3yOS for all pts was 86% (95% CI 79-93%), with a trend favoring DG, SO, and MCT vs other histologies (97% vs 83%, p=0.056) and Stage I/II vs III/IV (88% vs 81%, p=0.067). IGCCCG group was significantly associated with PFS and OS (Table). **Conclusions**: IGCCCG status can help estimate prognosis to CT for female GCT pts. Thus, STM should always be drawn prior to CT, and poor-risk pts might benefit from more intensive 1st-line CT. Salvage HDCT, especially if given early, can be curative.

**PFS and OS to CT by IGCCCG Group.**

| | Good (n=45)* | Intermediate (n=12) | Poor (n=10) | Log-rank P |
|---|---|---|---|---|
| **3y-PFS** | 84% | 83% | 20% | <0.001 |
| **3y-OS** | 89% | 89% | 40% | <0.001 |

* n = 44 for OS.

**5540^ General Poster Session (Board #322), Sat, 8:00 AM-11:45 AM**

**Independent radiologic review of AURELIA, a phase 3 trial of bevacizumab (BV) plus chemotherapy (CT) for platinum (PT)-resistant recurrent ovarian cancer (OC).** *Presenting Author: Amreen Husain, Genentech, Inc., South San Francisco, CA*

**Background:** AURELIA is a phase 3, randomized, open-label trial in patients (pts) with PT-resistant, recurrent OC (NCT00976911). Based on investigator (INV) assessment of radiographic data, CT + BV showed significant improvement vs CT alone in the primary end point of progression-free survival (PFS) (Pujade-Lauraine, JCO in press). Median PFS was 3.4 months for CT vs 6.8 months for CT + BV (stratified hazard ratio [HR], 0.38; 95% confidence interval [CI], 0.30–0.49; $P<.001$). As this was an open-label trial, an independent review committee (IRC) assessment of radiologic data was conducted retrospectively to confirm these results. **Methods:** Radiologic images were provided to the IRC for 92.2% of randomized pts; 82.5% of pts were IRC-evaluable. Data were reviewed in a blinded manner according to a prespecified charter following modified RECIST v.1.0. PFS analysis was based on the intent-to-treat population. **Results:** IRC results were consistent with those from the INV, demonstrating a statistically significant and clinically meaningful improvement in PFS with BV (Table). The concordance rate for progression status (yes, no) was similar across arms (CT, 69.9%; CT + BV, 68.2%), as was agreement on the date of progressive disease (PD; CT, 69.1%; CT + BV, 67.2%). The early discrepancy rates (INV-determined PD earlier than IRC-determined PD) were similar in the 2 arms (CT, 0.372; CT + BV, 0.364), whereas the late discrepancy rate was higher in the CT + BV arm (CT, 0.329, CT + BV, 0.463). The differential discordance of 0.134 suggests some degree of INV bias toward the CT + BV arm. **Conclusions:** The PFS analysis results from the IRC assessment were consistent with those from the primary INV-led PFS analysis, despite a trend for INV assessment of PD at a later date in the CT + BV arm in this trial. The results provided further evidence that INV-determined PFS based on RECIST is reliable and reproducible in OC clinical trials. Clinical trial information: NCT00976911.

| | IRC-assessed PFS | | INV-assessed PFS | |
|---|---|---|---|---|
| | CT (n=182) | CT + BV (n=179) | CT (n=182) | CT + BV (n=179) |
| **Median PFS, mo (95% CI)** | 3.9 (3.4–5.2) | 8.1 (6.9–9.6) | 3.4 (2.10–3.75) | 6.8 (5.62–7.79) |
| **Stratified HR (95% CI)** | 0.484 (0.370–0.632) | | 0.384 (0.300–0.491) | |
| **Log-rank p value** | <.0001 | | <.0001 | |

**5541^ General Poster Session (Board #323), Sat, 8:00 AM-11:45 AM**

**Phase I trial of pegylated liposomal doxorubicin in combination with BIBF 1120 (nintedanib) in platinum-resistant ovarian cancer: Hoosier Oncology Group GYN10-149.** *Presenting Author: Maria Creselda deLeon, Indiana University School of Medicine, Indianapolis, IN*

**Background:** The triple PDGFR$\alpha/\beta$, VEGFR1-3, FGFR1-3 angiokinase inhibitor BIBF 1120 (B) is active in ovarian cancer (OC). This phase I/II trial evaluates tolerability and efficacy of B combined with pegylated liposomal doxorubicin hydrochloride (D) in platinum-resistant OC. **Methods:** The primary endpoints (EPs) are to determine the maximum-tolerated dose (MTD, phase I) and response rate (RR, phase II) to D+B. Secondary EPs were PFS, toxicities and rate of clinical benefit. Translational EPs were treatment effects on circulating hematopoietic stem and progenitor cells (CHSPCs), containing 2 phenotypically distinct populations; pro-angiogenic (p) CHSPCs ($ViViD^-CD14^-glyA^-CD34^+AC133^+CD45^{dim}CD31^+$ cells) and non-angiogenic (n) CHSPCs ($ViViD^-CD14^-glyA^-CD34^+AC133^-CD45^{dim}CD31^+$ cells). Eligible pts had measurable OC, primary peritoneal (PP), fallopian tube and uterine (phase I only) cancer, up to 3 prior regimens, ECOG PS of 0-1 and normal end-organ function. B was given orally BID and D was given IV at 40mg/m$^2$every 28 days. 3+3 dose escalation was used, starting with B at 150mg BID. **Results:** Eleven pts were enrolled in phase I. Median age was 59 (range 26-82); 8 pts had OC, 2 uterine and 1 PP cancer. Histologic types: serous (73%), endometrioid (18%) and mucinous (9%) carcinoma. Dose level+1 (B at 150mg BID) was not tolerated due to grade 3 fatigue, and grade 2 diarrhea, causing treatment interruption (DLT). Among 6 pts at dose level-1 (B at 100mg BID), 1 pt with history of chemotherapy induced myelosupression had grade 4 neutropenia (DLT). Other toxicities were diarrhea (36.4%), fatigue (36.4%), vomiting (27.3%), headache (27.3%), allergic reaction (9.1%) and oral pain (9.1%). Three pts had PRs, 3 SD and 4 disease progression; 1 was not evaluable. A decrease in the pCHSPC/nCHSPC ratio was observed after 1 cycle (1.58, n=8) compared to baseline (1.68, n=10, p=0.4). At treatment discontinuation, the pCHSPC/nCHSPC ratio was 1.97 (n=4). Analyses are ongoing. **Conclusions:** In summary, D+B is tolerated at 40mg/m$^2$ and 100mg BID. An expanded cohort using generic liposomal doxorubicin and B at level -1 is planned before initiation of the phase II cohort. Clinical trial information: NCT01485874.

**5542 General Poster Session (Board #324), Sat, 8:00 AM-11:45 AM**

**Expression of angiopoietin (Ang) pathway markers and their relationship to progression-free survival (PFS) in TRINOVA-1.** *Presenting Author: Andres Poveda, Instituto Valenciano de Oncologia, Valencia, Spain*

**Background:** Trebananib, an investigational recombinant peptide Fc-fusion protein, targets Ang1 and 2. In TRINOVA-1, a randomized phase 3 study, trebananib plus paclitaxel (P) compared with placebo plus P significantly improved PFS (primary endpoint) in recurrent ovarian cancer. Biomarker evaluation was an exploratory endpoint. **Methods:** Women ($\geq$ 18 years, GOG $\leq$ 1) with recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer received trebananib 15 mg/kg IV QW or placebo IV QW plus P 80 mg/m$^2$ IV QW (3 wks on/1 wk off). Serum samples were collected pre-infusion at wk 1 to evaluate baseline levels of Ang1, Ang2, and soluble Tie2 (sTie2). Analytes were quantified using enzyme-linked immunosorbent assays (ELISA; R&D Systems). Analyses of PFS as a function of biomarker expression addressing prognostic and predictive testing included: 1) subpopulation treatment effect pattern plots (STEPP) for Ang1, Ang2, sTie2, Ang1/Ang2, and Ang2/Ang1 (prognostic test); 2) evaluation of Ang1, Ang2, sTie2, Ang1/Ang2, and Ang2/Ang1 as continuous variables (prognostic test); and 3) median thresholds to dichotomize Ang1, Ang2, and sTie2 levels (prognostic and predictive tests). **Results:** Serum samples were available for 834 of 919 enrolled women. Per STEPP, no threshold in biomarker expression was associated with PFS. Using continuous models, there was no linear association with PFS (Ang1, $p = 0.55$; Ang2, $p = 0.47$; sTie2, $p = 0.63$; Ang1/Ang2, $p = 0.17$; Ang2/Ang1, $p = 0.66$). Using median thresholds, low Ang1 (median, 23.30 ng/mL) or Ang2 (median, 2.86 ng/mL) levels were associated with improved PFS ($p = 0.044$ and 0.009, respectively) when not corrected for multiple testing. Those relationships were not consistent at the extreme Ang1 or Ang2 values. There was no evidence of an interaction of either Ang1 or Ang2 by treatment arm ($p = 0.10$ and 0.68, respectively). sTie2 (median, 27.8 ng/mL) was not predictive or prognostic of PFS. **Conclusions:** In TRINOVA-1, no consistent predictive or prognostic relationships between baseline levels of Ang1, Ang2, or sTie2 were observed. Clinical trial information: NCT01204749.

**5543 General Poster Session (Board #325), Sat, 8:00 AM-11:45 AM**

**Adjuvant radiation for patients (pts) with high-grade serous ovarian cancer (HGSC) and T-cell infiltration.** *Presenting Author: Aalok Kumar, British Columbia Cancer Agency, Vancouver, BC, Canada*

**Background:** CD8 positive intra-epithelial tumor infiltrating T cells (TIL) are associated with improved outcomes in ovarian cancer, particularly in HGSC. Radiotherapy (XRT) has immunologic effects including tumour necrosis, activation of antigen presenting cells and T cell recruitment. Adjuvant XRT in ovarian cancer was historically used at the BC Cancer Agency (BCCA). We hypothesized that adjuvant XRT for HGSC may have a beneficial impact on outcomes within the TIL+ subgroup. **Methods:** Stage I and II and optimally debulked (no visible residual disease) stage III HGSC pts treated at the BCCA from 1984to 2004 were included in this analysis. All cases underwent pathologic review to confirm histology and to score for TIL, either present ($\geq$1 CD8 cell / 6mm core) or absent via immunohistochemistry. Treatment was platinum based chemotherapy (3-6 cycles) and abdominal-pelvic radiotherapy (45 Gy and 32 fractions to pelvis and whole abdomen). Kaplan-Meier and Cox proportional hazards methods were used to correlate XRT use (yes vs. no) with overall survival (OS) and disease free survival (DFS). **Results:** We identified 205 pts, of whom 174 scored positive for TIL. Of the 174, 76 (44%) were treated with XRT and 98 (56%) no XRT. Most pts (97%) also received adjuvant chemotherapy. Median follow up was 6.5 years. Pts who received XRT were younger (mean age 56.6 vs. 63.5 years, p<0.001) and had lower stage disease (p=0.0008). On univariate analysis, XRT was associated with an increased median OS (10 vs. 6 years, p=0.03) and a non significant increased DFS. On multivariate analysis, adjuvant XRT did not impact OS or DFS (HR 0.99, 95CI 0.66-1.49,p=0.97 and HR 1.05,95CI 0.67-1.67,p=0.82 respectively). Stage 3 disease was associated with worse OS and DFS (HR 1.71, 95CI 1.03-2.85, p=0.04 and HR 2.26, 95CI 1.26-4.04,p=0.006 respectively). Older age was associated with decreased OS (HR 1.03, 95CI 1.01-1.04,p=0.005). **Conclusions:** In this population based cohort study, adjuvant XRT for early stage or microscopic residual stage III HGSC with TIL was not associated with an OS or DFS advantage. Adjuvant XRT has no defined role in the treatment of HGSC.

**5544 General Poster Session (Board #326), Sat, 8:00 AM-11:45 AM**

**Relative influence of factors determining a woman's preference for treatment options in ovarian cancer.** *Presenting Author: Laura Jean Havrilesky, Duke University Medical Center, Durham, NC*

**Background:** We examined relative preferences of women with ovarian cancer for symptoms, treatment-related side-effects, and progression-free survival (PFS) when considering a treatment regimen. **Methods:** Women with advanced or recurrent ovarian cancer were recruited at a single institution to a prospective discrete choice experiment. In each discrete choice, subjects were asked to choose between two treatment scenarios, modeled on the characteristics of standard intravenous (IV) and intraperitoneal/intravenous (IP/IV) treatments for ovarian cancer. Each scenario described 7 attributes with 2-3 levels each: mode of administration (IV versus IP/IV); visit frequency (weekly, twice per 3 weeks, once per 3 weeks); treatment related symptoms (mild to severe nausea and vomiting, abdominal symptoms, neuropathy, and fatigue); and PFS (15, 18, 21, and 24 months). We used a balanced overlap design with 10 versions of the survey. Each subject evaluated 12 random choice scenarios (in which levels of each attribute were varied). We applied mixed logit regression to model participants choices as a function of attribute levels. **Results:** 95 women completed the survey. Mean age 57; 81% Caucasian. 47% had experienced disease recurrence and 49% were currently receiving chemotherapy. Compared to scenarios with 15 months of PFS, the relative odds that a participant would choose a scenario with 18, 21, and 24 months of PFS were 1.5 (p=0.01), 3.4 (p<0.001) and 7.5 (p<0.001), respectively. However, subjects were willing to give up PFS to avoid severe treatment-related side effects (6.7 months to reduce severe nausea and vomiting during treatment to mild, 5.0 months to reduce severe neuropathy to mild, and 3.7 months to reduce severe IP–related abdominal symptoms to moderate). Findings were similar between women currently receiving chemotherapy and those who were not and between women with disease recurrence and those without. **Conclusions:** PFS is the predominant driver of patient preferences for chemotherapy. However, women are willing to trade significant PFS time for reductions in treatment-related toxicity. Patient preferences should be considered when interpreting clinical trial results and making treatment decisions.

**5545 General Poster Session (Board #327), Sat, 8:00 AM-11:45 AM**

**Pretreatment serum mitochondrial DNA (mtDNA) correlates with shorter progression-free and overall survival in patients with advanced ovarian cancer (OC).** *Presenting Author: Kassondra S. Grzankowski, Roswell Park Cancer Institute, Buffalo, NY*

**Background:** Mitochondrial damage-associated molecular patterns, comprised of mtDNA and formylated peptides, are released after cellular injury and activate innate immune responses. Extracellular mtDNA activates TLR-9 and other pathogen recognition receptors. While mitochondrial metabolism and DNA mutations have been widely studied in tumor cells, this study analyzes mtDNA at an extracellular level as a marker of injury. Since OC is associated with cellular necrosis, we reason that extracellular mtDNA may be a molecular prognostic marker. **Methods:** Serum collected in OC patients prior to primary surgery (n=41) and from age-matched cancer free women (n=3) was analyzed for mtDNA. Q-PCR with cytochrome B primers specific for mtDNA was done. The high group was pre-specified as patients with serum mtDNA > 5-fold above the mean control level, and the remainder was defined as the low group. Primary endpoint was PFS. **Results:** 41% had high levels of mtDNA. 76% in the high mtDNA and 74% in the low groups were Stage 3. Histology and grade were similar. The mean age at diagnosis was 69. Median PFS in the high and low groups was 228 vs. 489 days, respectively (p = 0.17). The high mtDNA group had quicker relapse (HR=2.7; p = 0.0278) and a reduced OS trend (HR=3.5; p = 0.0593) within the first year of surgery. Consistent with this effect, additional exploratory analysis showed that patients with serum mtDNA in the highest 15% had markedly reduced PFS (5 vs. 16 mo; p = 0.0015) and OS (8 vs. 50 mo; p = 0.00022) compared to the remaining patients. The relationship between pre-treatment serum mtDNA levels and PFS and OS involve a threshold effect rather than a direct linear relationship. Comparing pre-treatment serum mtDNA levels to published data on serum CA-125 levels from a Gynecology Oncology Group study that analyzed 1,299 patients with OC, we observed significantly greater effect sizes with serum mtDNA in predicting prognosis, with the greatest effect in the top 15% serum mtDNA group. **Conclusions:** Increased levels of circulating mtDNA correlated with significantly reduced PFS and OS. If validated in an independent cohort, pre-treatment serum mtDNA may be of value as a prognostic marker for OC.

**5546 General Poster Session (Board #328), Sat, 8:00 AM-11:45 AM**

**A randomized phase II trial of bevacizumab (BV) plus oral everolimus (EV) versus bevacizumab alone for recurrent or persistent epithelial ovarian (EOC), fallopian tube (FTC), or primary peritoneal cancer (PPC).** *Presenting Author: William P. Tew, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** BV monotherapy leads to compensatory upregulation of multiple signaling pathways, resulting in persistent mTOR activation, which if blocked, may circumvent resistance to anti-VEGF therapy.We evaluated the efficacy and tolerability of combining BV and oral everolimus (EV), an mTOR kinase inhibitor, in women with EOC/FTC/PPC. **Methods:** Eligible pts had persistent or recurrent EOC/FTC/PPC, measurable (RECIST 1.1) or detectable (CA125 ≥ 2x upper limit normal), 1-3 prior regimens, performance status (PS) 0-2, and no prior m-TOR inhibitor. All pts received BV 10 mg/kg IV every 2wks in 4wk cycles. Pts were randomized (1:1) to oral EV (10 mg daily) or placebo with stratification for platinum-free interval (PFI), measurable disease and prior BV. Primary endpoint was progression-free survival (PFS); secondary endpoints included safety and response evaluated every 8wks. **Results:** 150 evaluable pts were randomized to BV with (n=75) and without (n=75) EV. Arms were well-balanced for age (median 63: range 28-92), PS (0: 73%, 1-2: 27%), prior regimens (1: 37%, 2: 47%, 3: 16%), prior BV (11%), PFI (<6mos: 65%) and measurable disease (81%). The BV+EV vs BV median PFS was 5.9 vs 4.5 mos, respectively (hazard for progression 0.95 (95% CI, 0.66-1.37, p=0.39); pts with PFI>6mos had HR 0.615 (95% CI 0.33~1.15, p=NS). Median OS was 16.6 vs 17.3 mos (hazard of death 1.16 (95% CI, 0.72~1.87, p=NS). Among pts with measureable disease, objective responses were higher with BV+EV (19% vs 9%). Study removal due to toxicity was high with BV+EV (29%) compared to BV alone (12%). Toxicity (≥g3) most significantly associated with addition of EV were "other GI" (17 vs 1pts) and "metabolic/nutrition" (14 vs. 5pt). Most common toxicities ( ≥g2) were anemia (24 vs 6pt), neutropenia (20 vs 1pts), oral mucositis (22 vs 0pts), nausea (24 vs 9pts), fatigue (24 vs 15pts), and hypertension (20 vs. 21pts). **Conclusions:** The combination regimen (BV+EV) is active in this population but did not significantly reduce the hazard of progression or death and was associated with higher rates of study discontinuation for tolerability when compared to BV alone.

**5547 General Poster Session (Board #329), Sat, 8:00 AM-11:45 AM**

**High-dose chemotherapy (HDCT) for recurrent ovarian germ cell tumors (OGCT): Indiana University (IU) experience.** *Presenting Author: Natraj Reddy Ammakkanavar, Department of Hematology/Oncology, Indiana University School of Medicine, Indianapolis, IN*

**Background:** OGCT are rare subtype of ovarian cancer, accounting for less than 5% of malignant ovarian cancer cases. First-line cisplatin combination chemotherapy has a 70-80% cure rate. There is very little data for salvage chemotherapy. The objective of this study was to determine the outcomes with HDCT in patients with recurrent OGCT treated at Indiana University (IU). This represents the largest reported data with HDCT in OGCT. **Methods:** We performed a retrospective review of 12 patients with diagnosis of recurrent OGCT who underwent HDCT at IU during 1990-2013. Demographics, disease variables, treatments and outcomes were analyzed. **Results:** Median age at the time of HDCT was 25 years (range: 14 - 39 years). 11 of 12 patients had yolk sac tumor (median AFP: 1021). 7 patients had platinum resistant disease. Median number of prior chemotherapy treatments were 2 (range: 1- 4). At the start of HDCT, median serum alpha-fetoprotein (AFP) level was 792 for all patients. 4 of 12 patients had liver metastasis. 10 of 12 patients received 2 courses of HDCT cycles, consisting of carboplatin at 700mg/m2/day and etoposide 750mg/m2/day for 3 consecutive days followed by autologous stem cell rescue in each treatment cycle. 7 patients achieved complete response (CR) including 4 who are continuously disease free at 4+ months, 15+ months, 10+ years and 22+ years. 3 of the 5 patients, who received HDCT as a first-line salvage therapy, are continuously disease free. Only 1 of the 7 patients, who received HDCT as a second-line salvage therapy or later, is continuously disease free. 3 of the 5 patients with platinum sensitive disease are disease free. Median overall survival was 11.5 months (range: 4 months - 22 years). Toxicities noted were as expected and reported with HDCT for testicular germ cell tumors (NEJM 2007; 357:340-348). No treatment related deaths were noted. **Conclusions:** Our data demonstrates that HDCT is an effective treatment for recurrent OGCT. Better outcomes were observed for first line salvage and platinum sensitive recurrences.

**5548 General Poster Session (Board #330), Sat, 8:00 AM-11:45 AM**

**Analysis of outcomes in patients (pts) with recurrent ovarian clear cell carcinoma (ROCCC): Time to rethink our approach to treatment.** *Presenting Author: David Shao Peng Tan, Princess Margaret Cancer Center, Toronto, ON, Canada*

**Background:** Advanced stage primary OCCC is associated with a poor prognosis following primary surgery and chemotherapy, but scant data exists regarding response rates (RR = RECIST PR/CR), progression free (PFS) and overall survival (OS) following treatment (rx) for ROCCC. **Methods:** We conducted a retrospective review of pts with ROCCC treated at 2 cancer centres to evaluate RR, clinical benefit rate (CBR=PR/CR or SD with PFS ≥12wks), PFS (time from start of rx to RECIST/clinical PD) and OS (time from 1st relapse after primary rx to death) following rx, and response/ symptomatic benefit after palliative radiotherapy (PRT). Platinum (plt) resistance was defined as PD < 6mths after plt. **Results:** In total, 137/256 pts developed ROCCC. Recurrences by FIGO stage at diagnosis were: Stage 1A/B (15/49, 29%), Stage 1C (16/67, 24%), Stage 2 (40/62, 65%), Stage 3 (46/54, 85%), Stage 4 (20/21, 91%), p<0.0001. Pts received a median of 1 line (range = 1-6, total = 166) of rx with an overall RR of 13/142 (9%) evaluable lines of treatment. Across all rxs, median PFS was 11 wks (95% CI: 8,14) and median OS was 40 wks (95% CI: 28,52). At 1st relapse, 72/86 treated pts were evaluable for response with RR=14% (10/72), CBR=31% (22/72) and median PFS=12wks (95% CI: 9,15). At 2nd relapse, 36/42 treated pts were evaluable for response with RR=8% (3/36) and CBR=33% (12/36) and median PFS=14wks (95% CI: 8,20). No significant PFS difference was observed for plt-sensitive pts treated with plt-based or non-plt-based rx at 1st relapse (HR=1.2; 95% CI: 0.6, 2.5; p=0.57) or at any relapse (HR=0.9; 95% CI: 0.4, 1.7; p=0.65). Outcomes for all rxs are shown in the Table. 6/12 (50%) pts derived benefit following PRT. **Conclusions:** ROCCC is a chemoresistant disease with a short median OS of 10mths. PRT offers symptomatic benefit. More clinical trials to identify effective systemic rxs for ROCCC are urgently required.

**Individual rx outcomes across all lines of rx.**

| Rx | N | Plt Sensitive | No. evaluable | CR/PR% | CBR% | Median PFS wks |
|---|---|---|---|---|---|---|
| Plt-based | 63 | Yes (46) | 38 | 18 | 39 | 17 |
| | | No (17) | 14 | 14 | 36 | 11 |
| Paclitaxel | 8 | | 7 | 0 | 14 | 8 |
| Gemcitabine | 7 | | 7 | 14 | 14 | 4 |
| Doxorubicin | 29 | | 25 | 4 | 16 | 10 |
| Antiangiogenic agents | 15 | | 13 | 8 | 46 | 14 |
| Topoisomerase inhibitors | 30 | | 27 | 4 | 19 | 8 |
| Hormonal therapy | 8 | | 6 | 0 | 17 | 12 |
| Others | 6 | | 5 | 0 | 0 | 11 |

**5549 General Poster Session (Board #331), Sat, 8:00 AM-11:45 AM**

**Duration of systemic therapy for ovarian cancer: A systematic review and meta-analysis.** *Presenting Author: Adnan Nagrial, The Kinghorn Cancer Centre, The Garvan Institute of Medical Research, Sydney, Australia*

**Background:** The optimal duration of systemic treatment to maximise survival and quality of life (QOL) in ovarian cancer following surgery or in the recurrent setting is unclear. In addition maintenance therapy is not universally recommended in published guidelines. We performed a systematic review and meta-analysis of published randomized controlled trials (RCT) comparing longer versus shorter durations of systemic treatment as well as maintenance regimens. **Methods:** We searched MEDLINE, EMBASE, and CENTRAL to December 2013 for RCTs comparing (1) duration - a defined number of cycles of treatment versus a higher number of cycles of the same treatment and (2) maintenance - initial treatment versus the same initial therapy followed by additional cycles of a different treatment. The primary outcome was overall survival (OS). Secondary outcomes included progression-free survival (PFS), adverse events (AE) and QOL. Hazard ratios (HR), confidence intervals (CI) and p-values (p) were estimated with a fixed-effects or random-effects model based on the heterogeneity of included studies using Revman 5.2.3. **Results:** We included 22 eligible trials (6 assessing duration, 16 assessing maintenance treatment) including 7,609 patients. Longer duration of chemotherapy prolonged PFS significantly (HR 0.77, 95% CI 0.66 to 0.90, p = 0.001) but not OS (HR 0.95, 95% CI 0.81 to 1.12, p = 0.54). Maintenance therapy did not prolong PFS (HR 0.91, 95% CI 0.81 to 1.02, p= 0.11) or OS (HR 0.94, 95% CI 0.87 to 1.02, p = 0.15). However, subgroup analysis showed that the effect of maintenance therapy on PFS was greater in the recurrent cancer setting (HR 0.57 vs. 0.96, p value for interaction = 0.02). Effects of maintenance therapy on PFS were similar with the use of chemotherapy or targeted therapy (HR 0.96 vs. 0.84, p = 0.31). The AEs were more frequent with both longer durations of therapy and during maintenance therapy. QOL was assessed in only 5 trials with inconsistent results. **Conclusions:** A longer duration of therapy in ovarian cancer significantly increased PFS but not OS at the cost of increased AEs. Maintenance therapy improved PFS in the recurrent cancer setting. Future studies of extended and maintenance therapy should focus on QOL as well as survival.

**5550 General Poster Session (Board #332), Sat, 8:00 AM-11:45 AM**

**Protein network mapping of glucose metabolism in ovarian cancer.** *Presenting Author: Maria Isabella Sereni, George Mason University, Manassas, VA*

**Background:** Epithelial ovarian carcinoma (EOC) is the fifth leading cause of tumor related death in the female population, with a 5-year survival after diagnosis of only 30% of patients in case of an advanced disease. The aim of the study was to perform broad-scale drug target activation analysis of EOC to determine if the drug target activation architecture was different in early vs late stage EOC tumors, and if so then to identify new druggable targets for personalized therapy in the context of early vs late stage/advanced disease. **Methods:** 72 ovarian primary lesions collected from chemo-naïve EOC patients were analyzed. Highly enriched tumor epithelial cells were isolated by laser capture microdissection, lysed and subjected to reverse phase protein microarray analysis for multiplexed protein pathway activation mapping. The activation/phosphorylation level of 157 key signaling proteins involved in tumorigenesis and metastatic colonization was analyzed. Based on the FIGO staging at diagnosis, the patients were segregated into early stages (stage I-IIB, 15 patients) and advanced stages (stage IIC-IV, 57 patients). Wilcoxon rank-sum test was used to detect significant differences between the two groups in the drug target activation profile. **Results:** Activation of canonical AKT/mTOR and AMPK/ACC signaling pathway architecture (i.e.. AMPKalpha1 (S485), AMPKbeta1 (S108), ACC (S79), LKB1 (S428), AKT (S473), AKT (T308), mTOR (S2448); p=0.0007, p=0.0043, p<0.0001, p=0.0473, p=0.0031, p=0.0068, and p=0.0415 respectively) were found to be significantly higher in early stage tumors compared to advanced stage disease. **Conclusions:** Functional drug target activation mapping uncovered a systemic alteration of drug targets known to play a critical importance in the metabolic rate of tumors. Activation of AMPK-ACC signaling as well as AKT/mTOR networks in early stage EOC may be the result of the central role for pro-survival signaling activation and a compensatory hyperactivation of AMPK pathway in response to the Warburg effect and mTOR activation. These results, confirmed in an independent study set, suggest that the utilization of drugs targeting AMPK, such as metformin, could be very useful in advanced ovarian cancer.

**5551 General Poster Session (Board #333), Sat, 8:00 AM-11:45 AM**

**Trabectedin plus pegylated liposomal doxorubicin (PLD) prior to subsequent platinum chemotherapy in patients with platinum-resistant (PR) recurrent ovarian cancer (ROC): Results from OVA-301 follow-up.** *Presenting Author: Nicoletta Colombo, MaNGO and University of Milan-Bicocca, Milan, Italy*

**Background:** OVA-301, a randomized phase III study of trabectedin plus PLD (n=337) *vs.* PLD alone (n=335) in patients with ROC demonstrated a statistically longer progression-free survival (PFS) in the combination arm (median PFS: 7.3 *vs.* 5.8 months; HR: 0.79; $p$=0.0190) (Monk, JCO 2010). However, among PR patients PFS (4.0 *vs.* 3.7 months) and overall survival (OS; 14.2 *vs.* 12.4 months) were not statistically different (Monk, EJC 2013). Based on *in vitro* (D'Incalci, AACR 2013) and clinical (Casado, ASCO 2013) data, trabectedin may lead to an increased sensitivity to subsequent platinum even in PR patients. **Methods:** An exploratory analysis of OS, counted from the administration of trabectedin/PLD or PLD until death, was performed in PR patients retreated with third-line platinum after OVA-301. **Results:** Overall, 59 PR patients with a median age of 55 years (range 26-79) were analyzed. Similar proportions of patients in each arm received subsequent platinum (trabectedin/PLD: 27/115, 23.5%; PLD: 32/117, 27.4%). Both in trabectedin/PLD (55.6%) and PLD (68.8%) arm most had serous-papillary histology and a median progression-free interval of 4.5 (range 0.7-6) and 4.2 (range 1.1-5.9) months, respectively. A median of 6 trabectedin/PLD cycles (range 1-20) and 5 PLD cycles (range 1-9) was given. Trabectedin/PLD resulted in a 42% risk reduction of disease progression or death compared with PLD (median PFS: 5.6 vs. 5.0; $p$=0.062). Patients with PR ROC treated with trabectedin/PLD, followed by the subsequent reintroduction of platinum achieved a 38% decrease in the risk of death compared with PLD (median OS: 22.2 vs. 15.50; $p$=0.078). Besides, patients pretreated with trabectedin/PLD who received a platinum salt had a 7.8-months longer median OS than those retreated with a non-platinum regimen (median OS: 22.2 vs. 14.4; $p$=0.055). **Conclusions:** Our results hypothesize that the intercalation with trabectedin/PLD prior to subsequent platinum retreatment may contribute to prolong PFS with apparent sensitization of the PR patients to allow further platinum retreatment which could ultimately lead to longer survival. Clinical trial information: NCT00113607.

**5552 General Poster Session (Board #334), Sat, 8:00 AM-11:45 AM**

**Pertuzumab (P) plus chemotherapy (CT) for platinum-resistant ovarian cancer: Safety run-in results of the PENELOPE trial.** *Presenting Author: Antonio Gonzalez-Martin, GEICO and Medical Oncology Service, Centro Oncológico M. D. Anderson International Spain, Madrid, Spain*

**Background:** In platinum-resistant ovarian cancer, the monoclonal antibody P, which inhibits HER2 heterodimerization, improved PFS when added to gemcitabine in the subgroup of pts with low tumor HER3 mRNA expression [Makhija, 2010]. The 2-part PENELOPE trial (NCT01684878) is prospectively investigating P added to single-agent CT in this population. **Methods:** Part 1 (safety run-in) of PENELOPE evaluated P + either topotecan (TOP) or paclitaxel (PAC). Pts with platinum-refractory or -resistant recurrent ovarian, primary peritoneal, or fallopian tube cancer (progression [PD] during or within 6 mo of completing ≥4 platinum cycles) and low HER3 mRNA expression (concentration ratio ≤2.81 by central qRT-PCR testing on cobas z480) received IV P 840→420 mg q3w + investigator's choice of TOP (1.25 mg/m$^2$ d1–5 q3w; cohort 1) or PAC (80 mg/m$^2$ d1, 8, 15 q3w; cohort 2) until PD or unacceptable toxicity. The primary objective was to assess safety and tolerability. After all pts had received ≥3 cycles, the Independent Data Monitoring Committee (IDMC) assessed safety results to recommend which regimen(s) should be included in Part 2. **Results:** InPart 1, 50 pts were enrolled and treated between Oct 2012 and Jul 2013. At data cut-off (Aug 27, 2013), 8 TOP and 17 PAC pts remained on treatment. **Conclusions:** Both regimens were tolerable. Based on these results, the IDMC had no objection to the trial proceeding to Part 2 (double-blind randomized comparison of CT [TOP, PAC, or gemcitabine] + P or placebo). Clinical trial information: NCT01684878.

| | P + TOP (N=22) | P + PAC (N=28) |
|---|---|---|
| Median age, y (range) | 59 (41–80) | 64 (32–79) |
| ECOG PS, N (%) | | |
| 0 | 9 (41) | 13 (46) |
| 1 | 11 (50) | 9 (32) |
| 2 | 2 (9) | 6 (21) |
| Two prior CT lines, N (%) | 14 (64) | 20 (71) |
| Prior bevacizumab, N (%) | 6 (27) | 10 (36) |
| Platinum-free interval <3 mo, N (%) | 5 (23) | 11 (39) |
| Median No. of cycles (range) | | |
| P | 4 (1–11) | 4 (1–8) |
| CT | 4 (0–11) | 4 (1–8) |
| Primary reason for discontinuing P and CT, N (%) | | |
| PD | 9 (41) | 9 (32) |
| Symptomatic deterioration | 4 (18) | 0 |
| AE | 0 | 1 (4)[a,b] |
| Consent withdrawn | 1 (5) | 0 |
| Grade ≥3 AEs, N (%)[c] | 16 (73) | 7 (25) |
| Neutropenia | 4 (18) | 1 (4) |
| Febrile neutropenia | 3 (14) | 0 |
| Diarrhea | 3 (14) | 1 (4) |
| Anemia | 3 (14) | 0 |
| Asthenia | 3 (14) | 0 |
| Deaths | 6 (27) | 3 (11) |
| PD | 6 (27) | 2 (7) |
| AE | 0 | 1 (4)[a] |

[a]Infection. [b]1 further pt discontinued P (grade 1 hypersensitivity). [c]MedDRA preferred terms in >10%.

**5553 General Poster Session (Board #335), Sat, 8:00 AM-11:45 AM**

**A phase II study of intermittent sorafenib with bevacizumab (B) in B-naive and prior B-exposed epithelial ovarian cancer (EOC) patients.** *Presenting Author: Jung-min Lee, National Cancer Institute, National Institutes of Health, Bethesda, MD*

**Background**: We targeted the VEGF pathway at multiple points combining the VEGFR2/Raf inhibitor sorafenib (S) with bevacizumab (B), an anti-VEGF antibody. Our goals were to define efficacy and explore correlative endpoints for a B+S regimen in B-naïve (B-) or prior B-treated (B+) EOC pts. **Methods:** Eligible pts had recurrent EOC, ECOG PS 0-1, good end organ function, were B- or B+ (progression ≤ 6 mo from last B dose). The primary endpoint was objective response rate (CR+PR). A Simon 2-stage optimal design targeted a 40%, and 20% RR in B- and B+ pts, respectively. All pts received S 200mg bid days 1-5/wk and B 5mg/kg q2wk in 4 wk cycles. Pts were evaluated every 2 cycles using RECISTv1.0, underwent functional imaging, research biopsies, and serial FACT-O quality of life (QoL) studies. Pretreatment plasma cytokine concentrations of IL-6, IL-8, VEGF, and sVEGFR-2 were evaluated. **Results:** 54 EOC pts were enrolled (B- 41; B+ 13; median 49 yrs [27-79]). Median prior treatments exceeded 5. 48 pts (B- 35; B+ 13) were evaluable; 6 were not because of intercurrent illness (5), and withdrawal (1), absent progression prior to the first reassessment. Clinical benefit (CR+PR+SD≥4mo) occurred in 30/35 (86%) B- pts, PR occurred in 9/35 pts (26%; median duration 14mo; 5-22mo), and SD ≥4mo in 21/35 pts (median 6mo; 4-18mo). 7/13 (54%) B+ pts had SD with a median response of 6mo (4-23+mo). Therapy-related gr3/4 events included hypertension (33%), DVT or PE (9%), and renal hemorrhage, perforation, anal fissure, and HFS, 2% each. HFS resulted in S reduction to 200mg qd in 76% of pts at a median of 2 cycles (1-7). Pts experienced improvement in QoL scores. Pretreatment low IL8 (n=52 ITT) was predictive of PFS >4mo ($p<0.0001$; ROC AUC 0.8). Under analysis and to be presented are: pretreatment v. day 3 DCE-MRI and 18FDG-PET scan analysis, and RPPA tumor biopsy proteomics changes pretreatment to wk6. **Conclusions**: S+B yields promising clinical benefit in heavily pretreated B-EOC pts, with manageable toxicity, although did not meet the primary response endpoint. Extensive prospectively planned biomarker and functional imaging studies may yield information to focus therapy to those EOC patients who may best respond. Clinical trial information: NCT00436215.

**5554 General Poster Session (Board #336), Sat, 8:00 AM-11:45 AM**

**Surgical site infection after primary debulking surgery for epithelial ovarian cancer: Predictors and impact on survival.** *Presenting Author: Christine Tran, Mayo Clinic, Rochester, MN*

**Background:** Surgical site infection (SSI) following epithelial ovarian cancer (EOC) primary debulking surgery (PDS) occurs in 10-15% of patients. Perioperative factors associated with SSI as well as the impact of SSI on EOC survival were determined. **Methods:** All EOC cases that underwent PDS between 1/1/03 and 12/31/11 were retrospectively reviewed. SSIs were defined according to the American College of Surgeons National Surgical Quality Improvement Program and limited to the first 30 postoperative days. Bowel leaks were considered organ/space SSIs. Logistic regression models were fit to identify factors associated with SSI. Cox proportional hazards models were utilized to evaluate the association of patient and perioperative characteristics (including SSI as a time-dependent covariate) with overall survival (OS) and disease-free survival (DFS). **Results:** Among 888 cases, 96 (10.8%) developed an SSI: 32 superficial SSI, 2 deep SSI, and 62 organ/space SSI. Factors independently associated with superficial SSI were increasing BMI (OR 1.41 [95% CI, 1.12, 1.76] per 5 kg/m2), increasing operative time (1.24 [1.02, 1.50] per hour), and advanced stage (III/IV) (10.22 [1.37, 76.20]). Factors independently associated with organ/space SSI were history of GERD (2.13 [1.23, 3.71]), surgical complexity (intermediate 3.11 [1.02, 9.49]; high 8.07 [2.60, 25.09]), and residual disease (RD) (measureable ≤1cm 1.77 [0.96, 3.27]; >1cm (3.36 [1.48, 7.61]). Occurrence of superficial (HR 1.69 [1.12, 2.57]) or organ/space (HR 1.46 [1.07, 2.00]) SSI was independently associated with worse OS in a multivariable model adjusted for the following factors ($p<0.05$): age, ECOG performance status, ASA level, FIGO stage, ascites, RD, and histology. SSI occurrence did not independently influence DFS. History of stroke, ascites, and increasing RD and stage were associated with worse DFS. **Conclusions:** Development of SSI after PDS worsens OS. Most risk factors for SSI are not modifiable. Alternative measures to lower rates of superficial and organ/space SSI are needed as reduction of SSI may improve OS. Preoperative identification of SSI risk factors may also assist in risk assessment and operative decision making.

**5555 General Poster Session (Board #337), Sat, 8:00 AM-11:45 AM**

**Phase I/Ib clinical and immunologic assessment of immunotherapeutic vaccine, DPX-Survivac in women with ovarian, Fallopian tube, or peritoneal cancer (OC).** *Presenting Author: Michelle Wilson, Department of Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada*

**Background:** Survivin plays a key role in apoptosis, proliferation and angiogenesis. It is overexpressed in 90% of epithelial OC making it an attractive target. Increases in expression have been correlated with progression and drug resistance. DPX-Survivac is a vaccine containing a mix of survivin HLA class I peptides designed to evoke a cytotoxic T cell response against survivin. This Phase I/Ib de-escalation study reports the safety and immune potency of DPX-Survivac in combination with metronomic low dose oral cyclophosphamide (CPA) in OC. **Methods:** 30 Stage IIc-IV advanced or recurrent OC patients (pts) with no evidence of disease progression post chemotherapy were enrolled. Dose limiting toxicities (DLT) were defined as ≥gd3 AEs, ≥gd2 allergic or autoimmune reactions by CTCAE v4.03. Immune correlates (MDSCs; T regs; B cells) and vaccine induced T cell immunity (ELISpot; tetramer analysis; multi-parametric intracellular cytokine staining) were assessed in purified PBMC and blood. Clinical response was evaluated by RECIST and CA125. **Results:** No significant systemic AEs were seen. The most severe local injection site reactions were gd 3 skin ulcerations with 2 in cohort C. Phase Ib cohorts were de-escalated to 2 priming doses (0.25ml) 3 wks apart followed by boosters (0.1ml) every 8 wks with CPA. Immune response increased with dose (B vs. C p=0.013) and with use of CPA (A vs. C p=0.015). Despite de-escalation 6/6 pts in cohort 1 mounted a significant immune response by d77 with 1 gd 3 skin ulceration seen. In this cohort a PR by RECIST1.1 and GCIG CA125 criteria was confirmed in 1 pt with residual disease post platinum therapy and persisted on stopping vaccine and CPA. The PR correlated with a robust immune response verified by IFN-γ ELISpot and MHC tetramer assay. **Conclusions:** DPX-Survivac is well tolerated with proven immunogenicity. Early evidence of clinical activity is promising. A randomized phase II trial to assess vaccine efficacy in OC will commence in 2014. Clinical trial information: NCT01416038.

| | | Pts | | Priming DPX | | | Boost DPX (0.1mL) | | Skin ulceration | |
|---|---|---|---|---|---|---|---|---|---|---|
| Ph | Cohort | (n) | CPA | Dose (ml) | n | Freq wks | n | Freq wks | Gd | n |
| I | A | 6 | N | 0.5 | 3 | 3 | 0 | 0 | 2 | 1 |
| | B | 6 | Y | 0.1 | 3 | 3 | 0 | 0 | 3 | 1 |
| | C | 6 | Y | 0.5 | 3 | 3 | 0 | 0 | 3, 2 | 2, 1 |
| Ib | 1 | 6 | Y | 0.25 | 2 | 3 | 4 | 8 | 3 | 1 |
| | 2* | 6 | Y | 0.25 | 2 | 3 | 4 | 8 | n/a | n/a |

*recruited.

**5556^ General Poster Session (Board #338), Sat, 8:00 AM-11:45 AM**

**Independent review of AGO-OVAR 12, a GCIG/ENGOT-Intergroup phase III trial of nintedanib (N) in first-line therapy for ovarian cancer (OC).** *Presenting Author: Gunnar Kristensen, NSGO and Department of gynecologic oncology and medical informatics, Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway*

**Background:** N is an oral inhibitor of VEGFR, PDGFR, and FGFR. As reported earlier, in the AGO-OVAR12 trial, N compared to placebo (Pl), added to standard chemotherapy, significantly prolonged investigator (inv)-determined PFS (1° endpoint [EP]) in first-line OC. Here we report independent review committee (IRC)-determined PFS. **Methods:** IRC-PFS was predefined as sensitivity analysis to the 1° EP (database lock triggered by inv-PFS events). IRC-PFS was analyzed in the intent-to-treat population (n=1366), based on RECIST 1.1 and restrictive predefined clinical (clin) criteria. Debulking surgery details were provided to the IRC radiologist to support assessment of baseline (BL) tumor burden, and additional clin data to the IRC oncologist for a final integrative review. **Results:** Adherence to prescheduled imaging within 4 weeks of the prescribed date was high (>75%); independent review was completed for 94% of patients (pts). The IRC identified 4.3% of pts without tumor lesions at BL compared to 31.5% in on-site imaging; and 50.7% were stratified as free of residual tumor (integrating also surgery information) at randomization. Event concordance between IRC- and inv-PFS was very high (85.8%). Low discordance overall was primarily due to 19.5% (N) and 16.5% (Pl) of inv-determined PFS events (n=752 events) not detected by IRC, IRC detected an event in 9.2% (N) and 8.5% (Pl) of patients without inv-determined event (IRC total n=668 events). Concordance for event date was high, 75% of dates differed by <4 weeks. IRC-PFS was similar to inv-PFS (IRC: HR 0.86 [0.74-1.01], mPFS N=19.5 mo vs Pl=16.8 mo; inv: HR 0.84 [0.72-0.98], mPFS N=17.2 mo vs Pl=16.6 mo). Outcome of post hoc defined subgroup analysis (risk groups by stage and tumor burden) were also similar ('low-risk', IRC: HR 0.77 [0.62-0.96], mPFS N=27.8 mo vs Pl=21.9 mo; inv: HR 0.74 [0.61-0.91], mPFS N=27.1 mo vs Pl=20.8 mo). **Conclusions:** IRC-PFS (sensitivity analysis of 1° was highly concordant with inv-PFS regarding PFS events, event dates, and overall outcome. Consistency of BL tumor assessment by the IRC, site-radiologists and clinical inv was low, possibly affecting individual PFS assessment but not overall HR. Clinical trial information: NCT01015118.

**5557 General Poster Session (Board #339), Sat, 8:00 AM-11:45 AM**

**Inhibition of MEK1 increases carboplatin sensitivity in ovarian cancer.** *Presenting Author: Balazs Gyorffy, Ist Department of Pediatrics, Semmelweis University, Budapest, Hungary*

**Background:** Primary systemic treatments for ovarian cancer are paclitaxel and carboplatin chemotherapy. Platinum resistant cancers progress/recur in approximately 25% of cases within six months. We aimed to identify clinically useful biomarkers of platinum resistance. **Methods:** A database of ovarian cancer transcriptomic datasets including treatment and response data was set up by mining the GEO and TCGA repositories. Receiver operator characteristics (ROC) analysis was performed in R for each gene and these were then ranked using their achieved area under the curve (AUC) values. The most significant candidates were selected and *in vitro*functionally evaluated using RNA interference, qRT-PCR, MTT tests and FACS in four epithelial ovarian cancer cell lines (SKOV-3-, CAOV-3, ES-2, OVCAR-3). We collected 94 tumor samples and the strongest candidate was validated by IHC and qRT-PCR in these. **Results:** All together 1,152 eligible patients were identified, the median relapse-free survival was 24.8 months with 731 progressions. Based on the ROC analysis the eight most significant genes were *JRK, CNOT8, RTF1, CCT3, NFAT2CIP, MEK1, FUBP1* and *CSDE1*. The silencing of *MEK1, CSDE1, CNOT8, RTF1* and *FUBP1*, and the pharmacological inhibition of MEK1caused significant sensitization in the cell lines. Of the eight genes, *JRK* (p=3.2E-05), *MEK1* (p=0.0078), *FUBP1* (p=0.014), *CNOT8* (p=0.00022) also correlated to progression free survival. The correlation between the best biomarker candidate *MEK1* and survival was validated in two independent cohorts by qRT-PCR (n=35, HR=5.8, p=0.003) and IHC (n=59, HR=4.3, p=0.033). **Conclusions:** We identified *MEK1* as a promising biomarker candidate of response to platinum based chemotherapy in ovarian cancer.

**5558 General Poster Session (Board #340), Sat, 8:00 AM-11:45 AM**

**Ketoconazole as inhibitor of the enzyme CYP17 in locally advanced or disseminated granulosa cell tumors of the ovary (the GreKo I study) (gethi 11-03).** *Presenting Author: Laia Garrigos, Medical Oncology, Hospital del Mar, Barcelona, Spain*

**Background:** Granulosa-cell tumors (GCTs) of the ovary are a rare entity characterized by its genomic stability, presenting a punctual mutation at the FOXL2 gene, 402C→G (C134W), in the vast majority of cases. The protein encoded by this gene directly interacts with the Steroidogenic Factor-1 (SF-1) that regulates the expression of the enzyme CYP17. Since CYP17 inhibition has shown major activity in some cancers, we aimed to test the role of ketoconazole in GCT in a proof of concept trial. **Methods:** An open-label phase II trial was designed. Main inclusion criteria was adult women with advanced non-resectable GCT. Primary objective was radiological response, centrally assessed. Taking as a basis the two-stage Gehan model, 17 patients would need to be included in the first stage to demonstrate a treatment efficacy of at least 15% (type I error $\alpha = 0.05$, power of the test $(1 - \beta) = 0.8$). Treatment consisted on oral Ketoconazole 400 mg tid plus hydrocortisone 30 mg in morning and 20 mg in evening. 10 institutions, members of the Grupo Español de Tumores e Histologías Infrecuentes (GETHI) were involved. **Results:** From October 1st 2012 to January 31st 2014 seven patients were included. Recruitment was early finished due to ketoconazole shortage. Median age was 59.5 (range 44 to 63). All patients had 3 to 4 metastatic localizations and had received at least one prior treatment. With a median follow up of 4.6 months (range 2 to 11 months) all cases achieved tumor stabilization as best response. Only one patient has finally progressed thus, median Progression Free Survival (PFS) has not been reached. No grade >2 toxicity has been reported. A preplanned analysis of FOXL2 showed that the case that progressed did not present the pathognomonic mutation 402C→G (C134W) supporting partially the rationale of the study. Mature data with a follow up of 6 months for all cases and complete mutational analysis will be presented at the meeting. **Conclusions:** CYP17 inhibition seems to be a useful strategy in GCT. These results have prompted a second study (GREKO II) that will assess the role of orteronel, a new generation CYP17 inhibitor, in GCT. Clinical trial information: NCT01584297.

**5559 General Poster Session (Board #341), Sat, 8:00 AM-11:45 AM**

**Comparison of recurrent and nonrecurrent ovarian and uterine cancer patients undergoing adjuvant folate receptor vaccine therapy.** *Presenting Author: Erika J Schneble, San Antonio Military Medical Center, San Antonio, TX*

**Background:** Folate Receptor Alpha (FRa) (aka Folate Binding protein (FBP)) is an immunogenic protein that is over-expressed in breast, lung, endometrial (EC) and ovarian cancers (OC). In fact, FRa expression in malignant cells is 20-fold higher compared to normal cells. We are conducting a phase 1 clinical trial with E39, an HLA-A2 restricted, FRa peptide + GM-CSF vaccine, administered in the adjuvant setting to prevent recurrences in high-risk EC and OC patients (pts) rendered clinically disease-free after standard-of-care therapy. In this analysis, we compare *in vivo* immunologic responses (IR) and disease features between vaccinated recurrent (vR) and vaccinated non-recurrent (vNR) pts. **Methods:** HLA-A2+ pts enrolled into the vaccine group received 6 monthly intradermal inoculations of E39+250 mcg GM-CSF during the primary vaccine series (PVS). *In vivo* IR was assessed by both local reaction (LR) after each inoculation (R1-R5) and delayed hypersensitivity (DTH) reaction measured pre-vaccination (DTH1) and post-PVS (DTH2). The LR index is calculated by dividing LR at each time point by the corresponding LR at R0. **Results:** Overall, 30 pts have been enrolled. Of 14 control pts, 7 (50%) have recurred. Of 16 vaccinated pts, 4 (25%) have recurred after completing the PVS and 2 (12.5%) recurred prior to completing the PVS. One vaccinated pt withdrew due to an intercurrent illness leaving 6 vR and 9 vNR pts for analysis. vR were younger than vNR (60.4 v 65.6, p=0.14) although no significant differences in age, grade, stage, or nodal status existed between groups (all p>0.05). LR index was lower in vR pts at every time point (R1: 1.5 v 3.4, R2: 2.0 v 4.8, R3: 1.9 v 5.5, R4: 1.8 v 4.1, R5: 2.1 v 4.7). vR also displayed lower DTH1 (9.7mm±3.5 v 12.6mm±2.6, p=0.5) and DTH2 (14.4mm±11.4 v 7.4mm±4.8, p=0.78). **Conclusions:** Comparison between vR and vNR pts demonstrates recurrences are likely related to trends in both disease features (age but not stage) as well as diminished response to the vaccine as seen by LR and DTH. As decreased vaccine response may be related to more aggressive disease, the most viable way to address this is to vaccinate less advanced disease. Clinical trial information: NCT01580696.

**5560 General Poster Session (Board #342), Sat, 8:00 AM-11:45 AM**

**What factors influence advanced ovarian cancer patient (AOC pt) outcomes to phase I trial treatments?** *Presenting Author: Timothy Anthony Yap, The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, United Kingdom*

**Background:** Relapse to approved anticancer treatments is almost inevitable in AOC pt. Novel agents in phase I trials may benefit such pt. **Methods:** Retrospective study of pt records 6/1998-10/2010 from AOC pt allocated to Phase I trials including efficacy expansion phases of novel therapies in the Drug Development Unit at Royal Marsden Hospital (RMH). **Results:** 200 AOC pt were allocated to ≥1 trial each (281 allocations). 187 (94%) ECOG PS 0-1; 10 (5%) PS 2-3; 3 (1%) unknown. 51 (24%) platinum (pl) sensitive; 145 (67%) pl resistant; 20 (9%) unknown. 53 (27%) *BRCA* mutant, 9 (4%) *BRCA* wildtype and 138 (69%) unknown. 135 (68%) pt started ≥1 trial (mean 1.4 [1-8]; total 216 trials); 63 (32%) pt did not start due to progressive disease (PD). Median time from allocation to start of trial was 23 days. There were 43 (20%) RECIST complete/partial responses (CR/PR), including CR/PR with PARP inhibitors (18/79 [23%]), antiangiogenics (9/65 [14%]) and pl/taxane chemotherapy combinations (14/43 [33%]). Factors associated with CR/PR versus (v) those who did not start trial due to PD were: fewer prior treatments (mean 3 [1-6] v 4.3 [1-9]; p=0.02), pl sensitive v resistant (<0.001), CR/PR v PD with previous therapy (p<0.0001), better ECOG PS at allocation (mean 0.6 v 0.9; p=0.02), fewer metastatic sites (1.7 v 2.1; p=0.04), higher albumin (38 v 32g/L; p<0.0001) and hemoglobin (12.8 v 11.6g/dL; p<0.0001) levels, lower white cell counts (6.2 v 7.2; p=0.02) and baseline CA125 levels (1049 v 3649; p=0.02), *BRCA* mutation (p<0.0001), and better RMH-Prognostic Score (0.56 v 1.34; p<0.0001). Mean trial duration was 163 days (10-1483 days). Mean survival was 902 days for CR/PR pt v 117 days for pt who did not start treatment due to PD (p<0.0001). Treatments were well tolerated; of 385 adverse events, 351 (91%) Grade (G) 1/2; 34 (9%) G3/4. A substantial proportion of AOC pt (134/200 [67%]) received ≥1 (mean 1.3 [1-8]) subsequent lines of therapy after Phase I trials. **Conclusions:** Phase I trial treatments provided pt benefit in AOC although 32% of pt allocated to such trials failed to start treatment due to PD. These data suggest that phase I trial referrals should be considered earlier in AOC treatment pathways, particularly with the emergence of promising novel agents.

**5561 General Poster Session (Board #343), Sat, 8:00 AM-11:45 AM**

**Prognostic significance of urinary neopterin in ovarian cancer a study of the Austrian Gynecologic Oncology Group.** *Presenting Author: Christian Marth, Medical University of Innsbruck, Innsbruck, Austria*

**Background:** Neopterin is produced by activated macrophages upon stimulation with interferon-gamma (IFN-g) and thus elevated concentrations in patients indicate cellular immune response. Most studies in patients with malignant diseases found an association between higher neopterin concentrations with reduced survival and impaired prognosis, although it is not a classical tumor marker since it is not produced by cancer cells. **Methods:** In a study of the Austrian Gynecologic Oncology Group in 114 patients with cystadenomas and 17 patients with borderline ovarian tumors as well as 223 invasive ovarian cancer patients urinary neopterin was determined before and after primary therapy. **Results:** Elevated levels (cutoff 250 $\mu$mol/mol creatinine) were found less frequently in women with benign ovarian cystadenomas (24%) and borderline tumors (29%) compared to patients with malignant disease. We observed stage dependency with 16%, 25%, 65% and 91% in FIGO stage I-IV, respectively. By univariate analysis residual tumor, FIGO stage, age, histological type, and neopterin was significantly associated with overall and progression-free survival (OS and PFS). Median OS was 81 versus 24 months for patients with normal and elevated neopterin, median PFS was 52 and 12 months respectively ($p<.001$ for both). In a multivariate Cox regression analysis, residual tumor, neopterin and age were independently associated with OS, while only residual tumor was predictive for PFS. Thirty patients with surgically staged FIGO I or II invasive ovarian cancer were analyzed separately. Two of three patients with elevated levels died of disease in contrast to 2/27 deaths in women with normal neopterin ($p=.004$, Fisher's exact test). **Conclusions:** In ovarian cancer the negative impact of pretreatment urinary neopterin indicates a detrimental role of immune activation for the course of the disease.

**5562 General Poster Session (Board #344), Sat, 8:00 AM-11:45 AM**

**Surgical staging and its prognostic impact on patients with borderline ovarian tumors (BOT): A subanalysis of the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) ROBOT study.** *Presenting Author: Fabian Trillsch, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

**Background:** Incomplete surgical staging was shown to be a negative prognostic factor for patients with borderline ovarian tumors (BOT). However, little is known about the prognostic impact of each individual staging procedure. **Methods:** Clinical parameters of 950 patients with BOT (confirmed by central reference pathology) treated between 1998 and 2008 in 24 German AGO centers were analyzed. Staging quality was evaluated following German guidelines. In patients with adequate surgery regarding their reproductive organs (bilateral salpingo-oophorectomy or intended fertility preserving surgery in patients $\leq$55 years), other recommended staging procedures (omentectomy, peritoneal biopsies, cytology, and, for mucinous histology, appendectomy) were evaluated applying uni- and multivariate regression models with respect to progression-free survival (PFS), separately for serous and mucinous histology. **Results:** A total of 559 serous BOT (64.1%) were opposed to 268 mucinous BOT (30.7%). For patients with serous histology, each additionally skipped staging procedure raised the risk for recurrence by at least 25% (HR 1.25; 1.95; 2.37 respectively) becoming statistically significant in case of two or more missing steps. The most crucial procedures were omentectomy in serous and appendectomy in mucinous BOT with HR of 2.00 ($p=0.004$) and HR of 4.86 ($p=0.012$) in univariate analyses. Together with established prognostic factors as FIGO stage, tumor residuals, and fertility preservation, omentectomy (HR 1.91; 95%CI 1.15, 3.19; $p=0.01$) retained a statistically significant impact on PFS in multivariate analysis for serous BOT as did appendectomy in case of mucinous histology (HR 4.60; 95%CI 1.33, 15.86; $p=0.02$). **Conclusions:** Individual surgical staging procedures appear to have prognostic importance for BOT patients. Despite excellent overall prognosis, the risk for recurrence rises with each skipped surgical step. This should be considered when re-staging procedures following incomplete primary surgery are discussed.

**5563 General Poster Session (Board #345), Sat, 8:00 AM-11:45 AM**

**Genome-wide association study for identification of candidate SNPs associated with carboplatin and paclitaxel clearance in ovarian cancer patients.** *Presenting Author: Bo Gao, Blacktown Hospital, Sydney, Australia*

**Background:** Epithelial ovarian cancer (EOC) is generally treated by cytoreductive surgery and carboplatin/paclitaxel chemotherapy. Five-year survival is ~20% for patients with advanced disease. There is wide inter-individual variation in chemotherapy pharmacokinetics (PK), response and toxicity. Identifying single nucleotide polymorphisms (SNPs) that influence chemotherapy disposition may help optimize treatment. **Methods:** Carboplatin and paclitaxel concentrations were collected during cycle one (N=61) and three (N=7) of chemotherapy on 61 prospectively recruited Australian women with EOC. Paclitaxel concentrations were also obtained on 38 Dutch patients for meta-analysis. A genome wide association study (GWAS) was performed in all patients using Illumina OmniExpress arrays (719,665 SNPs). PK parameters were obtained using nonlinear mixed-effect modelling (NONMEM). Covariates associated with carboplatin and paclitaxel PK parameters were identified and for each SNP, both unadjusted and adjusted analysis were performed to test associations with carboplatin clearance (CL) and time of paclitaxel concentration $>$ 0.05 $\mu$mol/L ($T_{c>0.05}$). **Results:** There was a 5- and 4-fold inter-individual variation in carboplatin and paclitaxel CL respectively, with little intra-individual variation. Carboplatin CL correlated with relative thrombocytopenia ($p$ = 0.018) , whereas paclitaxel $T_{c>0.05}$ predicted relative neutropenia ($p$ = 0.002). In the GWAS, SNPs in *ABCC2* were associated with carboplatin CL ($p = 10^{-6}$), and a novel SNP in chromosome 1 (rs17130142) was associated with paclitaxel $T_{c>0.05}$ with genome wide significance ($p = 2.0 \times 10^{-9}$). **Conclusions:** Our GWAS approach identified SNPs associated with carboplatin and paclitaxel PK parameters. In the case of carboplatin, SNPs were identified in the ABCC2 gene, which encodes a known carboplatin transporter, indicating biological plausibility. These findings support a GWAS approach as an effective strategy for identification of novel pharmacogenomic markers. Validation of these candidates in further studies may provide novel biomarkers for EOC treatment optimisation.

**5564 General Poster Session (Board #346), Sat, 8:00 AM-11:45 AM**

**A phase II trial on the combination of bevacizumab and irinotecan in recurrent ovarian cancer.** *Presenting Author: Huichung Tina Ling, The Permanente Medical Group, Hayward, CA*

**Background**: Irinotecan and bevacizumab have single agent activity in both platinum sensitive and resistant recurrent ovarian cancer. We sought to evaluate the efficacy and safety of the combination in this setting. The primary endpoint is to estimate the progression free survival (PFS) at 6 months. Secondary objectives include overall survival (OS), observed response rate (ORR), duration of response, and toxicity. **Methods**: Ovarian cancer patients with recurrence after any number of prior regimens were eligible. Irinotecan 250 mg/m2 (amended to 175 mg/m2 after treatment-related toxicities in the first 6 patients) and bevacizumab 15 mg/kg were administered every 3 weeks until disease progression or toxicity. Response was assessed by RECIST every 2 cycles and by CA-125 criteria for those without measurable disease. **Results**: Of the 29 patients enrolled, 10 were platinum-sensitive and 19 were platinum-resistant. The median number of prior regimens was 5 (range 1-12): 13 patients had prior bevacizumab and 11 patients prior topotecan. The median number of study cycles given was 7 (range 1-34); 5 patients withdrew after 1 cycle (3 due to toxicity). Of the 24 patients assessable for response, 8 patients experienced partial response (PR), 13 maintained stable disease (SD), and 3 had progressive disease; 12 patients with PR/SD were platinum resistant. The ORR was 27.6% (95% CI: 0.127-0.472) and the clinical benefit rate was 72.4% (95% CI: 0.565-0.873) for the intention-to-treat population (n=29). Twelve patients had longer than 6 months of sustained response. Median PFS was 8.1 months (95% CI: 5.1-12.3 months); median OS was 15.9 months (95% CI: 13.4 months- upper bound not reached). The PFS rate at 6 months was 55.2% (95% CI: 0.397-0.766). The most common grade 3/4 toxicities included diarrhea (5 pts), neutropenia (3), hypertension (3), proteinuria (2), fatigue (2), nausea (2), abdominal pain (2), and GI perforation (1). No treatment-related deaths were observed. **Conclusions**: The combination of irinotecan and bevacizumab showed encouraging activity in heavily-pretreated patients with recurrent ovarian cancer. The median PFS of 8.1 months is comparable to other bevacizumab-containing doublets reported in the AURELIA trial. Clinical trial information: NCT01091259.

**5565 General Poster Session (Board #347), Sat, 8:00 AM-11:45 AM**

**Temsirolimus in women with platinum-resistant ovarian cancer or advanced/recurrent endometrial cancer: A multicenter phase II trial of the AGO Study Group (AGO-GYN 8).** *Presenting Author: Guenter Emons, Department of Obstetrics and Gynecology, University of Goettingen, Goettingen, Germany*

**Background:** Inhibition of mTOR with temsirolimus (T) might be an efficacious treatment of patients with epithelial ovarian cancer (OC) or endometrial cancer (EC). **Methods:** Patients (pts) with platinum and taxane resistant OC (n = 22) or with advanced/recurrent EC, who had not received previous chemotherapy (n = 22) were treated with weekly IV infusions of T (25 mg). Primary endpoint was progression free survival after 4 months (OC) or 6 months (EC). A two stage design was used with second stage of accrual if < 10 of the first 22 pts (OC) or < 7 of the first 22 pts (EC) had progressive disease after the first 8 weeks of T-treatment. **Results:** 22 pts each were treated in the OC and the EC cohort respectively. Median age was 56 years (OC) or 63 years (EC). After 8 weeks of treatment with T, 10 pts in the OC cohort and 7 pts in the EC group had progressive disease. Toxicity of T was mild: grade 4: 1 ileus (OC), grade 3: anemia 1, abdominal pain 1, ALT elevation 1, ascites 3 (OC), diarrhea 1, vomiting 2. **Conclusions:** T-treatment was well tolerated in our patients. It did, however, not meet the predefined efficacy criteria with 10 of 22 pts (OC) and 7 of 22 pts (EC) having progressive disease after 8 weeks of treatment. Clinical trial information: EudraCT Nr. 2011-000299-33.

**5566 General Poster Session (Board #348), Sat, 8:00 AM-11:45 AM**

**Weekly administration of bevacizumab, eribulin, and oxalilplatin in patients with platinum-resistant and refractory ovarian carcinomas: A phase II study.** *Presenting Author: Yuji Ikeda, The University of Tokyo, Hongo, Japan*

**Background:** Eribulin, inhibiting a protein component of tubulin, is a candidate for paclitaxel-refractory breast cancers, and Bevacizumab (B) is known to enhance efficacy of anti-cancer agents in ovarian cancers. A phase II study to evaluate weekly administration of B with eribulin and oxaliplatin (EriOX) in patients with platinum-resistant and refractory ovarian carcinomas (PR-ROC) was performed. **Methods:** Simon's two-stage design was used. In the first stage, 15 patients were accrued. If there were no responder in these patients, the study would be stopped. Otherwise, eight additional patients will be accrued for a total of 23. If three or more responder were observed in 23 patients, this design yields a type I error rate of 0.03 and power of 0.80 when the true response rate were 18%. Patients with PR-ROC were treated with weekly-B-EriOX consisting of B (2mg/kg), eribulin (1mg/m2) and oxaliplatin (30mg/m2). **Results:** Among 15 patients in the first stage, four responses were observed, and a total of 23 patients were analyzed in this study. There were no cases that discontinued the therapy due to toxicities. Median age of the patient was 58 years (range:38-71). Median number of previous regimen was 4 (range:2-8). Two patients (9%) had a complete response (CR), 3 patients (13%) had a partial remission (PR) and 9 patients (39%) had a stable disease (SD). The response rate and clinical benefit rate (CR+PR+SD) were 17% and 56%, respectively. Median progression-free survival was 3 months (range: 1-8+). Hematological adverse effects (AE) with grade 3/4 were observed in 4 patients (17%). Hypo albuminemia and edema with grade 3 were in 1 patient (8%), respectively. However, all AE were manageable and tolerable. **Conclusions:** Weekly B and EriOX administration had significant activity with mild AE in patients with PR-ROC. These results warrant further prospective study.

**5567 General Poster Session (Board #349), Sat, 8:00 AM-11:45 AM**

**Microscopic residual carcinoma at interval debulking surgery after neoadjuvant chemotherapy in patients with IIIc/IV Müllerian carcinoma.** *Presenting Author: Kyoko Nishikimi, Departments of Reproductive Medicine, Graduate School of Medicine, Chiba University, Chiba, Japan*

**Background:** Neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) is a treatment option in patients with bulky stage IIIC/IV müllerian carcinoma. Because disseminated tumors may have disappeared macroscopically following chemotherapy, a potential drawback of IDS is difficulty deciding which sites should be excised. We therefore evaluate microscopic residual carcinoma after NAC in each previously disseminated site. **Methods:** Fifty patients with stage IIIc /IV müllerian carcinoma with a poor general condition, or those with a widely metastatic tumor and extensive ascites who had an unresectable residual tumor at the time of initial laparotomy, were included in the study. At the time of the initial laparotomy, we performed either a salpingo-oophorectomy or biopsy only, and then marked the residual tumors >1 cm with silk sutures. We then recorded the site and size of the tumors and placed an implantable port system (IPS) in the pelvis for peritoneal washing cytology during NAC (platinum/taxane). IDS was performed after the patients were shown to be IPS-cytology negative. At the time of IDS, we excised the initially marked site even if the tumors were macroscopically negative, and then investigated whether or not microscopic residual carcinoma was present in each disseminated site. **Results:** Forty-one patients (38 high-grade serous carcinomas, 3 other histological types) underwent IDS (39 complete resection, 2 with residual tumor <1 cm). Microscopic examination revealed residual carcinoma in each site as follows: 82% (28/ 34) in the recto-uterine pouch/rectosigmoid colon, 71% (5/7) in the ileocecal area, 69% (20/29) in the paracolic gutters, 65%(15/23) in the small intestine and mesentery, 63% (5/8) in the transverse mesocolon, 57% (20/35) in the vesicouterine pouch, 53% (19/36) in the right diaphragm, 53% (18/34) in the lymph nodes, 50% (3/6) in the hepatic capsule, 44% (8/18) in the splenic capsule, and 40% (6/15) in the left diaphragm. **Conclusions:** Our results suggest that it is necessary to excise all sites during IDS after NAC in patients with a disseminated tumor >1 cm at the initial exploratory laparotomy, but with negative peritoneal cytology. Clinical trial information: UMIN000013079.

**5568 General Poster Session (Board #350), Sat, 8:00 AM-11:45 AM**

**Phase II study of gemcitabine and vinorebline in patients with persistent or recurrent platinum-resistant ovarian or primary peritoneal cancer: A study of the Korean Cancer Study Group.** *Presenting Author: Sook Hee Hong, Division of Oncology, Department of Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea, Seoul, South Korea*

**Background:** To evaluate the antitumor activity and safety of gemcitabine and vinorelbine in patients with persistent or recurrent platinum-resistant epithelial ovarian or primary peritoneal cancer **Methods:** A phase II trial was conducted by the Korean Cancer Study Group. Patients with cancer that progressed on platinum-based primary chemotherapy or recurred within 6 months were enrolled. One prior chemotherapy regimen for the treatment of persistent or recurren platinum resistant disease was allowed. Vinorelbine at 25mg/m$^2$ followed by gemcitabine 1000mg/m$^2$was administered intravenously on day 1 and 8 every 3weeks . Dose delay and adjustment was permitted for toxicity. Treatment was continued until disease progression or unacceptable adverse effects. **Results:** From December, 2011 to January, 2013, 44 patients were enrolled. A total of 219 cylces (median, four: range one to 24cycles) of vinorelbine and gemcitabine were administered, with fifteen (34.1%) of patients receiving six or more cycles. Two patients (4.5%) had a complete response and seven patients (15.9%) had partial responses, with a median duration response of 9.4 (95% Confidential Interval (CI) 4.6-18.3) months. Nineteen patients (43.18%) had stable disease for a median of 3.6 (95% CI: 2.5-4.4) months. Twelve patients (27.3%) had progressed disease. Four patients (9.0%) were not assessable. Median progression-free survival was 3.4 (95% CI: 2.5-4.2) months, and overall survival was 12.2 months. Grade 3 or 4 neutropenia, the most frequent toxicity occurred in 50% of patients. 4 patients experienced grade 3 febrile neutropenia and one patient experienced grade 4 febrile neutropenia. Non- hematologic toxicities were tolerable. A 25% dose reduction was required for 33patients (75%; 61.8% of cycles). No treatment related death observed. **Conclusions:** Gemcitabine and vinorelbine combination chemotherapy has sufficient activity in the treatment of recurrent platinum-resistant ovarian cancer at the dose and schedule tested to warrant further investigation. Clinical trial information: NCT01196559.

**5569 General Poster Session (Board #351), Sat, 8:00 AM-11:45 AM**

**Evaluation of the hematologic safety of same day versus standard administration of pegfilgrastim in gynecology oncology patients undergoing platinum-based chemotherapy.** *Presenting Author: Caroline C Billingsley, Ohio State University Wexner Medical Center, Columbus, OH*

**Background:** The safety of the timing of pegfilgrastim administration in women with gynecologic malignancies has been questioned. We aimed to assess the safety and efficacy of administration of pegfilgrastim on the same day (D1) as chemotherapy compared to standard administration (24-72 hours after chemotherapy) in patients with gynecologic malignancies. **Methods:** A retrospective review was conducted on gynecologic oncology patients who received pegfilgrastim to mitigate the myelosuppressive consequences of chemotherapy from January 1, 2002 through July 31, 2012. Data collected included demographics, pathology, blood counts, toxicity, chemotherapy regimen and day of pegfilgrastim administration. **Results:** 2071 injections of pegfilgrastim in 421 patients were identified. 506 doses of pegfilgrastim were given on D1 compared to 1565 standard administrations. The most common malignancy was ovarian cancer (79%). Median age was 60 years (23-90). 318 (76%) patients had stage III, IV, or recurrent disease and 83% of patients received their initial dose during their primary chemotherapy regimen. The most common chemotherapy regimen was carboplatin/paclitaxel (42%), followed by carboplatin/docetaxel (11%). The median ANC was 3888 cells/mL (68-57,724). Grade 3/4 neutropenia was observed in 2.6% of the D1 cohort versus 1.8% in the standard cohort (G3: 1.2% vs 1.3%, G4:1.4% vs 0.5%) (adjusted relative risk (aRR) 1.4 (90% CI: 0.8-3.2)). There was one episode of FN per group. Further comparing D1 to standard pegfilgrastim administration, dose modifications occurred in 6.5% and 4.9% (aRR: 1.3 (90% CI: 0.9-1.9), while treatment delays occurred in 7.3% and 9.4%, respectively (aRR: 0.8 (90%CI: 0.6-1.1)). **Conclusions:** The incidence of neutropenia, dose modification, and treatment delays did not differ substantially between patients who had pegfilgrastim administered on D1 compared to standard dosing. Pegfilgrastim can be safely administered on the same day as chemotherapy in patients receiving treatment for gynecologic malignancy. We report on the largest series of pegfilgrastim administration in gynecologic malignancies to date.

**5570 General Poster Session (Board #352), Sat, 8:00 AM-11:45 AM**

**Molecular analysis of non-epithelial ovarian cancer by histologic subtype.** *Presenting Author: Maise Al Bakir, Ovarian Cancer Action Research Centre, Imperial College London, London, United Kingdom*

**Background:** Non-epithelial malignancies of the ovary account for <2%–4% of all ovarian tumors. The classification of non-epithelial ovarian cancer can be broadly divided into two histological subtypes, ovarian germ cell tumors (OGCTs) and ovarian sex cord stromal tumors (OSCSTs). Molecular phenotypes of these groupings may identify genetic susceptibilities to existing therapies and thus improve patient care. **Methods:** 275 non-epithelial ovarian cancers (non-EOC) were profiled by Caris Life Sciences between 2009 and 2013 using a multiplatform approach. Within this cohort, patients could be further grouped according to histopathological subtypes, particularly OGCTs (n=42) and OSCSTs (n=217). Testing of FFPE tissues included a combination of sequencing (Sanger, NGS and pyrosequencing), protein expression (IHC), gene amplification (CISH or FISH), and/or RNA fragment analysis. **Results:** Of interest, the frequency of positive hormone receptor over-expression was higher in OSCSTs than OGCTs(AR 76%v 0%, PR 90% v 12%, ER 12% v 0%). Granulosa Cell tumors (n=173) were particularly strongly expressing for AR (81.7%), PR (95.9%) but not for ER (9.3%), with Alk, APC, and ATM mutations occurring rarely. Sertoli-leydig tumors (n=25) were characterized by high Topo2A (66.7%), TUBB3 (65%), BRAF (14.3%) and kras (20%) mutation, with lower AR (38%) and PR (60%) and higher ER (28%) expression than granulosa cell tumors. OGCT (n=42) cohorts exhibited RRM1 (51%), TLE3 (55%), TOP2A (87%), TUBB3 (51%), PTEN loss (67%) with mutations of P53 (56%) and PI3K (22%) also occurring. Kras mutation was observed in 1 of 9 OGCTs tested. **Conclusions:** Tumor profiling has identified molecular differences between non-EOC histological subtypes, by both expression and NGS mutational approaches in FFPE tissues. Identification of these changes can provide a rationale for treatment options not routinely considered or those associated with targeted therapies and warrant future clinical trials in this cancer type

**5571 General Poster Session (Board #353), Sat, 8:00 AM-11:45 AM**

**Relationship of pharmacokinetics (PK), toxicity, and initial evidence of clinical activity with IMGN853, a folate receptor alpha (FRa) targeting antibody drug conjugate in patients (Pts) with epithelial ovarian cancer (EOC) and other FRa-positive solid tumors.** *Presenting Author: Kathleen N. Moore, University of Oklahoma Health Sciences Center, Oklahoma City, OK*

**Background:** IMGN853 is a FR$\alpha$-targeting ADC that comprises a FRa-binding antibody conjugated with the potent maytansinoid tubulin inhibitor, DM4. FRa is highly expressed on many solid tumors, particularly EOC, endometrial, non-small cell lung cancer, and clear cell renal cancer **Methods:** The phase I primary objectives are to determine the maximum tolerated dose and recommended phase 2 dose. The secondary objectives include evaluation of safety, PK, pharmacodynamics and preliminary efficacy. Analysis of PK data and the relationship with ocular toxicity, the dose limiting toxicity at 7.0 mg/kg total body weight (TBW) and initial evidence of clinical activity from patients in this ongoing study is described. **Results:** Thirty pts have been enrolled across 7 dose levels 0.15 to 7.0 mg/kg TBW (IV) every 21 days (Q3W). The occurrence of ocular toxicity was associated with high $C_{max}$ (p=0.0004 Fisher exact test) and high early exposure levels, (area under the curve in the first 24 hours ($AUC_{0\text{-}24}$) (p=0.0001)). Covariate analysis indicated a correlation between weight and $C_{max}$ (Pearson r=0.48, p=0.02). Preliminary evidence of clinical activity (CA125 CGIC response criteria, partial response (PR), SD > 6 cycles) was observed in 10/24 patients receiving doses > 3.3 mg/kg (TBW). There was evidence of a threshold exposure level for activity around $AUC_{0-\infty}$>12,944 (hr ug/ml). In patients with these exposure levels, clinical activity was observed in 5/6 serous or transitional EOC pts and 2/4 endometrial pts. The final clinical activity threshold may vary slightly as additional pts are enrolled. Based on these results, and PK modeling, dosing by adjusted ideal body weight (ADJ) was identified as a means to decrease PK variability due to body weight dependence. The phase I trial has been amended to evaluate this hypothesis. **Conclusions:** Preliminary evidence of anti-tumor activity is encouraging, and results from the PK analysis suggest ADJ dosing should enable more pts to be treated within a clinically relevant therapeutic window. Clinical trial information: IMGN853-0401NCT01609556.

**5572 General Poster Session (Board #354), Sat, 8:00 AM-11:45 AM**

**Impact of neoadjuvant chemotherapy cycles prior to interval surgery in patients with advanced epithelial ovarian cancer.** *Presenting Author: Pierre-Emmanuel Colombo, ICM, Montpellier, France*

**Background:** Complete surgery with no macroscopic residual disease at primary or interval debulking surgery (IDS) is the principal goal of the surgical management of advanced epithelial ovarian cancer (EOC). In the case of neoadjuvant chemotherapy (NAC), IDS is generally recommended after 3 to 4 cycles, but few studies have specifically analyzed this point. The aim of this work was to evaluate the impact on survival of the number of NAC cycles before IDS in a large cohort of EOC patients. **Methods:** Data from patients with advanced EOC (stages IIIC-IV), operated between 1995 and 2010 were consecutively recorded in a prospective database and evaluated retrospectively. Patients treated withNAC/ IDS (group B) were analyzed according to the number of NAC cycles ($\leq 4$ = group B1; $> 4$ = group B2) and compared with patients receiving primary surgery (group A). Patients with complete resection were specifically analyzed in both groups. **Results:** Clinical data of 367 patients with advanced EOC were analyzed. 219 received upfront surgery (group A) and 148 had IDS after NAC (group B). The average follow-up was 82 months. In group B, 38 patients (26%) received more than 4 NAC cycles before IDS (group B2). Patients in group B2 presented more frequently stage IV disease (p=0.015). The rate of complete cytoreduction was higher in group B2 (67%) compared to groups B1 (62%) and A (44%) (p=0.002). Patients in group B2 had worse survival compared to patients in group B1 (p=0.04). Patients with complete surgery at the end of IDS and who had received more than 4 cycles of NAC had poor survival (p<0.001) with a relative risk of death after multivariate analysis of 3 (95% CI : 1.7-5.5]) with an independent impact from stage and performance status. Conclusions*:* Patients with advanced EOC receiving complete IDS after more than 4 cycles of NAC have poor prognosis. Despite worse prognostic factors observed in this group of patients, our study reinforces the concept of early and complete removal of all macroscopic tumors in the therapeutic sequence of EOC. These results call into question the interest of a delayed debulking in advanced cases thought to be unresectable after 3 to 4 cycles of NAC.

**5573 General Poster Session (Board #355), Sat, 8:00 AM-11:45 AM**

**Blocking and randomization to improve molecular biomarker discovery.** *Presenting Author: Li-Xuan Qin, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Randomization and blocking have the potential to prevent the negative impacts of non-biological effects on molecular biomarker discovery. Their use in practice, however, has been scarce. **Methods:** To demonstrate the logistic feasibility and scientific benefits of randomization and blocking, we conducted a microRNA study of endometrial tumors (n=96) and ovarian tumors (n=96) using a blocked randomization design to control for non-biological effects; we profiled the same set of tumors for a second time using no blocking or randomization. We assessed empirical evidence of differential expression in the randomized study and the non-randomized study. We conducted simulation studies to further evaluate the benefits of randomization and blocking on the accuracy of biomarker detection. **Results:** There was moderate and asymmetric differential expression (10%=351/3,523) between endometrial and ovarian tumors in the randomized dataset. Array effects were observed in the non-randomized dataset and 1,934 markers (55%) were called differentially expressed (DE). Among them, 181 were deemed DE (181/351, 53%) and 1,749 non-DE (1,749/1,934, 90%) in the randomized dataset. In the simulation study, when randomization was applied to all samples at once or within each of multiple batches balanced in sample groups, blocking improved the true positive rate (TPR) from 0.95 to 0.97 and the false positive rate (FPR) from to 0.02 to 0.002. When sample batches are unbalanced, randomization within each batch had a worse TPR (0.92) and FPR (0.10) regardless of blocking. Normalization improved the detection of true positive markers often at the price of increased false positive markers. **Conclusions:** Through empirical and simulated studies, we showed that blocking and randomization (across all samples or within balanced batches) can effectively improve the accuracy of detecting disease markers. They should be used to more fully reap the benefits of genomics technologies.

**5574 General Poster Session (Board #356), Sat, 8:00 AM-11:45 AM**

**Genome-wide association study (GWAS) of pazopanib efficacy and safety in patients with ovarian cancer who have not progressed following first-line standard therapy.** *Presenting Author: Giovanni Scambia, Universita Cattolica del Sacro Cuore Policlinico Agostino Gemelli, Rome, Italy*

**Background:** Pazopanib is an oral multi-kinase inhibitor of VEGFR-1, -2, -3, PDGFR-$\alpha$ and -$\beta$ and c-Kit. In the phase III AGO-OVAR16 study (NCT00866697), pazopanib maintenance therapy significantly increased progression free survival (PFS) in patients with ovarian cancer who have not progressed after first line therapy; however such benefit was not observed in a phase II study (NCT01227928) conducted in East Asian countries. In both studies, there is heterogeneity in patient response (safety and efficacy) to pazopanib; we hypothesized that germline genetic variation may contribute to this heterogeneity. **Methods:** GWAS analyses were conducted using combined patient data from the AGO-OVAR16 study (N=477, pazopanib) and the East Asian phase II study (N=73, pazopanib), which had similar eligibility criteria and treatment schedules. In aggregate N=387 patients receiving pazopanib provided consent for pharmacogenetic research. GWAS were conducted using normal, ordinal, and Cox regression models to test 30M genetic variants (genotyped or imputed) for association with PFS, overall survival, CA-125 change, bilirubin elevation, transaminase elevation, blood pressure change, hand foot syndrome, diarrhoea, fatigue, neutropenia, thrombocytopenia, and dose reduction or dose discontinuation. **Results:** At the genome wide significance level ($P \leq 5x10^{-8}$), common variants near *UGT1A1* were associated with bilirubin elevation ($P = 1.1x10^{-21}$), consistent with our previous observations in pazopanib treated patients with renal cell carcinoma. Common variants near a disintegrin and metalloprotease (ADAM) domain family genes *ADAM28–ADAM7* were associated with CA-125 change ($P = 2.9x10^{-10}$). No other common variants reached genome-wide significance. **Conclusions:** Some instances of isolated bilirubin elevation in pazopanib treated patients with ovarian cancer may be benign manifestations of Gilbert's syndrome. We identified a novel association between germline variants in *ADAM28–ADAM7* and CA-125 change; further studies of this finding may yield insights into mechanisms underlying differential response to pazopanib in patients with ovarian cancer.

**5575 General Poster Session (Board #357), Sat, 8:00 AM-11:45 AM**

**Frequency and timing of thoracic tumor spread in 198 consecutive patients with advanced-stage high-grade serous ovarian cancer (HGSC).** *Presenting Author: Atul B Shinagare, Dana-Farber Cancer Center Institute/Brigham and Women's Hospital, Boston, MA*

**Background:** HGSC is the most common type of ovarian cancer. While routinely used, the necessity of chest CT in these patients is unknown. We hypothesize that thoracic metastases in HGSC occur late, after development of abdominal disease. We aimed to describe the frequency and timing of occurrence of thoracic disease in advanced (stage III and IV) HGSC in relation to the abdominal disease. **Methods:** In this IRB-approved, HIPAA-compliant retrospective study, we included 198 consecutive patients with pathologically proven advanced HGSC seen from January 2012 through December 2012 (mean age 60 years, SD±9.5 years; median follow-up 40 months, IQR 25-63). Time to development of abdominal and thoracic disease and survival thereafter was recorded by review of thoracic and abdominal imaging and electronic medical records, and compared using Mann-Whitney test. Predictors of occurrence and time to development of thoracic disease were identified using multivariate analysis. **Results:** Abdominal disease developed in 177 patients (89%) and thoracic disease in 69 (35%). The first site of thoracic disease was visible on the abdominal CT in 51 (74%) patients (pleural effusion, n=27; epiphrenic and/or retrocrural lymph nodes, n=24), and of the remaining 18 (26%) patients with high thoracic disease (mediastinal, supraclavicular or axillary nodes, n=9; lung nodules, n=9) all except one had preexisting abdominal disease. Median time to development of thoracic disease was longer than abdominal disease (24 months, IQR 13-43 vs 13 months, IQR 7-25; p<0.0001) and survival after thoracic disease was shorter than after development of abdominal disease (13 months, IQR 6-28 vs 26 months, IQR 12-45; p=0.0002). Presence of abdominal disease was the only predictor of development of thoracic disease (p=0.0009; OR 12.08, 95%CI 2.36-221.20); time to abdominal disease predicted time to thoracic disease (p=0.003). **Conclusions:** Thoracic disease develops late in the course of advanced HGSC and occurs in patients with preexisting abdominal disease. Presence of abdominal disease is the only predictor of thoracic metastases. Therefore, potential exists for limiting the use of chest CT in patients with advanced HGSC.

**5576 General Poster Session (Board #358), Sat, 8:00 AM-11:45 AM**

**Effect of intraperitoneal chemotherapy on survival for ovarian cancer in clinical practice and frequency of use.** *Presenting Author: Alexi A. Wright, Dana-Farber Cancer Institute, Boston, MA*

**Background:** In 2006 the National Cancer Institute (NCI) issued a rare clinical alert recommending intraperitoneal chemotherapy (IP) to treat ovarian cancer after GOG-172, a randomized clinical trial comparing IP and intravenous chemotherapy (IV), demonstrated a 16-month survival advantage with IP. The aims of this study were to determine: (1) changes in IP utilization over time, (2) factors associated with adoption of IP therapy, and (3) the impact of IP on survival. **Methods:** Prospective cohort study of women with stage III, optimally-cytoreduced ovarian cancer treated at National Comprehensive Cancer Network (NCCN) institutions. Trends were evaluated in 823 patients between 2003-2012. In 603 patients, diagnosed after 2006, multivariable logistic regression and propensity-score analyses were used to examine factors associated with receipt of IP therapy and associations between treatment modality, adverse events, and overall survival. **Results:** IP utilization rose from 0% to 33% between 2003-2006, increased to 50% in 2007-2008, and decreased to 43% during 2009-2012. At treatment initiation 43% of patients received modified IP regimens, 29% received the GOG 172 regimen, and 28% received IP on a clinical trial. In adjusted analyses, younger age, fewer comorbid conditions, and clinical trial enrollment were associated with IP therapy (all P≤0.01). NCCN center was independently associated with receipt of IP; the adjusted proportion of patients receiving IP varied by site between 16% and 71% (P<0.001). After propensity-score weighted adjustment, patients receiving IP were more likely to switch to IV due to toxicity (AOR=2.01, 95% CI=1.30-3.12) compared with IV. Adjusted 5-year overall survival rates were 57% for IP vs. 44% for IV (hazard ratio=0.69, 95% CI=0.50-0.94). **Conclusions:** The use of IP therapy increased significantly over the past decade at NCCN centers. However, recently only a minority of eligible patients have received it. Despite frequent modifications, IP chemotherapy is associated with significantly improved survival in clinical practice. Future studies should examine whether site-specific variations in IP utilization reflect patients' informed treatment preferences.

**5577 General Poster Session (Board #359), Sat, 8:00 AM-11:45 AM**

**Identification of predictive factors of response to the BH3-mimetic molecule ABT-737: An ex vivo experiment in human serous ovarian carcinoma.** *Presenting Author: Stephanie Odile Lheureux, Centre de Lutte Contre le Cancer François Baclesse, Caen, France*

**Background:** Ovarian cancers are addicted to Bcl-$x_L$ and Mcl-1, anti-apoptotic members of the Bcl-2 family. Bcl-$x_L$ can be inhibited by the BH3-mimetic ABT-737. *In vitro*, ABT-737 can induce apoptosis of cancer cells, and its activity is potentiated by Mcl-1 inactivation. **Methods:** Here we assessed the sensitivity of human ovarian tumor nodes to ABT-737 when combined with carboplatin, which can indirectly inhibit Mcl-1. Fresh samples from 25 high-grade serous ovarian cancer (HGSOC) chemo-naïve patients who had undergone surgery were prospectively exposed *ex vivo* to ABT-737 alone or in combination with carboplatin. The treatment effect was studied on sliced tumor nodes by assessment of cleaved-caspase 3 immunostaining. We also studied the association between baseline Bcl-2 family protein expression (immunohistochemistry) and the response of nodes to treatment (NCT01440504). **Results:** ABT-737 induced massive apoptotic cell death as single agent but its efficacy was not improved by the addition of carboplatin. Bim was frequently expressed (20/25) and its absence or low expression was associated with the absence of response to ABT-737, p value = 0.019 by Fisher's test and sensitivity = 93%, (95% confidence interval, 66-100). Moreover, we observed that in tumors in which Bim was expressed, a low expression of Mcl-1 or phospho-ERK1/2 improved the proportion of responses. **Conclusions:** This pilot study showed that ABT-737 has promise as monotherapy for HGSOC in a specific subgroup of tumors. Bim, Mcl-1 and phospho-ERK1/2 appeared to be relevant biomarkers that could be used for the selection of patients in the design of clinical trials using navitoclax (an orally available compound related to ABT-737). Clinical trial information: NCT01440504.

**5578 General Poster Session (Board #360), Sat, 8:00 AM-11:45 AM**

**Molecular profiling in gynecologic cancer and matched targeted therapy: A step toward improving personalized medicine.** *Presenting Author: Ana C. Garrido-Castro, Vall d'Hebron University Hospital, Barcelona, Spain*

**Background:** In the wake of personalized medicine in Oncology, genetic tumor profiling has become a cornerstone to select patients (pts) for clinical trials, exploring new molecular targeted agents. **Methods:** As part of the Vall d'Hebron University Hospital Molecular Prescreening/Phase 1 Trials Program, advanced gynecologic cancer (GYNT) pts were screened for molecular alterations (MA) (KRAS/PIK3CA/AKT/BRAF mutations [mut]; PD-L1 expression; PTEN loss, H score<50) and allocated to receive matched targeted therapy (MTT). We present a summary of molecular characteristics and clinical outcomes, using previous treatment as reference to evaluate potential efficacy. **Results:** From 01/2012 to 11/2013, 86 consecutive GYNT pts (mean age: 53.3 yrs; median no. previous treatments: 3 [0-7]) were screened for MA; 60 (69.8%) ovarian (OvC), 18 (20.9%) endometrial (EC) and 8 (9.3%) cervical carcinomas (CC). Median time from diagnosis to molecular analysis was 2.96 yrs. MA were identified in 23 pts (26.7%) as specified in Table 1: 5 type-I/8 type-II OvC; 4 type-I/4 type-II EC; 2 CC. Fifteen pts received MTT according to MA. Six harbored PIK3CA mut; 5 were treated with $\alpha$-specific PI3K inh and 1 with PI3K/mTOR inh. Pts with KRAS mut (8) received MEK inh-based combinations: 6 MEK/PI3K inh, 1 MEK/AKT inh, 1 MEK/IGFR1 inh. A double-mutated pt (PIK3CA/KRAS mut) was treated with mTOR inh. Median PFS of the MTT population was 19.5 wks [CI95%: 10.7-NA], slightly superior to 17.0 wks [CI95%: 12.9-38.6] achieved with the immediately previous line of systemic therapy (p=0.121). **Conclusions:** Treatment based on MA may improve clinical outcome in heavily pre-treated GYNT, as results in this analysis were superior to standard therapy. Statistical significance was not reached, probably due to small sample size. Our work warrants further studies of MTT in larger less pre-treated population.

| | | GYNT (n, %) | | | | | |
|---|---|---|---|---|---|---|---|
| | | CC (8, 9.3) | | EC (18, 20.9) | | OvC (60, 69.8) | |
| | | ADK (2, 25) | SCC (6, 75) | Type I (7, 39) | Type II (11, 61) | Type I (13, 22) | Type II (47, 78) |
| PIK3CA (n) | AKT1 E17K | | 1 | | | | |
| | Q546K | | | 1 | | | |
| | E545K | | | | 1 | | 1 |
| | E542K | | | | | 1 | |
| | H1047R | | | | | 2 | 3 |
| | R88Q | | | 1* | | | |
| KRAS (n) | G12D | 1 | | 1 | 1 | 1 | 3 |
| | G12V | | | 1 | 1 | | |
| | G12S | | | | 1 | 1 | |
| | A59T | | | 1* | | | |
| PD-L1 (n) | | | | | | | 1 |
| PTEN loss (n, %) | | 0 (0) | | 9 (50) | | 16 (27) | |
| % MA per GYNT subtype | | 25 | | 100 | | 48.3 | |

*Double mut: 1 pt endometrioid EC.

**5579 General Poster Session (Board #361), Sat, 8:00 AM-11:45 AM**

**Expression III: Final results of an international survey in eight European countries with 1,830 patients—What are the differences in expectations from their doctors and therapy management of patients with primary and recurrent ovarian cancer? (NOGGO/ENGOT-ov4 study).** *Presenting Author: Gülten Oskay-Özcelik, NOGGO e.V., Berlin, Germany*

**Background:** The primary aim of this study was to investigate information needs and preferences among patients with ovarian cancer, in different European countries, focusing on patients with primary and recurrent ovarian cancer. **Methods:** A questionnaire was developed based on the experiences of "German-Expression II", and then provided to ovarian cancer patients via internet or print-version in 8 European countries (Austria, Belgium, France, Germany, Italy, Poland, Romania, Spain). Basic data and questions concerning the expectations and needs regarding their therapy management and doctor-patient communication were requested from the patient. **Results:** From December 2009 to October 2012, a total of 1,830 patients with ovarian cancer from 8 European countries participated in the survey, 902 patients with primary ovarian cancer and 731 with recurrent ovarian cancer. The median age was 58 years. Concerning the completeness and understandability of the explanations about the therapies from their doctors there was no significant difference in both groups. In contrast to patients with primary disease the recurrent patients measure the success of the therapy on the development of their CA 125. Recurrent patients attach more importance to know how long they must stay in the hospital and how many patients with their sickness are being treated for by their doctor. The three most important aspects for recurrent ovarian cancer patients to improve the therapy were: "therapy should be more effective," "therapy should not induce alopecia," "there must be more done to counter fatigue." **Conclusions:** This survey underlines the high need of ovarian cancer patients to discuss all details concerning treatment options and clinical management with only minor difference between the primary and recurrent ovarian cancer patients. It was also shown that more information about side effects of therapies and second opinion opportunities was needed.

**5580 General Poster Session (Board #362), Sat, 8:00 AM-11:45 AM**

**Phase II trial of oxaliplatin and 5-FU in patients (pts) with platinum-resistant recurrent (PRR) ovarian carcinoma (OVCA).** *Presenting Author: Joseph N. Kerger, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium*

**Background:** Based on clinical data and the partially non-cross-resistance of oxaliplatin with other platinum compounds, this phase II trial evaluated the safety and efficacy of a modified FOLFOX6 regimen in pts with PRR OVCA with a platinum-free interval of less than 6 months after any previous platinum-containing line of therapy. **Methods:** From 10/2008 till 08/2013, a total of 43 eligible pts with measurable (RECIST) and/or evaluable (CA125) disease were included in this study and received a median number of 8 courses (range: 1-14) of a modified FOLFOX6 regimen consisting in oxaliplatin 85 mg/m$^2$ d1, L-leucovorin 200 mg/m$^2$ d1 followed by a continuous iv infusion of 5-FU 2600 mg/m$^2$/48hrs every 2 weeks until disease progression or unacceptable toxicity. Pt characteristics: median age 57 years (range: 37-81), median PS 1 (0-2), serous histological subtype 60%, median number of previous lines 3 (1-12), prior exposure to carboplatin 100%, paclitaxel 98%, pegylated liposomal doxorubicin 63%, gemcitabine 23%, topotecan 23%, cyclophosphamide 14%, bevacizumab 9%. **Results:** Antitumor activity was seen in 35 cases with measurable disease: 1 CR + 15 PR, for an objective response rate of 46% (95%CI: 29-63%) and a median duration of response of 7.0 months (95%CI: 5.5-8.4 months); 13 SD (37%); 6 PD (17%). A clinical benefit rate (CR + PR + SD > 6 months) was observed in 21/43 (49%) pts (95% CI: 34-64%). Overall, the median time to progression was 5.8 months (95%CI: 4.9-6.5). Most side effects were moderate (G1&2): anemia in 88%, thrombocytopenia 67%, leucopenia 56%, neurological 81%, fatigue 72%, liver 51%, mucositis 41%, diarrhea 30%, renal 18%, hand-foot syndrome 9% of the pts. G3 toxicities included febrile neutropenia in 9%, neurological 9%, diarrhea 7%, mucosal 2% and liver toxicity 2% of the pts, leading to dose reductions in 13 pts (30%). Two hypersensitivity reactions to oxaliplatin also occurred. **Conclusions:** In this heavily pretreated patient population with PRR OVCA, this modified FOLFOX6 regimen exhibited a promising activity with an expected, but acceptable safety profile and might deserve further exploration, maybe in combination with biological or targeted agents. Clinical trial information: NCT01481701.

**5581 General Poster Session (Board #363), Sat, 8:00 AM-11:45 AM**

**Phase II clinical trial evaluating CRLX101 in recurrent ovarian, tubal, and peritoneal cancer.** *Presenting Author: Carolyn N. Krasner, Massachusetts General Hospital/Dana-Farber Harvard Cancer Center, Boston, MA*

**Background:** Ovarian cancer (Ov.Ca.) is the leading cause of death among gyn malignancies in the United States with over 20,000 new cases diagnosed in 2013. Limited treatment options exist for women whose tumors have progressed after 1st-line platinum-based therapy. Current approved therapy for relapsed Ov.Ca. includes the topo-1 inhibitor topotecan, which provides limited survival benefit and remains compromised by toxicity. CRLX101 is a novel cyclodextrin-containing polymer conjugate of camptothecin (CPT) that self-assembles into nanoparticles and delivers sustained CPT into cancer cells while reducing systemic exposure. *In vitro* and *in vivo*data suggest superior activity of CRLX101 compared to approved agents in Ov.Ca. models. The monotherapy MTD of 15 mg/m2 IV q. 2 wks. has now been administered to over 200 solid tumor pts (pts.) across 7 clinical trials. **Methods:** This phase 2 clinical trial evaluated CRLX101 in pts. with relapsed Ov.Ca. progressing after 1-3 prior regimens of chemotherapy, and included platinum refractory, resistant and sensitive pts. Pts. received CRLX101 every 14 days on 28-day cycles and underwent CT-based tumor evaluation every 2 cycles. The primary endpoint is progression free survival at 6 mos (PFS6) and secondary objectives include tumor response rate and safety. **Results:** Enrollment is this clinical trial is complete with 30 pts. having received 1-13 cycles of therapy and 5 pts. remaining on study. CRLX101 appears well tolerated with no drug-related SAEs, treatment discontinuations, or deaths observed. Related grade 3/4 AEs include G3 vasovagal reaction (n=1), G3 pneumonia (n=1), and G3 pulmonary embolism (n=1) . The primary efficacy endpoint has been met with mPFS of 161 days and 6 pts. achieving PFS $\geq$ 6 mos. Among 19 platinum resistant pts. with evaluable scans, 3 pts. (16%) achieved durable RECIST partial responses and 14 pts. (74%) achieved net tumor reductions. **Conclusions:** CRLX101 administered to pretreated pts. with relapsed Ov.Ca. appears safe, well tolerated, and effective. As CRLX101 appears to durably inhibit HIF-1$\alpha$ and demonstrates elsewhere notable synergy in combination with VEGF inhibiting agents, the drug is currently being evaluated in combination with bevacizumab. Clinical trial information: NCT01652079.

**5582 General Poster Session (Board #364), Sat, 8:00 AM-11:45 AM**

**Early-stage ovarian cancer: Clinical outcome and analysis of prognostic factors—Results from a prospective registry of GEICO (Spanish Group for Ovarian Cancer Research).** *Presenting Author: Belen Ojeda, GEICO and Hospital de la Santa Creu i Sant Pau, Department of Medical Oncology, Barcelona, Spain*

**Background:** Early stage ovarian cancer (ESOC) represents 10-15% of all Ovarian Cancer (OC) cases and the reported experience is limited. **Methods:** A centralized prospective register of ESOC (I-IIb) patients treated at GEICO centers was initiated on January 1998 and updated up to November 2013. Description of cases as well as correlation with Relapse Free Survival (RFS) and Disease Specific Survival (DSS) and an exploratory multivariate analysis was undertaken. **Results:** A total of 1179 cases with a median age of 48 (17-66) have been included: 983 (83.4%) Stages I, of which 369 (31.3%) were stage Ia, 49 (4,2%) stage Ib and 565 (47.9%) stage Ic, 169 (14,3%) were Stage II and 27 (2.3%) unknown. The most frequent histological type was Endometrioid (E) (n: 320, 27.1%), followed by Serous (S) (n: 297, 25.2%), Clear-cell carcinoma (CCC) (n: 244, 20.7%) and Mucinous (M) (n: 176, 14.9,%). Among E histology grade 1-2 vs grade 3 were present in 19.3% and 5.9% respectively while S grade 1 vs grade 2-3 were 5.9% and 15.2%. Surgical staging was categorized as complete surgery (22%), modified surgery (50%) and inadequate (28%). 1010 patients (88.3%) received adjuvant chemotherapy (ACT). With a median follow-up of 69 months (1-250), 16% of cases have relapsed and 8.1% were dead due to OC. Five-years RFS and DSS are 83% and 92% respectively. M and low grade E together have a 5-years RFS of 91% compared to other subtypes 79% (p<0.0001) and CCC a 5-years RFS 77%, compared to other subtypes RFS 85% (p<0.035). Prognostic factors including histology, histology and grade, stage and ACT were included in the multivariate analysis showing that stage (p=0.0001), low grade E (p=0.004) and ACT (p=0.005), remained of prognostic importance. **Conclusions:** In this large prospective cohort of ESOC, surgical staging remains inadequate in one fourth of cases according to current guidelines. E subtype is the most reported. Better prognosis is observed in low grade E, low stage and patients treated with ACT.

**5583 General Poster Session (Board #365), Sat, 8:00 AM-11:45 AM**

**Central pathology review of early-stage ovarian carcinoma: Description and correlation with follow-up—A study by the Spanish Group for Ovarian Cancer Research (GEICO).** *Presenting Author: Jose Antonio Lopez-Guerrero, Laboratory of Molecular Biology, Instituto Valenciano de Oncologia, Valencia, Spain*

**Background:** The reported experience with early-stage (FIGO stage I/IIB) ovarian carcinoma (ESOC) is limited. It represents 15% of all diagnosed cases and the impact on prognosis of their different histological subtypes has not been clearly defined. The aim of this study is to analyze the frequency of ESOC histologies and their correlation with follow-up. **Methods:** A centralized pathological review of ESOC was performed from samples belonging to the GEICO ESOC Registry, which includes 1179 patients. A total of 573 samples from 24 Spanish Hospitals were collected, stained with H&E and reviewed by two pathologists. Final diagnosis was achieved by consensus and compared with diagnosis of origin (DO). Histological classification was performed according to WHO criteria, except for serous subtype classified with 2-tier grading system (Malpica et al. Am J Surg Pathol 2004; 28:496-594). **Results:** Thirty-four cases (6%) were excluded after revision. The remaining 539 were classified as following: 130 (24%) high-grade serous (HGS), 24 (4%) low-grade serous (LGS), 45 (8%) high-grade endometrioid (HGE), 96 (18%) low-grade endometrioid (LGE), 75 (14%) mucinous (MUC), 134 (25%) clear cell carcinoma (CCC), 35 (6.6%) mixed (Mix) and 2 (0.4%) undifferentiated (U). Concordance with DO was of 76% (Kappa=0.495; p<0.0001), discrepancies being more frequent for Mix and U histologies. Median follow-up was 74 months (range: 0-250) and 105 (18%) recurrences were reported. The univariate analysis showed a 5-years recurrence free survival (RFS) of 70% for HGS vs 83% of other histologies (p=0.008); a 74% for CCC vs. 82% (p=0.06); and a 89% for LGE vs. 78% (p=0.021). The multivariate analysis showed that higher stage [HR= 3 (1.6-5.7); p=0.001], HGS [HR= 2 (1.2-3.3); p=0.005] and CCC [HR= 2.1 (1.3-3.4); p=0.003] constituted independent factors of poor prognosis. **Conclusions:** Frequency of histological subtypes in ESOC differs from advanced stages. HGS and CCC histological subtypes constitute independent poor prognostic factors in ESOC. The series herein reported could provide the basis for exploring molecular profiles in order to design specific clinical trials in ESOC.

**5584 General Poster Session (Board #366), Sat, 8:00 AM-11:45 AM**

**Autoantibodies (AA) against the EGF/EGFR and VEGFA/VEGFR1 as prognosticator in epithelial ovarian cancer (EOC) patients.** *Presenting Author: Elena Ioana Braicu, Charité Medical University, Berlin, Germany*

**Background:** Angiogenesis plays a major role in EOC. Anti-angiogenic therapy prolongs progression free survival in both primary and recurrent EOC, but no predictive biomarkers are currently known. **Methods:** In this study 132 healthy women and 201 primary EOC patients were enrolled. Most of the EOC patients had a FIGO IIIc (66%) and high grade serous ovarian cancer (96.4%). All EOC patients were treated with primary tumor debulking and platinum based chemotherapy. Mean follow up period was 62 months (range 19-149). Autoantibodies (AA) against epidermal growth factor (AA-EGF), epidermal growth factor receptor (AA-EGFR), vascular growth factor A (AA-VEGFA) and against vascular growth factor receptor 1 (AA-VEGFR1) were detected in preoperative serum samples using ELISA. **Results:** AA-EGF, AA-EGFR and AA-VEGFA, AA-VEGFR1 were detected in both control and EOC patients. AA concentrations were significantly lower in EOC (p<0.001). In the multivariate analysis AA-EGF, AA-EGFR, AA-VEGFA,AA-VEGFR1 were a significant predictor for mortality (p=0.001, 95%CI=0.12-0.154; p<0.001, 95%CI=0.0.047-0.83; p=0.001, 95%CI=0.118-0.173; p=0.001, 95%CI=0.125-0.167, respectively) and the combined endpoint (mortality or relapse) (p=0.001, 95% CI=-0.094-0.114; p=0.001, 95%CI=0.07-0.123; p=0.001, 95% CI=-0.093-0.028; p<0.01, 95%CI=-0.08-0.057). **Conclusions:** This is the first study that attests the existence of AA against EGF, EGFR and VEGFA, VEGFR1. AAs seem to have a protective role for the development of ovarian cancer. Furthermore higher AAs levels were associated with longer progression free and overall survival in EOC patients.

**5585 General Poster Session (Board #367), Sat, 8:00 AM-11:45 AM**

**Pharmacodynamic biomarkers from phase II study of the SMAC (Second Mitochondrial-Derived Activator of Caspases)-mimetic birinapant (TL32711; NSC 756502) in relapsed platinum-resistant epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC) (NCT01681368).** *Presenting Author: Kristen Paige Bunch, Women's Malignancies Branch, Center for Cancer Research, Bethesda, MD*

**Background:** Inhibitor of apoptosis (IAP) proteins prevent apoptosis in part by inhibiting caspases. IAPs also activate pro-survival NFkB signaling. SMAC is their endogenous inhibitor. Cancers, long known to avoid apoptosis, show IAP gene amplification and protein over-expression, or SMAC gene deletion and reduced protein. Birinapant (B) is a first in class bivalent peptidomimetic of SMAC. B mimics SMAC's modulation of IAPs including cIAP1, cIAP2, XIAP and ML-IAP. In preclinical models B depleted cIAP1, activated caspase 3 and inhibited growth of tumor cells. **Methods:** Phase II CTEP-sponsored single agent study of B in relapsed EOC, PPC or FTC. Patients received B 47mg/m$^2$ IV on days 1, 8 and 15 of a 28-day cycle. Percutaneous tumor biopsy was performed prior to cycle 1, and repeated on cycle 2 day 15. Plasma and PBMC were collected for additional research studies. **Results:** We collected pre-treatment biopsies on 11 patients, and paired on-treatment biopsies on 7 patients. Four cores were harvested at each timepoint; two cores were flash-frozen and two were fixed in formalin and embedded in paraffin. Correlative studies verified on-target activity of B and developed biomarkers of drug effect: Clinical trial information: NCT01681368. **Conclusions:** Birinapant is a promising novel therapeutic with clear evidence of IAP suppression in vivo. The biomarkers developed in this study will be incorporated into future clinical trials in order to better understand mechanisms of response and resistance to apoptosis-inducing therapies.

| Sample type | Number collected | Analysis | Markers |
|---|---|---|---|
| **Frozen tumor** | 11 pre, 7 on B | Simple western | cIAP1, cIAP2, caspase 3, caspase 8, PARP, NFkB-p65, NFkB-p100/p52, IkBa, cFLIP, RIP |
| | | Drug levels | -- |
| **Fixed tumor** | 11 pre, 7 on B | IHC | TNF, TRAIL, CD3, CD19, CD56, CD68 |
| **Plasma** | 11 (x6) cycle 1 PK | Drug levels | -- |
| **Plasma** | 11 (x2) pre/on B | Cytokines | TNF, TRAIL, IL-6, IL-8 |
| **PBMC** | 11 pre, 8 on B | Simple western | cIAP1, cIAP2, caspase 3, caspase 8, PARP, NFkB-p65, NFkB-p100/p52, IkBa, cFLIP, RIP |
| **Whole blood** | 11 pre, 9 on B | T, B, NK cell counts | CD3, CD4, CD8, CD19, CD56, CD16 |

**5586 General Poster Session (Board #368), Sat, 8:00 AM-11:45 AM**

**Current practice and use of neoadjuvant therapy in ovarian cancer in the National Cancer Database.** *Presenting Author: Angela Jain, Fox Chase Cancer Center, Philadelphia, PA*

**Background:** Most ovarian cancer (OC) patients can expect significant tumor cytoreduction with platinum based therapy, but unfortunately no better than a 10-20% chance of cure. A previous study demonstrated that neoadjuvant chemotherapy (NAC) was not inferior to primary surgery followed by chemotherapy, and survival depended on the ability to resect all macroscopic disease. This is a retrospective study using the National Cancer Database (NCDB) to understand national trends in using NAC in OC. **Methods:** We identified women with advanced stage OC diagnosed between 1998 and 2011 and treated with chemotherapy and surgery using the NCDB. Using Chi-squared tests and multivariate logistic regression, we analyzed rates of NAC by age, facility type, race, payor status, income, location, Charlson score, year of diagnosis and facility location. Due to data availability, survival analysis was restricted to patients diagnosed between 2003 and 2005. We used Kaplan-Meier curves and proportional hazards regression to assess overall survival in patients treated with neoadjuvant vs adjuvant chemotherapy. **Results:** Among the 58,048 patients, on multivariate analysis, women were more likely to receive NAC if they were older ($<50$, $>70$ years vs. 50-70 years, OR=0.61, 1.16, $p<0.0001$, respectively), have Medicaid or Medicare vs Private insurance (OR= 1.71, 1.21 respectively, $p<0.0001$), or had a Charlson score $\geq 1$ (OR=1.19, $P<0.0001$). Race and rural/urban location were not associated with differences in therapy type in multivariate analysis. Use of NAC increased from 8.94% of patients in 1998 to 26.72% of patients in 2011 ($p<0.0001$). In the survival cohort (12,554 patients) median survival was 30.7 months vs 41.1 months for neoadjvant vs adjuvant patients ($P<0.0001$), and this difference remained on adjusted analysis (HR 1.31, $p<.0001$). **Conclusions:** The use of neo-adjuvant chemotherapy in OC has increased over time. Although we found significantly lower survival among patients given neoadjuvant therapy, this result is limited by potential selection bias. We found that patients treated with neoadjuvant therapy also had risk factors such as increased co-morbidities, coverage by Medicaid, and older age.

**5587 General Poster Session (Board #369), Sat, 8:00 AM-11:45 AM**

**Patterns of care and overall survival in the Medicare ovarian cancer population.** *Presenting Author: Larissa Meyer, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Tumor reductive surgery and combination chemotherapy is the standard of care for advanced ovarian cancer. Comorbid conditions and poor performance status can affect treatment options. Population level outcomes data in the geriatric population is lacking for women with ovarian cancer. The objective of this study is to characterize the patterns of care and overall survival in women over the age of 65 with epithelial ovarian cancer. **Methods:** Using the SEER-Medicare database, a cohort of patients who died of epithelial ovarian cancer between 2002-2009 was identified. All patients had pathologic confirmation of disease to be included in the cohort. Charlson comorbidity score was used to estimate health status. Kaplan-Meier analysis, Chi-square and ANOVA test were utilized. **Results:** A total of 4,672 women were included in the analysis and stratified into 4 groups based on previous therapy: No chemotherapy or surgery (NoCS), surgery only (S), chemotherapy only (C) or surgery and chemotherapy (CS). Mean age for the groups were 81 years (NoCS), 79 years (S), 78 years (C) and 74 years (CS). 1026 women (22%) received no treatment for their ovarian cancer (NoCS). 627 women (13.4%) underwent surgery but no chemotherapy. 988 women (21%) received chemotherapy but never underwent surgery. 2,031 women (44%) of the cohort underwent surgery and chemotherapy. 9.6% of women in the (CS) group had a comorbidity index of $> 2$ compared to 21% (C) group, 18% (S) group and 23% of the (NoCS) group ($p<0.0001$). There was a significant difference in survival between the groups with median survival time of 1.2 months for women who received no treatment, 1.8 months for surgery alone, 7.9 months for chemotherapy alone, and 21.2 months for patients who underwent the standard of care treatment of surgery and chemotherapy ($p<0.05$). **Conclusions:** Over half of patients over 65 do not or are not able to receive optimal therapy for epithelial ovarian cancer. Younger age and lower Charlson comorbidity index are associated with ability to undergo surgery and chemotherapy. This subset of patients is able to reach a significantly improved median survival time of 21 months compared to $<2$ months for patients who do not receive chemotherapy.

**5588 General Poster Session (Board #370), Sat, 8:00 AM-11:45 AM**

**Primary versus interval debulking surgery and the risk to induce platinum resitance.** *Presenting Author: Alexandre Andre Balieiro Anastacio da Costa, Hospital A.C. Camargo, São Paulo, Brazil*

**Background:** Interval debulking surgery (IDS) is an option to treat patients with stage IIIC and IV ovarian carcinoma. Two randomized trials have shown similar survival for primary debulking sugery (PDS) and IDS. One of the concerns with IDS is the potentialy higher risk to induce platinum resistance when treating patients with larger disease volume. At least one retrospective analysis sugest that patients treated with IDS have a higher risk to develop platinum resistance at second relapse. **Methods:** We did a retroscpective review of medical records from 213 patients with stage IIIC and IV ovarian carcinoma treated at a single institution from 2000 to 2013. We analysed the association of baseline clinical and pathological characteristics with time to first platinum resistant relapse (TTPR), platinum resitant disease at first relapse, defined as a platinum free interval (PFI) after first line chemotherapy less than 6 months, and overall response rate (ORR) to chemotherapy at first platinum sensitive relapse. **Results:** For a median follow-up time of 58.6 months, the overall survival was 45.2 months and progression free survival was 18.3 months. Factors related to a shorter TTPR in univariate analysis were residual disease (RD) $>$ 10mm after surgery, CA 125$>$150 before first treatment (chemotheray or surgery) and IDS compared to PDS. In the multivariate cox regression model including these three variables and age and stage (IIIC vs IV), RD$>$10mm (HR 1.87, CI95% 1.37-2.44, $p<0.001$) CA 125$>$150 (HR 3.39, CI95% 1.31-8.81, $p=0.012$) and IDS (HR 1.79, CI95% 1.02-3.18, $p=0.043$) remained associated to a shorter TTPR. The only factor associated to a greater risk of a PFI$<$6 months at first relapse was RD$>$10mm (OR 1.59, CI95% 1.14-2.20, $p=0.005$) and the only factor associated to a worse ORR to chemotherapy at first platinum sensitive relapse was IDS (OR 4.32, CI95% 1.15-16.15, $p=0.030$. **Conclusions:** IDS may be associated to a greater risk of platinum resistance induction. Some of the bias in choosing PDS or IDS may not have been accounted in this analysis due to its the retrospective nature, but it supports the hypotesis of other papers and suggests that it would be interesting to see this analysis done in patients from PDS vs IDS clincal trials already published.

**5589 General Poster Session (Board #371), Sat, 8:00 AM-11:45 AM**

**Laparoscopic versus laparotomic cytoreduction in patients with advanced ovarian cancer submitted to NACT: Evaluation of oncologic safety.** *Presenting Author: Giovanni Favero, Department of Gynecology - Instituto do Câncer do Estado de São Paulo - ICESP Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil*

**Background:** Surgery represents the cornerstone in the treatment of advanced ovarian cancer (AOC). In contrast to other gynecological cancers, the use of laparoscopy in AOC is presently considered the ultimate frontier for the method. However, modern technology couple with skilled laparoscopic surgeons afforded performance of diverse oncologic procedures. In parallel, neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (DS) is an alternative for patients with AOC unresectable disease. In selected cases, complete endoscopic DS may be technically possible and considered an alternative to laparotomy. The current paucity of prospective trials addressing the use of laparoscopy in AOC after NACT motived us to investigate the oncologic safety of the method. **Methods:** Prospective pilot study with patients with initially unresectable advanced high-grade serous ovarian carcinoma (Stages IIIc or IVa) treated with six cycles of Carboplatin and Paclitaxel followed by DS between 2011 and 2014. Major inclusion criteria were: clinical complete response, normalization of the CA-125, absence of disease in critical areas according to radiology after NACT and optimal debulking surgery. Patients were randomized into laparoscopic versus laparotomic cytoreduction. **Results:** Twenty-one patients were included in the study; 10 patients in the laparoscopic group and 11 in the laparotomic group. The epidemiologic and oncologic features of the groups were not different. Median age was 58 years (45–78) and BMI was 29 Kg/m$^2$ (21 – 40). Complete resection of all macroscopic and microscopic disease (R0) in both groups was achieved in 100%. Surgical morbidity were equally uncommon; 2 patients needed a second procedure due to complications. Over a median follow-up period of 24.2 (15 – 36) months, 80% of the patients in the laparoscopic group and 88% in the open surgery group recurred (CI not reached). Nevertheless, the mean chemotherapy- free interval was significantly inferior in the laparoscopic group; 8,3 versus 15,3 months, respectively *(p – 0,02).* **Conclusions:** Laparoscopic cytoreduction seems to be not oncologically safe in patients with AOC submitted to NACT.

**5590 General Poster Session (Board #372), Sat, 8:00 AM-11:45 AM**

**Randomized phase II trial comparing IG-001 versus paclitaxel against first-line advanced ovarian cancer.** *Presenting Author: Vuong N. Trieu, Sorrento Therapeutics, Irvine, CA*

**Background:** IG-001 is a Cremophor-free, non-biologic, nanoparticle formulation of paclitaxel. Preclinical in vivo studies with IG-001 demonstrated a 3-fold increase in the MTD and a significantly increased antitumor efficacy over paclitaxel in multidrug-resistant human xenograft models. IG-001 has shown consistently positive response in Phase I/II clinical trials across five major cancer types: lung, breast, ovarian, pancreatic, and bladder cancers. The lack of effective therapy for chemoresistant patients with primary advanced epithelial ovarian cancer (EOC) underscores the need for new approaches to this disease. This study compared the response of IG-001 vs. paclitaxel in patients with primary advanced EOC. **Methods:** Preclinical efficacy of IG-001 vs. paclitaxel at equitoxic dose level was investigated in the paclitaxel resistant SKOV-3 xenograft model. Tumor bearing mice (n = 10/group) were treated i.v. with saline or equitoxic dose of paclitaxel (20 mg/kg) or IG-001 (60 mg/kg) on days 0, 4 and 8 (q3dx3). The safety and clinical efficacy of IG-001 vs. paclitaxel against EOC was evaluated in a Phase 1 (n = 18) and Phase II (n = 98) study. For the Phase I trial, six patients/dose level were treated with IG-001 at 220, 260, and 300 mg/m$^2$. Phase II trial was a randomized, two-arm trial for advanced EOC (Experimental Arm: n = 50, IG-001 [260 mg/m$^2$ IV] + Carboplatin [5 AUC IV 3 weeks, 6 cycles]; Control Arm: n = 48; paclitaxel [175 mg/m2 IV] + Carboplatin [AUC IV 3 weeks, 6 cycles]). **Results:** In the paclitaxel-resistant human SKOV-3 ovarian tumors, IG-001 was more effective than paclitaxel (p = 0.002, ANOVA). Though we did not reach MTD during our phase I study, 260 mg/m$^2$was designated as the dose level for the phase II study. IG-001 + Carbo vs. paclitaxel + Carbo in patients with EOC demonstrated significant overall response rate (P = 0.017, Chi-square test) after 6 cycles/patient with 46% and 26% achieving complete response, respectively. **Conclusions:** IG-001 was found to be effective against EOC in preclinical and clinical studies. IG-001/Carboplatin combination chemotherapy was well-tolerated in women with advanced EOC and produced a doubling of overall response rates relative to those obtained with paclitaxel/Carboplatin-containing regimen. Clinical trial information: NCT01276548.

**5591 General Poster Session (Board #373), Sat, 8:00 AM-11:45 AM**

**The impact of tumor molecular profile-directed treatment on survival in recurrent ovarian cancer.** *Presenting Author: Kate Eleanor Oliver, Walter Reed National Military Medical Center, Bethesda, MD*

**Background:** We sought to determine whether tumor molecular profile-directed treatment of recurrent ovarian, primary peritoneal and fallopian tube carcinomas influenced survival. **Methods:** With IRB approval, Caris Life Sciences, Ltd maintains the Caris Registry, a database of clinicopathologic and outcome variables from consenting patients whose tumors underwent molecular profiling. Molecular profiling was performed using a multiplatform approach to stratify agents by degree of potential therapeutic benefit. The Caris Registry was queried for all patients with a diagnosis of ovarian, primary peritoneal and fallopian tube carcinomas enrolled between 2010 and 2014. Patients were stratified based on chemotherapeutic agents employed during their disease course: the molecularly-guided (MG) cohort received at least one agent designated to be of potential benefit and no agents with potential lack of benefit while the non-molecularly-guided cohort (non-MG) received at least one agent with potential lack of benefit. Survival was calculated from the date of profiling and from the date of diagnosis to the date of death/censoring using the Kaplan-Meier method. **Results:** Of 445 patients identified in the registry, 90 were excluded due to non-invasive pathology, non-epithelial histology, and missing or ambiguous treatment information. Of the remaining 355 eligible and evaluable patients, 166 formed the MG cohort and the remaining 189 were assigned to the non-MG cohort. There were no significant differences in baseline clinicopathologic characteristics between the two groups. Patients in the MG cohort experienced significantly longer post-profiling survival when compared with patients in the non-MG cohort, HR 0.64 (CI 0.41 – 0.97, p = 0.03). Additionally, there was a trend toward longer overall survival in the MG cohort. **Conclusions:** Tumor molecular profile-directed treatment significantly improves post-profiling survival in patients with recurrent ovarian, primary peritoneal and fallopian tube carcinomas. Despite immature outcome data, trends toward improved overall survival were also demonstrated.

**5592 General Poster Session (Board #374), Sat, 8:00 AM-11:45 AM**

**A phase II study of medroxyprogesterone acetate plus metformin as fertility-sparing treatment for atypical endometrial hyperplasia and endometrial cancer.** *Presenting Author: Akira Mitsuhashi, Departments of Reproductive Medicine, Graduate School of Medicine, Chiba University, Chiba, Japan*

**Background:** Metformin, a drug widely used in the treatment of type 2 diabetes mellitus, has been shown to reduce the risk of cancer and relapse after treatment. To determine whether the concomitant use of metformin prevents recurrence after progestin therapy, we conducted a phase II study of medroxyprogesterone acetate (MPA) plus metformin as fertility-sparing treatment for atypical endometrial hyperplasia and endometrial cancer. **Methods:** Patients with endometrial cancer or atypical endometrial hyperplasia were treated with MPA (400 mg/day) and metformin (750 mg up to 2250 mg/day) for 24 weeks. In cases of partial histological regression but remarkable hormonal effects (partial response, PR), treatment was continued for another 12 weeks. Metformin was administered until conception, even after MPA was discontinued. The primary endpoint was the relapse rate after remission, and the secondary endpoints were the overall response rate and safety profile. An independent data and safety monitoring committee performed an interim analysis of efficacy and safety at 12 months after the completion of enrollment. **Results:** From July 2009 to December 2012, 36 patients (17 with endometrial cancer and 19 with atypical endometrial hyperplasia) were enrolled. Most patients were obese and had insulin resistance; the mean body mass index was ≥25 in 28 patients (mean, 31 kg/m$^2$; range, 19–51 kg/m$^2$) and the homeostasis model assessment for insulin resistance index was ≥2.5 in 25 patients (mean, 4.8; range, 0.7–21). One patient showed progression at 12 weeks (2.8%). At 36 weeks, 31 patients (86.1%) had achieved complete response (CR) and the remaining 4 (11.1%) had achieved PR. During a median follow-up period of 34 months (range, 12–54 months), relapse was confirmed in 2 of the 31 patients who had achieved CR, resulting in a relapse rate of 6.4% compared to a previously reported rate of 30-50% without metformin. The 3-year estimated relapse-free survival rate was 93%. None of the patients experienced severe toxicity. **Conclusions:** The use of metformin inhibited disease relapse after progestin therapy. Clinical trial information: UMIN 000002210.

**5593 General Poster Session (Board #375), Sat, 8:00 AM-11:45 AM**

**Phase 2 clinical trial of ixabepilone in metastatic cervical carcinoma.** *Presenting Author: Mauricio Emmanuel Burotto Pichun, National Cancer Institute at the National Institutes of Health, Bethesda, MD*

**Background:** Ixabepilone is a microtubule-stabilizing agent approved for metastatic breast cancer. Preclinical data indicates activity in taxane-sensitive and resistant cells. Metastatic cervical carcinoma (mCC) has a poor prognosis and no accepted second line therapies. This study assessed the efficacy and safety of Ixabepilone in previously treated mCC. **Methods:** Patients with histologically confirmed mCC and at least one prior regimen received ixabepilone [6mg/m$^2$/d X 5d] every 21 days. Primary endpoint was PFS by RECIST. Secondary endpoints were response rate, overall survival, and safety. We calculated the rate of tumor growth (g) as an additional efficacy measure. **Results:** Forty-one patients were enrolled; thirty four tumors were squamous. The median number of prior therapies was 2 (range1-6). Four patients (9.7%) had partial responses. Median time to progression in months was 2.3 for all, 3.84 for taxane-naive and 2.03 for taxane pre-treated patients ($p=0.13$). Consistent with this we found the rate of growth (g) in taxane-naive patients (0.0035/day) to be two-thirds the rate in taxane pre-treated patients (0.0053/day). Median overall survival (OS) was 5.84 months. Thirty-two patients discontinued treatment due to progression, two because of death, two for toxicity, and five for other reasons. The most frequent toxicities included vomiting (43%), sensory neuropathy (21%), and fatigue (60%). G3/4 toxicities were noted in 53% patients; all resolved without interventions **Conclusions:** Ixabepilone was well tolerated but showed very modest activity in second or higher line mCC. A trend to worse outcomes and a faster rate of growth was observed in taxane-pre-treated patients compared to taxane-naive patients. New strategies are needed for refractory mCC. Clinical trial information: NCT00924066.

**5594 General Poster Session (Board #376), Sat, 8:00 AM-11:45 AM**

**Phase II evaluation of dalantercept, a soluble recombinant activin receptor-like kinase 1 (ALK1) receptor-fusion protein, for treatment of recurrent/persistent endometrial cancer: GOG-0229N.** *Presenting Author: Vicky Makker, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Angiogenesis has a role in endometrial cancer (EC) progression and prognosis. Single agent bevacizumab had a response rate (RR) of 13% and 6 month progression-free survival of 40% in recurrent EC with 1-2 prior cytotoxics. ALK1 is selectively expressed on activated endothelial cells unlike constitutively expressed VEGFR2. ALK1 pathway is essential for vascular morphogenesis and the formation of functional capillary networks in developing vasculature. EC vasculature has variable ALK1 expression. Dalantercept (Dal), a first-in-class ALK1 receptor fusion protein, binds to BMP9/BMP10 and prevents ALK1 pathway activation. **Methods:** A 2-stage design was used to estimate number of pts with persistent/recurrent EC who survived progression-free without receiving non-protocol therapy (TPFS) for at least 6 mos and number of pts who had objective tumor response (ORR) and determine toxicity of Dal 1.2 mg/kg SC Q3W. Recurrent/persistent epithelial EC, measurable disease, and 1- 2 prior chemotherapy lines were required. Biologic adjuvant therapy was permitted. **Results:** 28 pts ages 47-79 years were enrolled. G1/2 Endometrioid (n=9, 32%) and serous (n=15, 54%) tumors were most common. 82% of pts had 1 prior regimen. Pts received 1-12 cycles of Dal; 13 pts (46%) received $\leq$2 cycles. Most common adverse events (AE) regardless of attribution were fatigue, anemia, constipation, and limb edema. Grade (G) 3 and 4 AEs occurred in 39% and 4% of pts. There was 1 G 5 AE possibly Dal associated: gastric hemorrhage in pt with history of radiation fibrosis/small bowel obstruction. All pts are off study treatment: 24 for disease progression (PD), 1 consent withdrawal, 2 for toxicity, 1 for death. By RECIST 1.1: ORR was 0%; stable disease 57%, PD 39%, and indeterminate 4%. 11% of pts had TPFS $>$ 6 mos; median PFS 2.1 mos (90% CI: 1.4-3.2) and median OS 9.4 mos (90% CI: 8.9-11.7). **Conclusions:** Dal has insufficient single agent activity in recurrent EC to warrant further investigation at this dose/schedule. Studies of IHC expression of VEGF, FGF, PDGF, TGF-$\beta$, ALK1, CD105, ALK1 gene expression, plasma concentration of VEGF, BMP9, BMP10, and ALK1 via ELISA are ongoing. Clinical trial information: NCT01642082.

**5595 General Poster Session (Board #377), Sat, 8:00 AM-11:45 AM**

**A cohort study of gastric-type adenocarcinoma (GAS) of the uterine cervix: Multi-institutional study by Gynecologic Cancer Study Group of the Japan Clinical Oncology Group (JCOG).** *Presenting Author: Shin Nishio, Kurume University School of Medicine, Kurume, Japan*

**Background:** GAS is a novel variant of mucinous adenocarcinoma of the uterine cervix. A Japanese group reported that GAS represents more aggressive disease compared with usual-type endocervical adenocarcinoma (UEA), possibly due to chemoresistancy (ASCO 2013). However, the conclusion remains to be confirmed by larger series. **Methods:** Patients were enrolled at the Gynecologic Cancer Study Group of the JCOG after receiving approval from Institutional Review Board. The study group comprised women with stage I to II disease who underwent surgery without receiving neoadjuvant chemotherapy between 2000 and 2009. The study variables included the incidence of GAS as evaluated by central pathological review (CPR) and the diffences in clinicopathologic features between GAS and UEA. In addition, outcomes of patients with each type were statistically compared. **Results:** Among 393 cases of endocervical adenocarcinoma enrolled, 328 cases met the CPR and eligibility criteria for further analysis. A total of 95 of 328 (28.9%) tumors were re-classified as GAS. As compared with UEA, GAS was more significantly associated with a bulky mass, deep stromal invasion, lymph vascular space invasion, parametrial invasion, ovarian metastasis, positive ascitic fluid cytology, pelvic lymph node metastasis, and pathological (p) T stage, but was not related to the degree of histological differentiation. Disease-free survival ($p<0.0001$) and overall survival ($p<0.0001$) were poorer in patients with GAS than in those with UEA. When the data were analyzed according to disease stage, patients with a diagnosis of pTIA-IB1 adenocarcinoma had poorer outcomes ($p<0.0001$), but the difference in outcomes as compared with patients who had pTIB2 or more advanced disease was not significant. **Conclusions:** GAS is significantly associated with histopathologic predictors of poor outcomes as well as with poorer survival outcomes, and therefore is considered to be distinct entity which should be distinguished from UEA. Clinical trial information:UMIN000007987

**5596 General Poster Session (Board #378), Sat, 8:00 AM-11:45 AM**

**Obesity and robotic surgery: Associated ventilator indices and perioperative pulmonary complications.** *Presenting Author: Weiya Zhang Wysham, University of North Carolina, Chapel Hill, NC*

**Background:** Robotic surgery has been shown to be feasible in obese patients. However, there remains concern about the safety of robotic surgery in obese women who need gynecologic surgery, as the positioning required for pelvic surgery can exacerbate obesity-related changes in respiratory physiology. Our objective was to evaluate success and complication rates in obese women undergoing robotic gynecologic surgery and to assess variables that may be associated with complications. **Methods:** A retrospective chart review was performed on 1,035 obese patients who underwent robotic gynecologic surgery at two academic institutions between 2006 and 2012. Primary outcome was pulmonary complications. Secondary outcome was all-cause complications. Univariate logistic regression analysis was used to determine associations between patient baseline variables (age, BMI), operative variables (case length, trendelenburg time), ventilator parameters (tidal volume, peak inspiratory pressure) and complications (pulmonary, cardiac, other). **Results:** 146 patients (14%) had any complication. Only 33 patients (3%) had a pulmonary complication. Mean BMI was 39. Only increasing age was associated with a higher rate of pulmonary complications ($p=0.03$). None of the other patient variables including BMI, operative variables, or ventilator parameters were associated with pulmonary complications. Both age and longer case time were associated with a higher rate of all-cause complications ($p<0.0005$ and $p=0.0028$ respectively). **Conclusions:** The vast majority of obese patients can successfully tolerate robotic gynecologic surgery, and have overall low complications rates and even lower rates of pulmonary complications. Obesity was not predictive of robotic surgery tolerance or complications and can be safely undertaken in obese and even morbidly obese patients without significant complications.

**5597 General Poster Session (Board #379), Sat, 8:00 AM-11:45 AM**

**Pelvic sentinel lymph node status and risk of aortic nodal metastasis in patients with endometrial cancer.** *Presenting Author: Robert W. Holloway, Florida Hospital Cancer Institute, Orlando, FL*

**Background:** Pelvic sentinel lymph node (SLN) mapping is hypothesized to improve the accuracy of surgical staging. The clinical relevance of isolated tumor cell (ITC) metastasis compared to H&E micro- or macro-metastases in pelvic SLN are unknown. The purpose of this study was to evaluate aortic nodal status (infra-renal [IR] or infra-mesenteric IM]) in relation to pelvic SLN in patients with clinical stage I endometrial cancer (EC). **Methods:** 80 patients with EC underwent robotic-assisted laparoscopic hysterectomy and pelvic SLN mapping (isosulfan blue and/or indocyanine green with near-infrared imaging) from 4/11-8/13. A systematic pelvic and aortic lymphadenectomy to the left renal vein was performed and data were gathered prospectively. SLN were ultra-sectioned and evaluated with both H&E and IHC stains. The dataset was examined for peri-operative and clinico-pathologic factors including presence and type of lymph node (LN) metastasis (ITC vs. H&E). The disease status of pelvic SLN was compared to aortic nodal status. **Results:** Mean age was 65.9±12.0 yr, BMI 33.8±8.4 kg/m$^2$, height 65.3±10.6 inches, operative time 178±33 min, and length of hospital stay 1.4±1.1 days. Histologies included: endometrioid G1 (18.8%), G2 (45%), G3 (12.5%), and type II cancers (23.8%). Mean depth of invasion (DOI) was 43.1±30.4% (39% cases >50% DOI) and lymphovascular space invasion was present in 46.3% of cases. Mean pelvic and aortic LN yields were 26.6±16.4 and 12.7±6.4, respectively. 34 (42.5%) patients had pelvic LN metastasis with 33 having (+) SLN [7 (21.2%) ITC vs. 26 (81.8%) H&E]. 15/80 (18.8%) patients had aortic LN metastasis [2 IR, 8 IR+IM, and 5 IM] and all cases had (+) SLN. 15/33 (45.5%) patients with SLN metastasis had aortic metastasis. The risk of aortic metastasis with ITC-SLN was 2/7 (28.6%) vs. 13/26 (50%) for micro- plus macro-metastasis SLN. There were no cases with isolated infra-renal or infra-mesenteric LN metastasis. **Conclusions:** These findings suggest that SLN metastasis whether identified by IHC isolated tumor cells or H&E pose a significant risk for aortic LN metastasis. The phenomenon of "isolated infra-renal metastasis" in EC appears uncommon with pelvic SLN mapping.

**5598 General Poster Session (Board #380), Sat, 8:00 AM-11:45 AM**

**Systemic chemotherapy compared with radiation therapy as adjuvant therapy after radical surgery in high-risk stage IB-IIB cervical adenocarcinoma.** *Presenting Author: Toshiyuki Seki, Jikei University School of Medicine, Tokyo, Japan*

**Background:** Radiation therapy (RT) and concurrent chemo-radiation therapy (CCRT) are commonly used adjuvant therapies for FIGO stage IB-IIB cervical cancer patients regardless of their histological subtypes. However, given that patients with adeno/adenosquamous carcinoma (AC) reportedly have poorer prognosis compared to patients with squamous cell carcinoma (SCC), a more effective adjuvant therapy targeting AC patients should be investigated. Hence, we conducted this study to evaluate the efficacy of systemic chemotherapy (CT) to AC patients compared with RT/CCRT. **Methods:** The medical records of the patients with IB-IIB cervical cancer who underwent primary surgery at our 4 institutes from January 2001 to December 2010 were retrospectively reviewed, and the patients with pathologically confirmed bulky tumor (≥4cm), nodal metastasis, and/or parametrium invasion were included. The patients were classified into 3 groups; group 1: patients with SCC who received RT/CCRT, group 2: patients with AC who received RT/CCRT, and group 3: patients with AC who received CT. At first, to determine the efficacy of RT/CCRT to AC patients compared to SCC patients, the progression-free survival (PFS) of group 1 and 2 was compared. Secondly, to investigate the efficacy of CT compared to RT/CCRT for AC patients, the PFS of group 2 and 3 was compared. **Results:** A total of 135 patients were enrolled (group 1: 90, 2: 23, and 3: 22). The median follow up period was 48 (range: 1-132) months. There was no statistical difference in the proportion of patients with nodal metastasis, parametrial involvement, and bulky tumor between each group. A significant difference in PFS curves was detected between group 1 and 2; AC patients treated with RT/CCRT had poorer prognosis than SCC patients treated with RT/CCRT (RR: 2.504 (95%CI: 1.284-8.871), p=0.014). A significant difference in PFS curves was also detected between group 2 and 3; AC patients had more favorable prognosis when treated with CT compared to RT/CCRT (RR: 0.288 (95%CI: 0.109-0.965), p=0.043). **Conclusions:** Adjuvant RT/CCRT may be less effective for AC patients, and CT has a potential benefit greater than that of RT/CCRT for AC patients.

**5599 General Poster Session (Board #381), Sat, 8:00 AM-11:45 AM**

**Endometrial cancer survivors: What is their knowledge about obesity?** *Presenting Author: Leslie Horn Clark, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

**Background:** Obesity is a well-established risk factor for development of endometrial cancer (EC); it has been linked to decreased survival, worse surgical outcomes, and poor quality of life in EC patients. We sought to assess EC survivor's awareness of obesity and its role in EC. **Methods:** Following IRB approval, women diagnosed with EC from 2011 – 2012 were identified. Patients with persistent/recurrent disease or those actively undergoing treatment were excluded. A pre-survey invitation to participate was sent 1 week prior to the survey. Surveys were mailed to 233 women. Reminder postcards were sent 2 weeks following the survey. Demographics, weight and weight assessment, patient's health behaviors, and information regarding physician counseling was collected. Along with descriptive statistics, the kappa statistic was reported as a measure of agreement. **Results:** Of 233 surveys sent, 46% (n=108) were returned. The median BMI of responders was 29.8 (range 17.1-64.8) When asked to identify their BMI into four categories, 14% self-reported as "normal weight", 3% as "underweight", 39% as "a little overweight", and 44% as "a lot overweight". Self-reported BMI assessment was compared to actual BMI and good to moderate agreement was noted (weighted kappa 0.66). 85% of women correctly identified their BMI category. When asked if they were obese, 96% (43/45) of obese patients correctly answered "yes" (kappa 0.86). 52% (n=46) reported attempted weight loss following their diagnosis. Of those not attempting weight loss, reasons included: not needing to (37%), not wanting to (23%), not knowing how (14%), not having time (12%), and not having money (20%). Only 34% of patients reported being counseled by a gynecologic oncologist to lose weight. 92% of patients correctly identified obesity as a risk factor for EC. **Conclusions:** EC survivors are relatively knowledgeable about the role of obesity in EC and their own personal weight. Patients were generally motivated to make lifestyle changes after their cancer diagnosis. Unfortunately, only 1/3 of patients reported their providers encouraged weight loss. Gynecologic oncologists should take full advantage of the "teachable moment" for this highly obesity-driven cancer.

**5600 General Poster Session (Board #382), Sat, 8:00 AM-11:45 AM**

**Feasibility of circulating tumour cell (CTC) enumeration and molecular profiling (MP) as a biomarker in advanced endometrial cancer (aEC).** *Presenting Author: Charlotte Rose Lemech, Sarah Cannon Research Institute, London, United Kingdom*

**Background:** CTCs are prognostic and predictive markers in many solid tumours. There are no validated biomarkers to assess treatment (tx) response or molecular therapies in aEC. We conducted a feasibility study to determine whether CTCs were detectable and suitable for MP in aEC. **Methods:** As of January 2014, 30 patients (pt) with aEC had baseline (B) and up to 3 follow-up (FU) blood samples at intervals of 2-3 months (m) up to 6m. CTCs were evaluated using the Veridex CellSearch platform, with stathmin (S) antibody in the 4$^{th}$channel. EpCAM, S and phospho-S6 immunohistochemistry (IHC) was performed on pt FFPE tumour tissue. **Results:** 17/30 (57%) pt had detectable CTCs [1 CTC (n=6), 2 (5), 4 (2), 7 (1), 8 (1), 22 (1), 172 (1)]. 11/17 CTCs were S positive (+), 1 S negative (-) and 5 non-evaluable (NE). Of the 17 CTC+ pt: 11 were sampled at B and during first-line C for mEC; 6 were CTC+ at B but FU was not available (5 died, 1 refused). Of the 11 CTC+ pts sampled during tx: 7pt were B CTC+ and had decreased CTC during C, 6 of which correlated with CT response and 1 of the 6 had increased CTC on 3$^{rd}$FU correlating with CT progression (PD); 4pt were B CTC- and became CTC+ during tx, 2 at PD and 2 are in FU. 18 available FFPE blocks had EpCAM+ staining on IHC, consistent with aEC epithelial origin. **Conclusions:** To our knowledge, this is the first published data confirming CTC enumeration and molecular analysis is feasible in aEC. 57% of pt were CTC+ which was associated with increased stage and tumour burden. Of the 11 pt sampled at B and during tx, 8 (72%) had CTC counts that correlated with CT response. FU is ongoing. CTC may be useful as a biomarker of response as well as molecular profiling in aEC.

**Pt clinicopathological (CP) profiles.**

| | CTC + n=17 (%) | CTC - n=13 (%) |
|---|---|---|
| **Median age (y)** | 66 | 66 |
| **Met sites <2/≥2** | 3/14 (18/82) | 4/9 (31/69) |
| **Mean Ca125 (range)** | 242 (6-2362) | 115 (4-787) |
| **FIGO stage III/IV; IV at diagnosis** | 1/16 (6/94); 8 | 4/9 (31/69); 1 |
| **Type 2 EC** | 11 (65) | 8 (62) |
| **Grade 3** | 14 (82) | 10 (76) |
| **Myometrial invasion >50%** | 9* (64) | 6^ (60) |
| **LVSI** | 8* (57) | 4^ (40) |
| **Cervical invasion** | 5* (36) | 2^ (20) |
| **Surgery alone** | 4~ | 2° |
| **Adjuvant chemotherapy (C) or radiation (R) or both** | 0,1,4~ | 3,5,2° |
| **C for metastatic (m) EC** | 15 | 7 |

*from 14 (3 biopsy only) ^from 10 (1 biopsy only, 2 NE). ~from 9. °from 12.

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**5601 General Poster Session (Board #383), Sat, 8:00 AM-11:45 AM**

**Prediagnostic diabetes, body mass index, and survival of endometrial cancer: A prospective study.** *Presenting Author: Kristina Lindemann, Oslo University Hospital, Norwegian Radium Hospital, Department of Gynecological Cancer, Oslo, Norway*

**Background:** Diabetes and obesity are well known risk factors of endometrial cancer (EC). However, the associations of these factors with survival after EC diagnosis are not established. The aim of this population-based study was to assess the association between diabetes, BMI and risk of all-cause and EC-specific mortality. **Methods:** During 1984-1986 and 1995-1997 two health surveys were conducted in the Nord-Trøndelag county in Norway (HUNT 1 and 2). Women in both surveys who developed EC were identified through individual linkage to the Cancer Registry of Norway. Our primary outcome measure was risk of death from any cause after the diagnosis of EC. Follow-up time was calculated from the date of EC diagnosis until the date of death or the end of follow-up, June 30th 2012. Secondary outcome was death due to EC adjusted for competing causes of death. Both Cox proportional hazards models and Fine and Grey models (competing risk models) adjusted for age, stage of cancer and histological subtype were fitted. In stratified analyses, we studied the risk associated with diabetes in normal weight (BMI $<25$ kg/m$^2$) and overweight/obese women (BMI $\geq 25$ kg/m$^2$). **Results:** Among the 31 865 women included in the HUNT surveys, 337 women who developed EC were eligible for survival analyses. During a median follow-up of 6.6 years (range 0.1-27), 166 (49%) of the women died. We found no statistically significant association between BMI and overall or EC specific mortality. However, the overall risk of death in EC patients with diabetes was more than doubled as compared to patients without diabetes (HR 2.14; 95% CI: 1.26-3.63). Also, the EC specific mortality was more than doubled in women with diabetes (SHR 2.69, 95% CI: 1.09-6.66). In stratified analyses, normal weight women with diabetes had higher, but not statistically significant, risk of both overall and EC-specific death compared to overweight/obese women. **Conclusions:** Diabetes, but not BMI, was associated with increased risk of all-cause and EC-specific mortality. This association between diabetes and mortality may be especially pronounced in normal weight women.

**5602 General Poster Session (Board #384), Sat, 8:00 AM-11:45 AM**

**The effect of raloxifene hydrochloride for the prevention of health care problems of patients who underwent surgeries for endometrial cancer: A multicenter clinical trial.** *Presenting Author: Koji Nakamura, Department of Obstetrics and Gynecology, Osaka University Faculty of Medicine, Suita, Japan*

**Background:** The removal of ovaries is necessary at the surgery for endometrial cancer. However, since the loss of ovaries cause several health problems in patients, the establishment of the prevention therapy after surgeries should be required. We conducted a multicenter clinical trial and assessed the effect of raloxifene on bone mineral density (BMD), bone metabolism and lipid profile of the patients who underwent surgeries for endometrial cancer. **Methods:** 77 women were enrolled after their surgeries. After a written informed consent, participants were randomized into two groups: group I; 39 women received alfacalcidol (1 $\mu$g/day) alone and group II; 38 received the study drug, raloxifene hydrochloride, at a dose of 60 mg/day with alfacalcidol. All patients received supplemental calcium 1.2g/day. BMD, serum bone markers (NTx and BAP) and lipid profiles were evaluated at the enrollment, 6, 12, and 24 months after the enrollment. **Results:** 64 (83%) finished 24-month follow-up. No significant differences between the groups were seen in the baseline data. At 24 months, lumbar and femoral neck BMD were significantly increased in group II compared with group I (3.0% vs -0.8% ($p=0.009$), +2.0% vs -2.8% ($p=0.003$)). In group II, values of total cholesterol as well as LDL-cholesterol were significantly reduced by 8.4% ($p=0.0006$), 14.9% ($p<0.0001$), whereas in group I, no significant reduction were seen. In group II, both serum NTX and BAP values were significantly reduced by 16.1% ($p=0.0006$), 24.7% ($p<0.0001$). Recurrence was found in two (2.6%) case in group I and no severe adverse events were noted in any cases throughout the study period. In sub-analyses, the patients who received chemotherapy showed significantly higher response to raloxifene. **Conclusions:** The treatment of raloxifene to the patients after surgeries not only significantly increased lumbar and femoral neck BMD, but decreased serum bone markers as well as total and LDL-cholesterol values with safety profiles. It suggests that raloxifene could constitute a good therapeutic option to improve the health care problems of the patients with endometrial cancer after surgeries. Clinical trial information: UMIN000013039.

**5603 General Poster Session (Board #385), Sat, 8:00 AM-11:45 AM**

**Effects of temozolomide and bevacizumab in patients with pretreated relapsed uterine leiomyosarcoma.** *Presenting Author: Naoki Sasaki, National Defense Medical College, Tokoorzawa, Japan*

**Background:** Treatments for patients with uterine leiomyosarcoma (ULM) include anthracyclin-based chemotherapy and Docetaxel/Gemcitabine, but these regimens are not satisfactory. Temozolomide (T) has been reported to show a moderate response rate in advanced or recurrent ULM. In addition, ULM has a plenty of vascularity, unlike leiomyoma. Thus, we evaluated the effects of T combined with bevacizumab (B) in patients with pretreated/relapsed ULM. **Methods:** Simon's two-stage design was used. In the first stage, 7 patients were accrued. If there were no responder in these patients, the study would be stopped. Otherwise, seven additional patients will be accrued for a total of 14. If three or more responder were observed in 14 patients, this design yields a type I error rate of 0.03 and power of 0.81 when the true response rate were 30%. Enrolled patients with pretreated/relapsed ULM were treated with weekly B (2mg/kg; days 1, 8, and 15, q4w) and T (80mg/day, daily), and treatment continued until disease progression. **Results:** Among 7 patients in the first stage, two responses were observed, and a total of 14 patients were analyzed in this study. Among 14 cases, two (14%) had a complete response (CR) and three (21%) had a partial response (PR). Additionally, six patients (43%) had a stable disease (SD) for at least three months. The response rate (CR+PR) and clinical benefit rate (CR+PR+SD>3mo) were 35% and 78%, respectively. The median progression-free survival was 10.5 months (range from 3 to 44 months). There were no treatment-related deaths or CTCAE grade 4 toxicities, and no dose reduction due to toxicity was observed. **Conclusions:** T combined with B was effective in patients with relapsed ULM with tolerable toxicity profile. Remarkably, two cases achieved a complete remission more than 6 months. The regimen could be a candidate for the patients with ULM in further prospective studies.

**5604 General Poster Session (Board #386), Sat, 8:00 AM-11:45 AM**

**Carboplatin-based chemoradiotherapy in advanced cervical cancer: An alternative to cisplatin-based regimen?** *Presenting Author: Ana Morais Sebastião, Instituto do Cancer do Estado de Sao Paulo- Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil*

**Background:** Cisplatin based chemoradiotherapy (cis-RT) is the standard treatment in locally advanced cervical cancer (CC). Carboplatin chemoradiotherapy (carbo-RT) has not been validated in prospective phase III studies, although it is used in the presence of renal impairment, advanced age or comorbidities. **Methods:** Retrospective analysis of patients (pts) with CC stage IIB-IVA consecutively treated at Instituto do Cancer do Estado de Sao Paulo from May/2008 to December/2012. Primary endpoint was PSF and secondary OS and ORR (CR + PR). Survival was assessed by Kaplan-Meier curves, compared by the log-rank test, frequencies were compared by chi-square test **Results:** We analyzed 184 pts, 159 treated with cis-Rt and 25 carbo-RT. All received whole pelvic region external-been RT (45Gy and boost-12-14Gy- followed by brachytherapy-4x700cGy). Chemo was weekly cis (40mg/m2) or carbo (AUC2). Median age was 50.42 (21-80) in cis-RT and 64.18y (42-83) in carbo-RT. Most pts have squamous cell carcinoma and ECOG 0-1. Carbo-RT pts have more advanced disease: 52% stage IIIb-IVA vs 36.1% in cis-RT. At least one comorbidity was present in 41.8% in cis-RT and 84% in carbo-RT pts. Five or more chemo cycles were applied 87.3% in cis-RT and 84% pts in carbo-RT ($p=0.749$). PFS at 3 y was 24m in cis-RT (95% CI 18.8-29.3) vs 27.5m in carbo-RT (95% CI 25.6-29.4) ($p=0.249$). OS in 3y was 30.3m (95% CI 26.2-32.7) in cis-RT pts and 31.4m in carbo-RT (95% CI 29.9-32.9) ($p=0.298$). ORR (95.3% vs 95.4%) ($p=0.911$) and grade $\geq$ 3 toxicities (8.5% cis-RT vs 11.8% carbo-RT) ($p=0.757$) were similar. In multivariate analysis, only the ORR was a significance predictor of survival **Conclusions:** Patients with advanced CC treated with carbo-RT have no different 3 year OS, PFS ORR and toxicities when compared to cis-RT. Carbo-RT may be a treatment alternative in patients that could not receive cisplatin

**5605 General Poster Session (Board #387), Sat, 8:00 AM-11:45 AM**

**Population-based analysis of mortality over time in endometrial cancer.** *Presenting Author: Michael Joseph Eblan, Department of Radiation Oncology, The University of North Carolina, Chapel Hill, NC*

**Background:** Endometrial cancer is the most common gynecologic malignancy in developed countries. In this population-based study, we analyzed mortality over a 25-year period**. Methods:** 62513 patients in the Surveillance, Epidemiology & End Results (SEER) database diagnosed with endometrial cancer between 1980 and 2005, with at least 5 years' follow-up, were included. Cases with multiple malignancies or secondary endometrial cancer were excluded. Multivariate analysis examined factors associated with all-cause mortality (ACM) and cancer-specific mortality (CSM) using Cox proportional hazards model and Fine-Gray competing risk model, respectively. **Results:** There were 10886 deaths from endometrial cancer and 10184 from other causes. ACM and CSM decreased in more recent years (Table). Older age at diagnosis, black race, advanced stages, higher grade and sarcoma histology were associated with increased hazards for ACM and CSM. Receipt of total hysterectomy, external beam radiation therapy (EBRT) and implant were associated with decreased ACM. **Conclusions:** When accounting for patient, diagnostic and treatment factors, ACM and CSM have decreased over time for endometrial cancer. However, racial disparity in mortality outcomes persists.

**Factors associated with ACM and CSM.**

| | | ACM HR (p) | CSM HR (p) |
|---|---|---|---|
| Year of diagnosis (REF=2000-2005) | 1995-1999 | 1.06* | 1.05 (0.11) |
| | 1990-1994 | 1.19* | 1.17* |
| | 1980-1989 | 1.13 (0.12) | 1.52* |
| Age at diagnosis (REF=85+) | 80-84 | 0.74* | 0.88 (0.04) |
| | 75-79 | 0.55* | 0.82* |
| | 70-74 | 0.38* | 0.73* |
| | 65-69 | 0.27* | 0.67* |
| | 60-64 | 0.21* | 0.60* |
| | 50-59 | 0.13* | 0.44* |
| | <50 | 0.08* | 0.33* |
| Race (REF=White) | Black | 1.41* | 1.24* |
| | Other | 0.94 (0.06) | 0.96 (0.42) |
| | Unknown | 0.52* | 0.45* |
| Stage (REF=Unstaged) | Local | 0.74* | 0.50* |
| | Regional | 1.66* | 1.66* |
| | Distant | 4.00* | 4.02* |
| Grade (REF=I) | II | 1.29* | 2.12* |
| | III | 2.12* | 4.30* |
| | IV | 2.36* | 4.53* |
| | Unknown | 1.62* | 3.05* |
| Histology (REF=Type 2) | Type I AdenoCa | 0.82* | 0.70* |
| | Sarcoma | 1.41* | 1.53* |
| Surgery (REF=Total Hysterectomy) | Subtotal Hysterectomy | 1.44* | 1.47* |
| | Radical Hysterectomy | 1.08 (0.64) | 1.09 (0.67) |
| | None | 3.29* | 2.40* |
| Radiation (REF=None) | Implant | 0.81* | 0.83* |
| | EBRT | 0.98 (0.24) | 1.19* |
| | EBRT + Implant | 0.85* | 1.06 (0.13) |

Also controlled for marital status, regional income and education level, urban/rural, SEER region and lymph node dissection. *p value <.0.

**5606 General Poster Session (Board #388), Sat, 8:00 AM-11:45 AM**

**Absence of occult micrometastases in histologically negative lymph nodes among patients with distant recurrent endometrial cancer.** *Presenting Author: Amanda Lynn Jackson, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

**Background:** Lymph node metastasis is a criterion for adjuvant therapy in endometrial cancer (EC). The incidence of immunohistochemical (IHC) stain-positive micrometastases in H&E-negative lymph nodes is low in surgically staged EC. Ultrastaging, however, is used to detect low volume disease in sentinel lymph node dissection. Our goal was to determine the frequency of occult micrometastases in histologically negative lymph nodes in patients who have distant recurrent endometrial cancer. **Methods:** The records of patients diagnosed with endometrial cancer from 2005 to 2010 were reviewed. Twenty patients that were previously reported to be negative for lymph node metastases using conventional histologic analysis presented with distant recurrent high-grade endometrioid adenocarcinoma. All nodal tissue was submitted for review and ultrastaging with H&E and IHC staining to detect micrometastasis. Two pathologists interpreted slides and positive IHC staining for micrometastases was defined as positive staining of cells <2 mm in greatest dimension. **Results:** 1063 patients underwent surgery for endometrial cancer. Twenty patients with early stage, high-grade node negative endometrioid cancers presented with a distant recurrence to sites other than isolated vaginal, pelvic or retroperitoneal sites; 2 patients were excluded secondary to unavailable pathologic samples. The histological grade was 2 in 9 patients and 3 in 9 patients. Nine patients had Stage IA disease, 6 Stage IB, and 3 Stage II. 536 lymph nodes were reviewed from the cohort of 18 patients; the median number of lymph nodes per patient was 27.5(10-52). No micrometastases were identified in any of the lymph nodes. **Conclusions:** It was previously shown that the incidence of IHC stain-positive micrometastases in H&E-negative lymph nodes is low in surgically staged endometrial cancers. Our study shows that in patients with a distant recurrence the incidence remains very low, suggesting alternative routes of metastasis for these patients and questions the utility for ultrastaging in sentinel lymph nodes to predict distant recurrences.

**5607 General Poster Session (Board #389), Sat, 8:00 AM-11:45 AM**

**A retrospective analysis of the relationship between diabetes, metformin use, and survival in advanced endometrial cancer patients treated with chemotherapy.** *Presenting Author: Obiageli Chinaka Ezewuiro, University of Chicago, Chicago, IL*

**Background:** Pre-clinical data suggests that the diabetic medication, metformin, has anti-cancer effects. We hypothesized that advanced stage endometrial cancer (EC) patients who used metformin would have improved survival. **Methods:** We conducted a single institution retrospective review of women receiving chemotherapy in the setting of stage III, IV or recurrent EC or carcinosarcoma from 1992 to 2011. **Results:** We identified 418 pts with stage III, IV or recurrent EC, of whom 237 received chemotherapy, and 220 were included in the study. Median age at time of chemotherapy was 64.8 (range 21.1-87.0); race: 56% white, 40% African American (AA), 4% other. Histologies were 28% endometrioid, 28% serous, 16% carcinosarcoma, 7% clear cell and 21% other. Median OS was 24.5 months (95%CI: 20.1-28.5). AA pts had worse OS than whites (p=.02), with median OS of 16.9 (95%CI: 12.7-24.6) vs 28.5 (95%CI: 23.4-35.2) months, respectively. Older patients had worse OS (p=0.001). 43 pts had diabetes and 19 of them were taking metformin at the time of chemotherapy. Median OS for diabetics taking metformin, diabetics not taking metformin, and non-diabetics was 51.9 (95%CI: 17.9-127.5), 13.3 (95%CI: 8.0-24.6) and 24.2 (95%CI: 20.1-29.8) months. OS difference between the three groups was not statistically significant (p=0.12), but when comparing survival only among the diabetic groups, patients treated with metformin had a borderline statistically significant longer OS (p=0.066, logrank test). The difference was also borderline significant in the multivariate Cox regression model adjusted for race and age (HR=2.12, p=0.057). **Conclusions:** In this study of advanced EC, patients receiving chemotherapy who were concurrently treated with metformin had improved survival. Our study adds to the body of evidence suggesting potential anti-cancer effects of metformin and supports prospective testing of metformin added to standard chemotherapy for advanced EC. Supported by NCI K12CA139160 and CTSA-ITM CS UL1 RR024999 to TG, NCI 2K12HD00849-22 and University of Chicago Cancer Center to IR.

**5608 General Poster Session (Board #390), Sat, 8:00 AM-11:45 AM**

**Resection margin and locoregional control in vulvar cancer: A subset analysis of the AGO CARE-1 multicenter study.** *Presenting Author: Linn Lena Woelber, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

**Background:** Recently, the standard of minimal pathological resection margin distance of 8mm in surgery for primary vulvar cancer has been challenged since several single center analyses failed to show impact of smaller margins for disease control. **Methods:** The AGO CaRE-1 study is a retrospective survey of treatment patterns and prognostic factors in vulvar cancer. Patients with primary squamous-cell vulvar cancer FIGO stage 1B and higher (UICC-TNM version 6) treated at 29 gynecologic cancer centers in Germany 1998-2008 were included in a centralized database. While a total of 1,618 patients were documented, this subgroup analysis focuses only on surgically staged node-negative patients with complete tumor resection and known margin distance without radio/chemotherapy (n=289). **Results:** Median age of the 289 analyzed patients was 66 years (22-94); 141 (48.8%) had pT1b, 140 (48.4%) pT2 and 8 (2.8%) pT3 tumors. 125 (43.3%) underwent complete, 127 (43.9%) partial vulvectomy and 37 (12.8%) radical local excision. The median minimal resection margin was 5 mm (1mm–33mm); median follow-up was 38.8 months. 46 patients (15.9%) developed disease recurrence, thereof 34 (11.8%) at the vulva, after a median of 18.3 months. Vulvar recurrence rates were 12.6% in the group of patients with a resection margin <8mm and 10.2% in patients with a margin ≥8mm. Other sites of recurrent disease were groins (8 cases; 2.8%), pelvis (1 case; 0.3%) and distant (3 cases; 1.0%). When analyzed as a continuous variable, margin distance had no significant impact on disease-free survival (HR per mm increase 0.945, 95% CI 0.886 – 1.009, p=0.090). Similarly, neither uni- nor multivariate analysis adjusted for age, tumor stage, tumor grade, depth of invasion and tumor diameter could reveal a significant difference in disease-free survival between the subgroup of patients with a margin ≥8 or <8mm (multivariate HR 0.642, 95% CI 0.355 – 1.162, p=0.143). Results were consistent when looking at vulvar recurrences only. **Conclusions:** Tumor-free resection margins are crucial for loco-regional control in vulvar cancer. The need for a minimal margin of 8mm could, however, not be observed in the large cohort of the AGO-CaRE database.

**5609 General Poster Session (Board #391), Sat, 8:00 AM-11:45 AM**

**Evaluation of the diagnostic accuracy of cervical biopsy and determination of associated risk factors for positive margin status in recurrent cervical dysplasia after leep or conization.** *Presenting Author: Diana Peta-gay English, Yale School of Medicine, New Haven, CT*

**Background:** Severe dysplasia on a cervical biopsy is often followed by an excisional procedure such as a loop electrosurgical excisional procedure (LEEP) or cone biopsy. The objective of this study was to determine the prevalence and associated risk factors for positive surgical margins on cold knife conization or LEEP as well as the recurrence of dysplasia after these procedures. Secondary objective was to determine the correlation of cervical biopsy revealing CIN II with degree of dysplasia found on final pathology. **Methods:** This is a descriptive analytical study of 118 patients who underwent a LEEP or cone biopsy during a 12 year period (1999-2011) by trained gynecologic oncologists at our institution. Medical records were reviewed from a prospectively maintained pathology database. Cases were identified through a search performed for all patients in this period with a CIN II diagnosis. All pathology specimens were reviewed by one of four board specialized gynecologic pathologists. The need for cervical biopsy was determined based on pap results according to the ASCCP guidelines. Univariate analysis was performed with the chi-square test and the Student's t-test. **Results:** Of the 118 patients, 29 cases had a positive cone/LEEP margin (24.6%). Of the patients with positive margins, 48.2 % of these patients were considered to be immuno-compromised due to factors such as chronic steroid use and smoking, chemotherapy or HIV positivity. Recurrence of abnormal pap smears within 2 years of an excisional procedure was 19% in the margin negative group and 31% in the margin positive group ($P < 0.0001$). The positive predictive value of cervical biopsy for determining CIN II on an excisional procedure was 94.1%. **Conclusions:** Positive surgical margins on LEEP/cone biopsy is not uncommon and increases the risk for abnormal cervical cytology in the subsequent years post-procedure. Cervical biopsies when performed by trained physicians correlate well with final pathology on cone biopsy/LEEP. Risk factor assessment continues to be important in following patients after cervical excisional procedures.

**5610 General Poster Session (Board #392), Sat, 8:00 AM-11:45 AM**

**ADXS11-001 immunotherapy targeting HPV-E7: Final results from a phase 2 study in Indian women with recurrent cervical cancer.** *Presenting Author: Partha Basu, Chittaranjan National Cancer Institute, Kolkata, India*

**Background:** ADXS11-001 immunotherapy is a live attenuated *Listeria monocytogenes* (*Lm*) bioengineered to secrete a HPV-16-E7 fusion protein targeting HPV transformed cells. The *Lm* vector serves as its own adjuvant and infects APC where it cross presents, stimulating MHC class 1 and 2 pathways resulting in specific T-cell immunity to tumors. Here we describe final results from *Lm*-LLO-E7-015, a randomized P2 study designed to evaluate the safety and efficacy of ADXS11-001 with and without cisplatin in 110 patients with recurrent cervical cancer in India; previously treated with chemotherapy, radiotherapy or both. **Methods:** Patients were randomized to either 3 doses of ADXS11-001 at $1 \times 10^9$ cfu or 4 doses of ADXS11-001 at $1 \times 10^9$ cfu with cisplatin chemotherapy (40 mg/m$^2$). Naprosyn and oral promethazine were given as premedications and a course of ampicillin was given 72h after infusion. Patients received CT scans at baseline and 3, 6, 9, 12 and 18 months. The primary endpoint was overall survival. **Results:** The final 12 month survival was 36% (39/110) and 18-month survival was 28% (31/110). The response rate was 11% (6 CRs and 6 PRs/110) with tumor responses observed in both treatment arms; 35 additional patients had stable disease $> 3$ months, for a disease control rate of 43% (47/110). Average duration of response in both treatment groups was 10.5 months. Activity against different high-risk HPV strains was observed. The incidence of SAEs possibly related or related to ADXS11-001 was 2% (G3). The majority of non-serious adverse events were predominately infusion associated, and either resolved on their own or responded to symptomatic treatment. **Conclusions:** The addition of cisplatin to ADXS11-001 did not significantly improve survival outcomes or tumor responses. Baseline ECOG performance status, type of prior therapy, or aggressiveness of disease had no effect on survival outcomes and tumor responses. The 36% 12 month survival, 28% 18 month survival, and 11% response rate observed in this recurrent disease setting is encouraging and suggests that ADXS11-001 is an active agent in recurrent cervical cancer. Additional sub-analyses will be presented at the meeting.

**TPS5611 General Poster Session (Board #393A), Sat, 8:00 AM-11:45 AM**

**ICON8: An international randomized trial comparing two dose-dense regimens, 3-weekly carboplatin plus weekly paclitaxel (CwT), and weekly carboplatin-paclitaxel (wCwT), to standard 3-weekly treatment in women with newly diagnosed ovarian, fallopian tube, and primary peritoneal cancer.** *Presenting Author: Jane Hook, Medical Research Council Clinical Trials Unit at University College London, London, United Kingdom*

**Background:** Three-weekly intravenous carboplatin-paclitaxel (CT) is a standard of care for the first-line treatment of ovarian cancer. Dose-dense weekly (w) CwT improved survival in the JGOG3016 trial (Katsumata, Lancet Oncol 2012) but its benefit was unclear in GOG262 (Chan, 18th ESGO Meeting 2013), as most women received bevacizumab in addition to CT or CwT. ICON8 is the largest trial of dose-dense therapy in ovarian cancer. It will compare the efficacy and safety of CT with CwT and wCwT regimens. **Methods:** ICON8 (NCT01654146) is a Gynecologic Cancer Intergroup, 3-stage phase III trial open at 111 centres in the UK, S Korea, Mexico, Ireland, Australia, and New Zealand. Patients (pts) with histologically proven FIGO Stage IC-IV ovarian, fallopian tube, primary peritoneal cancer or ovarian carcinosarcoma, age ≥18 years and ECOG PS 0-2 are eligible. Pts may enter after immediate primary surgery (IPS) or receive neoadjuvant chemotherapy + delayed primary surgery (DPS) after cycle 3. ICON8 is the first trial designed to permit variation in timing of surgery; randomization is stratified by IPS/DPS. Pts are randomized (1:1:1) to receive 6 21-d cycles of (1) carboplatin AUC5 + paclitaxel 175mg/m$^2$ q3w, (2) carboplatin AUC5 q3w + paclitaxel 80mg/m$^2$ q1w or (3) carboplatin AUC2 + paclitaxel 80mg/m$^2$ q1w. Stage 1 (safety and feasibility) is complete (Hook, 18th ESGO Meeting 2013). The IDMC reviewed stage 2 (activity) in January 2014 and recommended that recruitment continue to all arms. Stage 3 (efficacy) is powered for dual primary outcome measures: progression free and overall survival. Secondary outcomes are toxicity, quality of life and cost effectiveness. 1,000 of 1,485 women have been recruited. Accrual is expected to complete in Q4 2014. Collection of tumor tissue, germline DNA and serial plasma is ongoing in parallel (TRICON8) with 90% pts participating. ICON8B, an extension in high risk pts comparing CwT with or without bevacizumab and CT + bevacizumab is planned. The trial is sponsored by the MRC and funded by Cancer Research UK, CRUK/10/030. Clinical trial information: NCT01654146.

**TPS5612 General Poster Session (Board #393B), Sat, 8:00 AM-11:45 AM**

**A phase 3 study of trabectedin (T) plus pegylated liposomal doxorubicin (PLD) versus PLD for treatment of advanced-relapsed epithelial ovarian, primary peritoneal, or fallopian tube cancer.** *Presenting Author: Robert L. Coleman, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Ovarian cancer (OVC) is the eighth most common cancer among women globally, with approximately 60%–70% of cases being diagnosed at an advanced stage (III or IV). Five-year survival rate for stage IV is <20%. In a previous pivotal trial, patients with OVC who relapsed after first-line platinum-based chemotherapy (PCT) demonstrated superior progression free survival (PFS) when treated with the T+PLD combination vs. PLD monotherapy (7.3 vs. 5.8 months; HR=0.79; p=0.019). In a subgroup analysis by platinum free interval (PFI), T+PLD showed an improved overall survival (OS) for patients with PFI of 6–12 months (HR=0.64). Given this demonstrated efficacy, we are conducting a global phase 3 registration trial to investigate the OS of T+PLD vs. PLD in patients with platinum sensitive epithelial OVC, peritoneal or fallopian tube cancer, in the third-line setting. **Methods:** In this open-label, active-controlled trial, approximately 670 women who have received 2 prior lines of PCT will be enrolled at approximately 135 sites in 9 countries. Key inclusion criteria: all women must be platinum sensitive defined as no evidence of disease progression for ≥6 months after the last dose of first-line PCT, and have known BRCA mutation status prior to randomization. Key exclusion criteria: OVC with mucinous histology and >2 prior lines of chemotherapy. Patients will be stratified by PFI (6–12 months vs. >12–24 months vs. >24 months), ECOG performance status (0 vs. 1), BRCA 1 or 2 mutation status (yes vs. no), and prior PLD therapy (yes vs. no). Stratified patients will be randomized (1:1) to receive PLD (30 mg/m$^2$, 1.5 h, i.v.) followed by T (1.1 mg/m$^2$, 3 h, i.v.) every 3 weeks or PLD alone (50 mg/m$^2$, 1.5 h, i.v.) every 4 weeks. Primary endpoint is OS. Secondary endpoints include PFS, overall response rate (ORR), safety, and pharmacokinetics of T. Planned study duration is 64 months. An interim OS analysis is planned after 308 deaths. Final OS analysis will be done after ≥514 deaths have been observed. As of 29 January 2014, 11 patients have been randomized. Clinical trial information: NCT01846611.

**TPS5613 General Poster Session (Board #394A), Sat, 8:00 AM-11:45 AM**

**PENELOPE/AGO-OVAR 2.20: A double-blind placebo (PLA)-controlled randomized phase III ENGOT trial evaluating chemotherapy (CT) with or without pertuzumab (P) for platinum-resistant ovarian cancer.** *Presenting Author: Christian Kurzeder, Kliniken Essen Mitte, Essen, Germany*

**Background:** Adding P to gemcitabine (GEM) for platinum-resistant ovarian cancer improved progression-free survival (PFS) in a subset of patients (pts) with low tumor HER3 mRNA expression [Makhija 2010]. PENELOPE (NCT01684878) comprises a safety run-in (Part 1, complete) and PLA-controlled randomized assessment of CT ± P (Part 2, below). **Methods:** Eligible pts have: measurable/non-measurable recurrent platinum-resistant epithelial ovarian, primary peritoneal or fallopian tube cancer (progression during or within 6 mo of completing ≥4 platinum cycles); centrally tested low HER3 mRNA expression (concentration ratio ≤2.81 by qRT-PCR on cobas z480); and have received ≤2 prior lines of CT. The primary Part 2 objective is to determine if PFS (assessed by independent review committee; IRC) is superior with P + CT vs PLA + CT. The key secondary endpoint is overall survival (OS). Both endpoints are part of a closed testing procedure. Additional endpoints include investigator-assessed PFS, objective response rate (RECIST v1.1), safety (NCI CTCAE v4.0), quality of life (including EORTC QLQ-C30 and QLQ-OV28) and pharmacokinetic parameters. Translational studies aiming to scrutinize and validate the preselection concept by correlating markers of signal pathway activation with efficacy have been implemented. Additional exploratory analyses will include gene expression profiling. Investigators select CT (topotecan, paclitaxel or GEM) before 1:1 randomization to P or PLA. Treatment is continued until progression or unacceptable toxicity. Stratification factors are: selected CT; prior anti-angiogenic therapy; and platinum-free interval (<3 vs 3–6 mo). The planned Part 2 enrollment is 154 pts. Recruitment to each CT cohort is capped at 1/3 of the total sample size. Primary PFS analysis will be done after 109 IRC-assessed PFS events, providing 95% power to detect a PFS hazard ratio (HR) of 0.50 (median PFS 1.4→2.8 mo) with 2-sided log-rank at $\alpha$=0.05. Final OS analysis is planned after 129 deaths in Part 2, providing 80% power to detect an OS HR of 0.61 (median OS 8.4→13.8 mo); 2-sided log-rank at $\alpha$=0.05. By 27 Jan 2014, 62 pts were randomized. Clinical trial information: NCT01684878.

**TPS5614 General Poster Session (Board #394B), Sat, 8:00 AM-11:45 AM**

**A randomized, open-label, phase II study assessing the efficacy and the safety of bevacizumab in neoadjuvant therapy in patients with FIGO stage IIIc/IV ovarian, tubal, or peritoneal adenocarcinoma, initially unresectable.** *Presenting Author: Roman Rouzier, Institut Curie, Saint-Cloud, France*

**Background:** We hypothesize that improving the response rate of stage IIIC or IV and non-optimally resectable ovarian cancer patients to neoadjuvant chemotherapy would improve the optimal debulking rate at interval debulking surgery (IDS) and ultimately the survival. In the ICON7 and OCEANS trials, addition of bevacizumab to chemotherapy has been shown to improve the response rates. We assume that its administration in the neoadjuvant setting would improve the response rate and consequently will help to achieve optimal debulking rate at IDS. **Methods:** This study, named ANTHALYA, is a multicenter, open-label, randomised phase II study, conducted in 15 sites in France. 90 patients with FIGO stage IIIC/IV ovarian, tubal or peritoneal adenocarcinoma, initially unresectable are to be enrolled. At inclusion, patients are randomised (2:1) to receive 4 cycles of neoadjuvant carboplatin and paclitaxel chemotherapy either combined to 3 cycles of bevacizumab in the treatment arm (not given the cycle before surgery) or alone in the control arm. The control arm will be used to assess the complete resection rate in the arm treated without bevacizumab in the neoadjuvant setting. The primary objective for this study is to evaluate the efficacy of neoadjuvant bevacizumab and chemotherapy measured by the complete resection rate after IDS. Complete resection is defined as the removal of all macroscopic residual tumour at IDS (CC score = 0). The secondary objectives for this study are as follows: (1) to evaluate the safety profile of bevacizumab when added to carboplatin and paclitaxel in the neoadjuvant setting; (2) to assess the efficacy of bevacizumab measured by Objective Response Rate (ORR) for neoadjuvant period and after all courses of treatment, assessed according to RECIST criteria and CA-125 levels; and (3) to evaluate progression-free survival (PFS). Exploratory analysis are conducted to evaluate the biomarkers profile and to explore prognosis and predictive markers. Clinical trial information: NCT01739218.

**TPS5615 General Poster Session (Board #395A), Sat, 8:00 AM-11:45 AM**

**Measuring subjective improvement of palliative chemotherapy in women with platinum-resistant or -refractory ovarian cancer: The symptom benefit study (ANZGOG-0701/ GCIG/PoCoG).** *Presenting Author: Michael Friedlander, Prince of Wales Hospital, Sydney, Australia*

**Background:** The objective of chemotherapy in women with platinum resistant recurrent ovarian cancer is symptom palliation. Response rates or time to progression are used to assess "clinical benefit", but fail to incorporate subjective benefit. There is international consensus that a valid measure of subjective symptom benefit is required. The aims of Stage 2 of this study are to assess the validity, reliability and statistical efficiency of a new patient-reported outcome measure, the Measure of Ovarian Symptoms and Treatment concerns (MOST, developed in Stage 1), relative to the best candidate scales of existing ovarian cancer specific quality of life measures (QLQ-C30/OV28, FACT-O/FOSI), develop criteria for defining subjective symptom benefit, determine how many women have subjective benefit with palliative chemotherapy and develop a prognostic model to better predict benefit, time to progression and survival in this heterogeneous group of patients. **Methods:** Prospective observational cohort study in women with platinum resistant or refractory recurrent ovarian cancer who are about to commence palliative chemotherapy. Changes in perceived ovarian cancer symptoms are assessed from baseline to post treatment using QLQ-C30/OV28, FACT-O/FOSI and MOST. Eligibility: Women with platinum resistant/refractory epithelial ovarian, primary peritoneal or fallopian tube cancer with life expectancy > 3 months and ECOG PS 0-3 who are about to start palliative (2nd or subsequent line) chemotherapy. Trial status: Stage 2 opened in Feb 2011 with a target recruitment of 750 patients. To date 623 patients have been recruited from Australia, New Zealand, Ireland, Germany and Italy, Canada, the UK, the US, France, Sweden, Norway and Japan. **Summary:** This study will identify the most statistically efficient measure of subjective symptom benefit of palliative chemotherapy for use in endpoint analysis in clinical trials. Ultimately, it will help physicians and patients make more informed decisions regarding treatment options based on the likelihood of benefit and their potential impact on symptom control and improved quality of life. Clinical trial information: ACTRN12607000603415.

**TPS5616 General Poster Session (Board #395B), Sat, 8:00 AM-11:45 AM**

**SOLO1 and SOLO2: Randomized phase III trials of olaparib in patients (pts) with ovarian cancer and a *BRCA1/2* mutation (BRCAm).** *Presenting Author: Kathleen N. Moore, University of Oklahoma Health Sciences Center, Oklahoma City, OK*

**Background:** In a pivotal Phase II trial (NCT00753545), maintenance treatment with the oral PARP inhibitor olaparib (400 mg bid; capsules) led to a significant PFS improvement vs placebo in pts with platinum-sensitive, relapsed serous ovarian cancer (Ledermann et al *NEJM* 2012), with the greatest PFS benefit seen in pts with a BRCAm (HR=0.18, 95% CI 0.10–0.31, *P*<0.00001; Ledermann et al ASCO 2013). Two AstraZeneca-sponsored Phase III trials of olaparib maintenance monotherapy have been initiated in ovarian cancer pts with a BRCAm: SOLO1 (NCT01844986); SOLO2 (NCT01874353). **Methods:** SOLO1 and SOLO2 are double-blind multicenter studies in which pts are being randomized (2:1) to receive olaparib (300 mg [2 x 150 mg tablets] bid) or placebo. Both trials are recruiting pts with high-grade serous or endometrioid ovarian cancer, including primary peritoneal and/or fallopian tube cancer, who have a known deleterious (or suspected deleterious) BRCAm and who are in complete or partial response following the completion of platinum-based chemotherapy. To be eligible for SOLO1, pts must have newly diagnosed, advanced (FIGO stage III–IV) disease and have responded to first-line platinum therapy, whereas pts in SOLO2 must have completed ≥2 lines of platinum therapy. All eligible pts will have a BRCAm and will undergo germline BRCA testing (Myriad Integrated BRAC*Analysis*) as part of the trials. For both trials, the primary objective is PFS by blinded independent central review using RECIST v1.1. Radiologic scans will be performed at baseline and every 12 weeks for 120 (SOLO1) or 72 (SOLO2) weeks, and every 24 weeks thereafter. Blinded treatment will continue until objective disease progression. Primary analyses will be performed at ≈60% maturity using log-rank tests. Other objectives for both trials include: overall survival; time to earliest progression (RECIST or CA-125); time from randomization to second progression (PFS2); HRQoL; tolerability. Enrollment began in Sep 2013. As of Jan 2014, both trials have recruited approximately 10% of the target patient population. Target recruitment: SOLO1, n≈344 randomized pts (≈110 sites worldwide); SOLO2, n≈264 randomized pts (≈80 sites worldwide). Clinical trial information: NCT01844986 and NCT01874353.

**TPS5617 General Poster Session (Board #396A), Sat, 8:00 AM-11:45 AM**

**A phase 2 study of live-attenuated listeria monocytogenes cancer immunotherapy (ADXS11-001) in the treatment of persistent or recurrent cancer of the cervix (GOG-0265).** *Presenting Author: Warner King Huh, The University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL*

**Background:** This is a Gynecologic Oncology Group (GOG) Phase 2 study (NCT01266460, GOG 0265) of ADXS11-001 in patients with persistent or recurrent cancer of the cervix. ADXS11-001 is a live attenuated *Listeria monocytogenes* (*Lm*) immunotherapy bioengineered to secret a HPV E7 fusion protein targeting HPV-E7 transformed cells. A previous Phase I dose escalation study evaluated the safety of ADXS11-001 in patients with advanced cervical cancer (Maciag PA. Vaccine. 2009 Jun 18;27(30):3975-83). The primary objectives of this study are: to evaluate the tolerability and safety of ADXS11-001; and to assess the activity of ADXS11-001 in patients with persistent or recurrent cancer of the cervix. Secondary objectives are progression-free survival, overall survival and objective tumor response. **Methods:** Patient eligibility criteria: Females age $\geq$ 18 years with persistent or recurrent squamous or non-squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix with documented disease progression (disease not amenable to curative therapy). Patients must have measurable disease as defined by RECIST 1.1; have had one prior systemic chemotherapeutic regimen for management of their disease; have adequate organ function and must be free of active infection and not on antibiotics. This protocol is a 2-stage design with 12-month survival as the primary endpoint and with a planned sample size of up to 67 patients. Patients will receive ADXS11-001 at a dose of $1x10^9$ CFU on Day 1 and repeat every 28 days for 3 total doses in the absence of disease progression or unacceptable toxicity, with each dose followed at 72 hours by a 7 day course of ampicillin, 500 mg QID. Tumor tissue and serum samples may be collected periodically for translational research. After completion of study treatment, patients are followed every 3 months for 2 years and then every 6 months for 3 years. As of January 31, 2014, enrollment has been completed in the 9 patient safety lead-in portion of the study and enrollment continues. Clinical trial information: NCT01266460.

**TPS5618 General Poster Session (Board #396B), Sat, 8:00 AM-11:45 AM**

**The MEK Inhibitor in Low-Grade Serous Ovarian Cancer (MILO)/ENGOT-ov11 study: A multinational, randomized, open-label phase 3 study of binimetinib (MEK162) versus physician's choice chemotherapy in patients with recurrent or persistent low-grade serous carcinomas of the ovary, fallopian tube, or primary peritoneum.** *Presenting Author: Bradley J. Monk, University of Arizona Cancer Center, Phoenix, AZ*

**Background:** Low-grade serous (LGS) carcinomas of the ovary, fallopian tube and primary peritoneum are rare and unique tumors for which current therapies (chemotherapy, hormonal) have demonstrated limited efficacy. As LGS carcinoma is characterized by mutations in genes of the RAS/RAF/MEK/ERK signaling pathway, such as BRAF and KRAS, evaluating therapies that target this pathway is warranted. This study will evaluate the efficacy of the MEK1/2 inhibitor binimetinib (MEK162) vs physician's choice chemotherapy in patients with LGS carcinoma. This study will enroll patients regardless of RAS/RAF mutational status; however, tumor tissue will be retrospectively analyzed for mutations in RAS/RAF and other genes (NCT01849874). **Methods:** This is a 2-arm, open-label, 2:1 randomized Phase 3 study of binimetinib vs physician's choice chemotherapy (pegylated liposomal doxorubicin, paclitaxel or topotecan). Eligible patients must have LGS carcinoma that is recurrent or persistent following at least 1 prior platinum-based chemotherapy and no more than 3 prior lines of chemotherapy, and must have RECIST v1.1-defined measurable disease confirmed by independent central review. Prior to randomization, independent central review of a patient's tumor specimen is required to confirm LGS diagnosis. Prior treatment with a MEK or BRAF inhibitor is prohibited. Randomization is stratified by last platinum-free interval and number of prior systemic therapy regimens. The primary endpoint is progression-free survival as determined by blinded independent central review; secondary endpoints include overall survival, overall response, duration of response, disease control rate, safety, quality of life and pharmacokinetics of binimetinib. Binimetinib is administered 45 mg BID orally. Patients receive therapy until disease progression or unacceptable toxicity. This study will enroll 300 patients worldwide. Clinical trial information: NCT01849874.

**TPS5619 General Poster Session (Board #397A), Sat, 8:00 AM-11:45 AM**

**ARIEL 2/3: An integrated clinical trial program to assess activity of rucaparib in ovarian cancer and to identify tumor molecular characteristics predictive of response.** *Presenting Author: Elizabeth M. Swisher, University of Washington, School of Medicine, Seattle, WA*

**Background:** PARP inhibitors (PARPi) are active in patients (pts) with mutations in BRCA, a critical component of homologous recombination repair (HRR). PARPi activity extends beyond BRCA, most likely in tumors with other mutations leading to homologous recombination deficiency (HRD), although the best molecular predictors of PARPi response are unknown. Platinum sensitivity, often used as a surrogate predictive indicator for PARPi response, does not adequately identify all pts likely to respond. Next generation sequencing (NGS) analysis of tumor tissue can identify somatic BRCA mutations as well as other gene alterations in the DNA repair pathway and thus may be a superior method for selection of pts for PARPi therapy. Rucaparib, an oral PARPi, is being developed for treatment of high grade ovarian cancer (HGOC). A novel, integrated, translational-clinical program (ARIEL) is ongoing to identify pts who may benefit from rucaparib treatment. **Methods:** ARIEL2 (NCT01891344) is a Phase 2 trial of rucaparib that aims to identify a molecular HRD signature that predicts response. The signature will be applied prospectively to the analysis of ARIEL 3 (NCT01968213), a Phase 3 study in a similar population. ARIEL2 is ongoing. Eligible pts (n=180) have relapsed, platinum-sensitive HGOC and measurable disease. All pts have a pre-dose biopsy and provide archival tumor tissue. Tumor tissue HRR status assessment uses Foundation Medicine's NGS platform and Univ. of Washington's BROCA-HR panel, with the initial HRD algorithm developed using in vitro/in vivo and TCGA (and similar) bioinformatic data. Key efficacy analyses to be correlated with tumor HRR status are PFS and response (RECIST v1.1, GCIG CA-125). The number of *gBRCA* pts is limited to maximize analysis of non-*gBRCA* response predictors. The optimized algorithm will then be tested prospectively in ARIEL3 (n=540), an ongoing, randomized (2:1), placebo-controlled maintenance trial in platinum-sensitive HGOC in remission after platinum-based therapy. The primary endpoint of ARIEL3 is PFS in HRD subgroups determined by NGS analysis of archival tumor tissue using the ARIEL2 optimized algorithm. Clinical trial information: NCT01891344 and NCT01968213.

**TPS5620 General Poster Session (Board #397B), Sat, 8:00 AM-11:45 AM**

**Phase II study of oral ENMD-2076 administered to patients with ovarian clear cell carcinoma: A trial of the Princess Margaret Phase II Consortium.** *Presenting Author: Cristina Martin-Lorente, Princess Margaret Cancer Centre, Toronto, ON, Canada*

**Background:** Ovarian clear cell carcinoma (OCCC) represents nearly 15% of all epithelial ovarian carcinomas (EOC). This histology is associated with resistance to chemotherapy and a worse prognosis. VEGF has been found to be strongly expressed in OCCC. Somatic mutations in the ARID1A (the AT-rich interactive domain 1A gene that encodes BAF250a, a key component of the SWI/SNF chromatin remodeling complex) has also been demonstrated in 46-57% of OCCCs. Alteration of this chromatin remodeling complex may result in upregulation and overexpression of Aurora A. ENMD-2076 is a multi-target kinase inhibitor, which has selective activity against Aurora A and multiple antiangiogenesis and lymphangiogenesis targets. In a Phase II study in platinum-resistant EOC, 58% of the patients treated with single agent ENMD-2076 showed partial response or stable disease, the PFS at 6 month was 22% with a median time to progression of 3.6 months. Two out of 3 patients with OCCC who were enrolled had a longer PFS than the median. **Methods:** This is a multi-center, Phase II study, in patients with recurrent OCCC to assess response rate and progression free survival rate, as primary endpoints, and duration of overall response, as a secondary endpoint, of single agent ENMD-2076 275 mg/day. Exploratory endpoints include association of somatic mutations in PI3KCA, ARID1A and PTEN, and ARID1A and PTEN expression with outcome and response. Patients ECOG $\leq$2, with histologically documented diagnosis of recurrence OCCC, any number of prior treatment regimens (chemotherapy, biologics or other target therapies except for Aurora A targeted therapies), and measurable disease (RECIST criteria 1.1) are eligible. Based on data from previous studies, a sample size of 36 patients will provide 95% power to detect an improvement in response rate from 10 to 30% and 90% power to detect an increase in 6 month PFS from 20 to 40%. Since September 2013, 6 patien Clinical trial information: NCT01914510.

**TPS5621 General Poster Session (Board #398A), Sat, 8:00 AM-11:45 AM**

**The PARAGON phase 2 trial of anastrozole in women with potentially hormone responsive recurrent/metastatic gynecologic neoplasms.** *Presenting Author: Katrin Marie Sjoquist, NHMRC Clinical Trials Centre (CTC), University of Sydney and Cancer Care Centre, St George Hospital, Sydney, Australia*

**Background:** Gynaecological cancers of several pathological subtypes express estrogen and/or progesterone hormone receptors (ER/PR). Previous studies, [all or mostly] retrospective, have reported variable rates of tumour response and clinical benefit. Prospective studies are needed to determine the activity of aromatase inhibitors in women with potentially hormone responsive recurrent gynaecological cancers, and to determine possible predictors of response. **Methods:** PARAGON is a Gynecologic Cancer InterGroup phase 2 trial lead by the Australia New Zealand Gynaecological Oncology Group and NHMRC Clinical Trials Centre, in collaboration with Cancer Research UK and the Belgian Gynaecological Oncology Group. The study is designed to facilitate research in rare tumours. The protocol enrols postmenopausal women with recurrent gynaecological cancers of 7 different subtypes: epithelial ovarian cancer (EOC) with only rising CA125 after first line chemotherapy; platinum resistant/refractory EOC; low grade EOC; endometrial carcinomas; endometrial stromal sarcomas; miscellaneous sarcomas; and, granulosa cell and other sex cord stromal tumours. ER/PR positivity must be demonstrated by immunohistochemistry. Each subgroup will enrol 25-50 patients with defined stopping rules based on response and reviewed by an independent data monitoring committee (IDMC). Study treatment is anastrozole 1 mg daily until disease progression or unacceptable toxicity. The primary endpoint is clinical benefit (complete response, partial response, or stable disease at x months). Secondary endpoints include progression free survival, response duration, aspects of QoL, toxicity. Blood and tumour samples are being collected for translational studies and confirmation of ER/PR positivity. Recruitment commenced in 2011 in Australia, New Zealand and the United Kingdom. 236 of 350 planned patients have been enrolled to February 2014. Accrual to the platinum resistant/refractory subgroup closed on 9 December 2013. Anastrozole is being provided by AstraZeneca for study participants in Australia and the UK. This study has been partially funded by a grant from Cancer Australia (APP632740). Clinical trial information: ACTRN12610000796088.

**TPS5622 General Poster Session (Board #398B), Sat, 8:00 AM-11:45 AM**

**Double-blind, placebo-controlled, randomized, phase 2 study to evaluate the efficacy and safety of maintenance therapy with anti-TA-MUC1 monoclonal antibody PankoMab after chemotherapy in patients with recurrent epithelial ovarian carcinoma.** *Presenting Author: Jonathan A. Ledermann, UCL Cancer Institute, University College London, and University College London Hospitals, London, United Kingdom*

**Background:** PankoMab is a potent humanized glyco-engineered IgG1 recognizing the tumor-specific carbohydrate/protein epitope TA-MUC1 expressed virtually only on tumor cells of a wide variety of cancers with up to 95% expression in ovarian (OvCa), NSCL and breast cancers. Phase 1 study results were presented at ECCO 2013 (C. Sessa et al., Abstract 849). Drug was well tolerated, clinical benefit (CB: CR, PR and SD) observed in pts. with solid tumors with CB rate of 40% incl. 1 CR of 485 d out of 20 pts. with OvCa. OvCa was selected as target indication for a randomized phase 2 maintenance therapy trial of PankoMab in TA-MUC1 positive pts. **Methods:** Study design: Randomized, placebo-controlled, double-blind Phase 2 multinational study at 40 sites in 8 European countries. Pts. with outcome of CR, PR or SD after most recent line of chemotherapy (CT) are randomized in a 2:1 ratio for treatment with either PankoMab or placebo. Treatment regimen: 500 mg starting dose followed by 1700 mg 7 d later, to be repeated q3w. Pt. stratification by: (i) Duration of treatment-free interval of the most recent platinum based CT preceding the CT to which the pt. has just responded, (ii) Type of response to CT the patient has just received, (iii) Number of prior lines of CT. Sample size: Total of210 assuming median PFS of 4 m. in placebo and 6 m. in PankoMab arm (HR 0.67; overall 1-sided significance level 0.05). Study endpoints: Primary: PFS using modified immune related RECIST v1.1 criteria; secondary: OS, tumor response, safety, QoL, correlation of efficacy/safety with TA-MUC1 IHC score, soluble TA-MUC1 levels, Fc□ receptor status, and PK. Main entry criteria: TA-MUC1 pos. tumor samples, recurrent epithelial OvCa; 2 – 4 lines of previous CT; CR, PR, or SD after most recent CT; ≤5 wk. interval between last CT dose and randomization.; treatment-free interval of ≤12 mo. before most recent CT; sensitive or resistant but not refractory to most recent platinum based CT; ECOG PS ≤1. Current status: All sites initiated, 36 pts. pre-screened, 6 pts. enrolled, results expected 2015. EudraCT: 2013-000931-28. Clinical trial information: NCT01899599.

**TPS5623 General Poster Session (Board #399A), Sat, 8:00 AM-11:45 AM**

**A first-in-human dose escalation and dose-finding phase I/II trial of IMAB027 in patients with recurrent advanced ovarian cancer (GM-IMAB-002-01).** *Presenting Author: Dirk Jaeger, National Center for Tumor Diseases, University of Heidelberg, Heidelberg, Germany*

**Background:** Ovarian cancer is a commonly diagnosed incurable disease with approximately 29,000 deaths annually. Surgery followed by platinum-based chemotherapy is the initial standard of care. However, the majority of patients relapse and therapy options are very limited. 25-53% of ovarian cancers express claudin 6 (CLDN6) a carcino-embryonic transmembrane protein, which is absent from normal adult tissue. IMAB027 is a chimeric antibody specifically binding to CLDN6 and not cross-reacting with other proteins. Based on preclinical data and compassionate use data, IMAB027 may provide a well tolerable treatment option with a high potential to be clinically beneficial. **Methods:** This first-in-human, open-label, combined dose escalation Phase I/II trial assesses the safety/tolerability and the clinical efficacy of IMAB027 in patients with ovarian cancer. The Phase I part includes two stages: stage 1 comprises an intra-patient accelerated dose escalation and stage 2 a classical 3+3 inter-patient dose escalation design to determine the MTD based on DLTs and to define the recommended dose for the subsequent Phase II part. The Phase II part is a single-arm, safety/tolerability study with a planned enrolment of about 60 patients. Our novel combinatory approach enables a smooth transition of patients from Phase I to Phase II and ensures continuous treatment of patients benefitting from IMAB027. An independent DSMB is continuously monitoring the conduct of the study. The trial was approved by responsible local regulatory authorities/ethics committees and is registered at ClinicalTrials.gov (NCT02054351). Eligible patients had to have CLDN6+ ovarian cancer which was either symptomatic or asymptomatic (patients with CA125-rise without detectable tumor lesions, who had at least one line of standard treatment). Currently, there is no treatment available for asymptomatic patients with a high risk of disease recurrence. IMAB027 may provide a non-aggressive treatment solution for such patients. In addition, we evaluate an extensive set of biomarkers with prognostic potential, and correlation analysis with clinical outcome will be performed. Clinical trial information: NCT02054351.

**TPS5624 General Poster Session (Board #399B), Sat, 8:00 AM-11:45 AM**

**Randomized phase II study of 3 versus 6 courses of neoadjuvant carboplatin-paclitaxel chemotherapy in stage IIIC or IV epithelial ovarian cancer.** *Presenting Author: Claudio Zamagni, Addarii Medical Oncology Unit, S.Orsola-Malpighi Hospital, Bologna, Italy*

**Background:** The role and the duration of neoadjuvant chemotherapy (NACT) in advanced epithelial ovarian cancer (AOC) are still debated. A phase III randomized trial showed that 3 courses of NACT followed by surgery were not inferior to primary debulking surgery followed by chemotherapy (CHT) for patients (pts) with AOC. Moreover, the absence of residual tumor after surgery was found to be the single most important independent prognostic factor. In our preliminary experience pts with bulky stage IIIC or IV AOC were treated with 6 courses of NACT followed by surgery and we observed a complete cytoreduction rate up to 63% ; the survival data did not suggest a detrimental effect of such strategy. Considering the lack of evidence regarding the best standard of care for pts with AOC, a randomized study of 3 *vs* 6 courses of NACT was designed to verify if 3 more courses of NACT are associated to an increase of complete cytoreductive surgery rate (CCSR) (primary end-point). **Methods:** this is a multicenter randomized, phase II study of 3 *vs* 6 courses of NACT in AOC. The main eligibility criteria are ECOG PS ≥ 2, histologically confirmed FIGO stage IIIC-IV epithelial ovarian cancer, unsuitable for complete primary cytoreductive surgery (inoperability confirmed by open laparoscopy or laparotomy). Pts will receive 3 or 6 courses of i.v. carboplatin AUC 5 and paclitaxel 175 mg/m$^2$ every 3 weeks, followed by surgery.Tumor tissue will be collected for analyses of prognostic and predictive biomarkers, including ESR1 mRNA, HER2 and HER3 expression, BRCA1, BRCA2 and PI3KCA mutations. By hypothesizing a CCSR of 43% in Arm A (3 courses) and 63% in Arm B (6 courses), with a two-sided alpha error of 0.05 and a power of 0.80, 214 pts (107 in each arm) are to be enrolled in 2 years. An interim analysis has been scheduled after the first 120 pts in order to end the enrollment in the phase II and to start a phase III (with survival as primary endpoint) in case of the endpoint for efficacy (CCSR) will be reached at that time. The sample size of the interim analysis was calculated by considering the same alpha error (0.05) but a lower power value (0.50) than those of the global sample size calculation. The first patient was enrolled in January 2014. Clinical trial information: 2013-002520-17.

**TPS5625 General Poster Session (Board #400A), Sat, 8:00 AM-11:45 AM**

**A phase 3 randomized double-blind trial of maintenance with niraparib versus placebo in patients with platinum-sensitive ovarian cancer (ENGOT-OV16/NOVA trial).** *Presenting Author: Ursula Matulonis, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Niraparib is a potent, oral poly(ADP-ribose)polymerase (PARP)1/2 inhibitor with efficacy in both germline BRCA mutation (gBRCA-mut) ovarian cancer (OvCa) and BRCA negative (nongBRCAmut) high grade serous OvCa (HGSC). Ph I data established a RP2D of 300 mg with anti-OvCa activity and is well-tolerated. **Methods:** The ENGOT-OV16/NOVA study is a double-blind, 2:1 randomized, placebo controlled international ph III study of oral niraparib versus placebo in patients (pts) with platinum (plat) sensitive recurrent OvCa. Primary objective is to evaluate efficacy of niraparib as maintenance therapy in pts who have plat sensitive OvCa as assessed by the prolongation of progression free survival (PFS). PFS will be independently evaluated in a cohort of gBRCAmut pts and in pts who have HGSC histology and are nongBRCAmut. Secondary objectives are: (1) bridge the centralized BRCA mutation test method to the candidate companion diagnostic test, if needed; (2) evaluate add'l measures of clinical benefit including pt reported outcomes, PFS2, chemotherapy free interval, overall survival; (3) evaluate the safety/tolerability of niraparib vs placebo; (4) evaluate QTc in a subset of niraparib-treated OvCa pts. A recent food effect sub study in 15 pts demonstrated no effect of a high fat meal on the PK's of a single 300 mg dose of niraparib in OvCa pts. Main study eligibility includes: histologically confirmed OvCa, fallopian tube or peritoneal cancer, HGSC histology or known gBRCAmut, plat sensitive recurrence, completion of at least 2 previous courses of plat-containing therapy and sensitivity to both via radiographic imaging, normal or CA125 decrease by 90% after last plat, agreement by pt to undergo gBRCA status prior to randomization, availability of FFPE archival tumor, ECOG PS 0-1, normal organ function, and can take PO. The main study is sized to address PFS endpoint w/ an accrual goal of 360 pts. As of 04 February 2014, 37 pts have been enrolled and randomized in the study. The trial will be open at $>$100 sites in 15 countries in collaboration with ENGOT (NSGO, AGO, NCRI, GEICO, BGOG, GINECO, MaNGO, AGO Austria, MITO). Clinical trial information: NCT01847274.

**TPS5626 General Poster Session (Board #400B), Sat, 8:00 AM-11:45 AM**

**Open-label phase II clinical trial of orteronel (TAK-700) in metastatic or advanced nonresectable granulosa cell ovarian tumors: The GREKO II study.** *Presenting Author: Alicia Hurtado, Hospital Universitario Fundación Alcorcón, Alcorcón, Spain*

**Background:** Granulosa-cell tumors (GCT) of the ovary are a rare entity characterized by its genomic stability. A punctual mutation at the FOXL2 gene 402C→G (C134W) is present in up to 90% of cases. FOXL2 is a transcription factor that physiologically regulates the expression of the Steroidogenic Factor-1 (SF-1). This factor is known downregulate the expression of the enzyme CYP17 (key in androgens and 17-OH-progesterone synthesis). Thus FOXL2 mutations could impact hormonal synthesis by CYP17 in GCT. In fact, a previous study by our group has found clinical activity of ketoconazole, a well known CYP17 inhibitor, in this tumor (GREKO I trial). Orteronel (TAK700) is a selective inhibitor of 17, 20-lyase, that is being developed as an endocrine therapy for relevant hormone-sensitive cancers such as prostate and breast cancer. Orteronel is expected to suppress sex hormone levels in both circulation and relevant hormone-dependent malignant tissue. Thus we aimed to test the clinical activity of such drug in GCT. **Methods:** An open-label phase II single arm clinical trial has been designed for women with metastatic or locally advanced nonresectable granulosa cell ovarian tumor that harbors the somatic mutation FOXL2 402C→G (C134W) and who have not received prior treatment with any CYP17 inhibitor. Treatment will consist on Orteronel 300mg BID, given orally, continuously in a 28-day treatment cycle. The primary objective is to assess the clinical benefit rate. Since this is an extremely unfrequent disease, 10 Spanish institutions will get involved. The active support of a big collaborative group (GETHI) will guarantee candidates to be refereed to such institutions. An extensive translational research will be included in order to improve our scarce knowledge of GCT. Clinical trial information: 2013-003128-35.

**TPS5627 General Poster Session (Board #401A), Sat, 8:00 AM-11:45 AM**

**The REZOLVE phase II trial to evaluate the safety and potential palliative benefit of intraperitoneal bevacizumab in patients with symptomatic ascites due to advanced, chemotherapy-resistant ovarian cancer.** *Presenting Author: Katrin Marie Sjoquist, NHMRC Clinical Trials Centre (CTC), University of Sydney and Cancer Care Centre, St George Hospital, Sydney, Australia*

**Background:** We hypothesise that intraperitoneal (IP) administration of bevacizumab will reduce formation, and delay time to re-accumulation, of ascites in patients with malignant ascites and chemotherapy-resistant ovarian and related cancers. The aim is to evaluate the activity of IP bevacizumab in delaying re-accumulation of ascites in patients with chemotherapy resistant ovarian, peritoneal and fallopian tube cancers with symptomatic ascites. The primary objective is to evaluate the activity of IP bevacizumab to reduce formation or delay re-accumulation of malignant ascites (median time from first to second therapeutic ascitic drainage). Secondary outcomes: (1) safety (2) activity of a second dose of IP bevacizumab (median time from second to third therapeutic ascitic drainage) (3) HRQOL. Correlative objectives include assessment of molecular mechanisms of ascites formation and changes in inflammatory markers over time. **Methods:** Eligibility: Patients with platinum resistant/refractory recurrent ovarian cancer with symptomatic, cytologically confirmed malignant ascites that has recurred following therapeutic ascitic drainage within 4 weeks prior to study registration, who are no longer receiving chemotherapy. Treatment: Patients will undergo therapeutic drainage and bevacizumab (5 mg/kg) administered as an IP infusion in 100ml saline followed by 400mL saline over 30-60 minutes. This procedure may be repeated, providing the paracentesis occurs at least 42 days after each administration of bevacizumab. Post-drainage abdominal ultrasound will document remaining fluid volume. Ultrasound and estimation of ascites volume will be performed within 48 hours prior to each clinical assessment (every 3 weeks while on study). 16 patients will give 80% power with 95% confidence to exclude a rate of 20% in favour of a clinically meaningful rate of 54% of patients paracentesis-free at 6 weeks **Summary:**Study is open at 3 of 5 planned sites and 1 patient has been recruited. Funding: Cancer Australia (APP1050134) and seed funding from the Ovarian Cancer Research Foundation. Clinical trial information: ACTRN12611000801910.

**TPS5628 General Poster Session (Board #401B), Sat, 8:00 AM-11:45 AM**

**A phase III trial of postoperative chemotherapy or no further treatment for patients with node-negative stage I-II intermediate- or high-risk endometrial cancer. ENGOT-EN2-DGCG/EORTC 55102.** *Presenting Author: Mansoor Raza Mirza, Danish Gynecologic Cancer Group, Copenhagen, Denmark*

**Background:** Patients with medium and high-risk stage I and II endometrial cancers have, despite radical surgery, high risk for local and distant progression. Adjuvant radiotherapy was unable to improve survival. Two phase III studies failed to show any difference in survival between radiotherapy and chemotherapy, though both studies had suboptimal chemotherapy regimens/included good prognosis patients. The GOG-122 phase 3 study in stage III and IV found significant improvement in survival in the chemotherapy arm. It is of utmost importance to clarify the role of adjuvant combination chemotherapy comparing to no further treatment in this patient population. Paclitaxel-Carboplatin combination chemotherapy is effective and well tolerated. **Methods:** This multicenter, open-label, 1:1 randomized, phase 3 investigator-initiated study is evaluating postoperative chemotherapy compared with no further treatment in patients with medium- or high-risk, node negative stage I, or stage II endometrial cancer (stage 1: grade 3 endometrioid or any type 2 histology; stage 2: all patients). Patients have undergone hysterectomy and bilateral salpingo-oopherectomy and pelvic lymphadenectomy (minimum 12 pelvic nodes. Para-aortic LNE is optional). Adjuvant brachytherapy is permitted in both arms, though external beam radiotherapy is not allowed. Primary endpoint is overall survival, and secondary endpoints include disease specific survival, progression-free survival, rates of isolated pelvic, distant and mix relapses, quality of life, compliance and toxicity. Carboplatin (AUC5) and paclitaxel (175mg/m2) is given iv every 3 weeks, total 6 courses. This trial will enrol 678 patients. This trial is enrolling patients. Interested institutions are welcome to join the study. Clinical trial information: NCT01244789.

**TPS5629 General Poster Session (Board #402A), Sat, 8:00 AM-11:45 AM**

**Phase II study of XL184 (cabozantinib) in recurrent or metastatic endometrial cancer: A trial of the PMH, Chicago, and California Phase II Consortia.** *Presenting Author: Michelle Wilson, Department of Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada*

**Background:** Recurrent endometrial cancer (EC) has a poor prognosis with few therapeutic options. Targeting angiogenesis through VEGF inhibition has demonstrated real but limited efficacy. Simultaneous inhibition of angiogenesis and putative resistance mechanisms may provide more durable therapeutic responses. MET/HGF (hepatocyte growth factor) paracrine signaling has been implicated in more aggressive tumour biology, angiogenesis and resistance to VEGF targeting in EC. XL-184 (cabozantinib) is an orally bioavailable, multi-targeted inhibitor with activity against MET and VEGFR2 in addition to TIE2, RET, AXL and KIT. **Methods:** This phase II, multicenter single arm trial has a planned enrollment of 36 pts utilizing a Simon 2-stage design to evaluate co-primary endpoints of response rate and 12 week progression-free-survival (PFS) in pts with serous, endometrioid or mixed histology EC (experimental cohort). Eligible pts must have radiographic progression after 1 line of chemotherapy for metastatic disease, or progression within 12 months of adjuvant chemotherapy; prior radio- and hormonal therapy is allowed. Stage I has a planned accrual of 18 pts, study will proceed to stage II with observation of $> 2$ partial responses (PR) and $> 6$ 12-wk PFS. Pts are also accrued to an exploratory cohort (maximum 30 pts) of rare histology EC (clear cell, carcinosarcoma). XL-184 is administered at a starting dose of 60mg orally once daily on a continuous 28 day cycle. Adverse event (AE) reporting is as per CTCAE v4.0. Pts undergo first CT evaluation after 1 cycle, those with SD or PD and $\leq$ grade 1 toxicity are eligible for dose escalation. Response assessment is completed every 2 cycles (starting with cycle 3) and per RECIST 1.1. Correlative studies will explore associations between tumour response and baseline mutational and met amplification status. To date 14 (experimental) and 6 (exploratory) pts have been enrolled. Median age is 64 (range 51-80). All pts have received chemotherapy and 70% prior radiation. 44 cycles have been completed (median 2 range 1-5). Once the final pts have been accrued to the experimental arm, a decision to proceed to stage II will be made. Clinical trial information: NCT01935934.

**TPS5630^ General Poster Session (Board #402B), Sat, 8:00 AM-11:45 AM**

**ZoptEC: Phase III study of zoptarelin doxorubicin (AEZS-108) in platinum-taxane pretreated endometrial cancer (Study AEZS-108-050).** *Presenting Author: David S. Miller, The University of Texas Southwestern Medical Center, Dallas, TX*

**Background:** A platinum-taxane combination is commonly used both as adjuvant and first line therapy for advanced, recurrent, and metastatic endometrial cancer (EC). Zoptarelin doxorubicin (AEZS-108) is a hybrid anticancer agent in which doxorubicin is chemically linked to zoptarelin, a D-$Lys_6$-analogue of luteinizing hormone releasing hormone (LHRH). Zoptarelin doxorubicin was initially evaluated in tumor types reported to express receptors for LHRH. Depending on the method used to determine LHRH receptor expression, LHRH receptors have been found in 40% to 90% of ECs. A Phase II study of zoptarelin doxorubicin in EC patients showed activity, including those previously treated with platinum-taxane [Emons et al. 2014]. **Methods:** This open-label, randomized-controlled study compares the efficacy and safety of AEZS-108 and doxorubicin (ClinicalTrials.gov Identifier: NCT01767155; EudraCT No: 2012-005546-38; ZoptEC**:** Zoptarelin doxorubicin in endometrial cancer). The study is expected to include 500 EC patients progressing after prior therapy with platinum-taxane-based chemotherapy. There are about 120 expected study sites in North America, Western and Central/Eastern Europe, and Israel. Patients are centrally randomized in a 1:1 ratio and receive either AEZS-108 (267 $mg/m^2$) or doxorubicin (60 $mg/m^2$) intravenously, every 3 weeks and for up to 9 cycles. Response will be evaluated every 3 cycles during treatment, thereafter every 12 weeks until progression. All patients will be followed for survival as the primary efficacy endpoint (EP). The final analysis is planned after about 384 deaths have occurred, interim analyses after about 128 (futility only) and 192 deaths. Secondary EPs include progression-free survival (PFS), objective response rate (ORR), and clinical benefit rate (CBR). Quality of life will be compared based on EORTC QLQ-30 and EN-24 questionnaires. A substudy in about 40 patients compares the pharmacokinetics of AEZS-108 and doxorubicin and doxorubicinol. Clinical trial information: NCT01767155.

**TPS5631 General Poster Session (Board #403A), Sat, 8:00 AM-11:45 AM**

**A phase 1/2 study of ipilimumab in women with metastatic or recurrent HPV-related cervical carcinoma: A study of the Princess Margaret and Chicago N01 Consortia.** *Presenting Author: Stephanie Odile Lheureux, Princess Margaret Cancer Centre, Toronto, ON, Canada*

**Background:** Cervical cancer (CC) is the second cause of cancer-related mortality in women worldwide. Response to second-line chemotherapy is infrequent and the poor outcome of patients with advanced disease (median survival 9 months) warrants novel therapeutic strategies that exploit abnormal tumor biology. Based on new evidence that host-dependent immunologic status and HPV-induced immune evasion are responsible for persistent HPV infection, the prime causal factor of CC, immunotherapy is an attractive emerging strategy to target this disease. Ipilimumab is a fully humanized monoclonal antibody that blocks cytotoxic T-lymphocyte antigen-4 (CTLA-4), a molecule that acts to downregulate the T cell immune response. **Methods:** A 2-step multicenter trial was designed to evaluate ipilimumab IV in metastatic or recurrent HPV-related CC (NCT01693783). Eligible patients require measurable disease progression and at least one previous platinum based line of chemotherapy. A safety phase I cohort was planned with ipilimumab 3 mg/kg every 21 days for four cycles in 6 evaluable patients. After demonstration of safety, a phase II trial was planned with ipilimumab 10 mg/kg at the same schedule; followed by four additional cycles maintenance therapy at the same dose every 12 weeks for patients with radiologic confirmed response or stabilization. The primary objective is to assess the safety and the objective response rate at the end of cycle 4. 18 evaluable patients are scheduled and if at least 1 partial response is seen, an additional 14 patients will be enrolled. Immune assessment studies are performed on peripheral blood collected prior to and following ipilimumab therapy and on archived and fresh tumour tissue obtained prior to treatment and within the first week of cycle 2. This trial was activated in September 2012. The phase I cohort is now completed, and 8 patients have been enrolled in the phase II. The overall median age of study subjects is 49 (range 36-60) with a majority of squamous histology type (13/14 patients). A median of 3 cycles have been administered, and 12 patients have undergone pre- and post-treatment biopsies. Clinical trial information: NCT01693783.

**TPS5632 General Poster Session (Board #403B), Sat, 8:00 AM-11:45 AM**

**A phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone: Outback (ANZGOG0902/GOG0274/RTOG1174).** *Presenting Author: Linda R. Mileshkin, Peter MacCallum Cancer Center, Melbourne, Australia*

**Background:** Cervical cancer is a global health problem and the most common cause of cancer-related death among women in developing nations. Despite the recently developed cervical cancer vaccine, many women will continue to die from cervical cancer for many decades unless existing treatments can be improved. Unscreened women often present with locally-advanced disease that has a 5-year overall survival (OS) rate of 60% or less following standard chemo-radiation. Although some evidence suggests that adjuvant chemotherapy following chemo-radiation may be of value, its role remains controversial. **Methods:** OUTBACK is a randomised phase III Gynecologic Cancer InterGroup (GCIG) trial designed and led by the Australia New Zealand Gynaecological Oncology Group (ANZGOG) in collaboration with the NHMRC Clinical Trials Centre. Participating countries (groups) include Australia & New Zealand (ANZGOG), the USA (GOG, RTOG), Saudi Arabia, and Canada (RTOG). OUTBACK is suitable for women with locally advanced cervical cancer (FIGO stage $IB_1$ & node positive, $IB_2$, II, IIIB or IVA). The primary objective is to determine if the addition of adjuvant chemotherapy to standard cisplatin-based chemo-radiation improves OS. Women are randomized to either (A) standard cisplatin-based chemo-radiation or (B) standard cisplatin-based chemo-radiation followed by 4 cycles of carboplatin and paclitaxel chemotherapy. Secondary objectives are to compare progression-free survival, treatment-related toxicity, patterns of disease recurrence, quality of life and psycho-sexual health, and the association between radiation protocol compliance and outcomes. Blood and tumour samples are collected from consenting patients for future translational studies. 780 women will be enrolled to determine if the addition of adjuvant chemotherapy can improve the 5-year OS rate by $\geq$ 10%. OUTBACK opened in Australia & New Zealand in 2011 and in early 2012 the trial opened in the USA. 285 patients have been recruited from 145 active sites. The IDMC last reviewed the trial in September 2013 and recommended that the trial continue as planned. Clinical trial information: ACTRN12610000732088.

**6000 Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**The *KRAS*-variant and cetuximab response in RTOG 0522.** *Presenting Author: Joanne B. Weidhaas, Yale School of Medicine, New Haven, CT*

**Background:** The *KRAS*-variant, a germ-line mutation in a microRNA-binding site in *KRAS*, predicts increased cancer risk and unique cancer biology for many cancers. RTOG 0522 is a phase III trial of cisplatin/radiation +/- cetuximab for patients with locally advanced head and neck cancer. Here we tested the hypothesis that the *KRAS*-variant would predict cetuximab response for these patients. **Methods:** Germline DNA was isolated from blood or buffy coat and tested for the *KRAS*-variant in Mira Dx's CLIA-certified laboratory. Hazard ratios (HR) were estimated by Cox model. Where proportional hazards assumption was invalid, models included time-dependent covariates. **Results:** 413/891 eligible patients on 0522 (46.4%) were tested for the *KRAS*-variant, and 70/413 were positive (16.9%). For progression-free survival (PFS) in the *KRAS*-variant group, there was a significant cetuximab benefit in year 1 (HR 0.31, p=0.04) and a significant interaction between treatment and time (p=0.02), confirming different effects in the first year and after. HR after year 1 was 1.76, but this did not reach statistical significance (p=0.29). The number of events in the *KRAS*-variant group (32) was too small for formal multivariate analysis, but HRs were stable after adjustment for single covariates (age, pack-years, Zubrod, site, p16, stage). In the *KRAS*-wildtype group, HRs for cetuximab effect were 1.00/1.07 with/without adjustment for covariates, similar to the overall trial (1.08). For overall survival (OS) in the *KRAS*-variant group there was a significant cetuximab benefit in years 1-2 (HR 0.19, p=0.03) and a significant interaction between treatment and time (p=0.02) confirming different cetuximab effects in years 1-2 and after. The HR after year 2 was 2.34, but this did not reach statistical significance (p=0.23). HRs were stable after adjustment for single covariates. In the *KRAS*-wildtype group, HRs for cetuximab effect were 0.90/0.93 with/without adjustment for covariates, similar to the overall trial (0.95). **Conclusions:** Our findings suggest that locally advanced head and neck cancer patients with the *KRAS*-variant appear to positively respond to cetuximab, resulting in better short-term PFS and OS. These results warrant further validation through a prospective study. Clinical trial information: NCT00265941.

**6001 Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**Impact of p16 status on the results of the phase III cetuximab (cet)/radiotherapy (RT).** *Presenting Author: David I. Rosenthal, MD Anderson Cancer Center, Houston, TX*

**Background:** This is a retrospective analysis of the phase III IMCL-9815 trial assessing the role of HPV status in LASCCHN patients (pts) receiving RT+cet or RT by measuring p16 status. **Methods:** The intent-to-treat (ITT) population (424 pts) was randomized to RT+cet or RT. p16INK4A status was determined by immunohistochemistry. **Results:** 312/424 (74%) of the ITT pts were p16 evaluable. Baseline characteristics in the ITT and p16 evaluable pts were similar. In both p16+ and p16- pts, the addition of cet to RT improved locoregional control (LRC), overall survival (OS), and progression-free survival (PFS) (Table). Univariate analyses showed a more pronounced treatment effect of RT+cet vs RT in p16+ pts across all endpoints in both the ITT and the oropharyngeal (OPC) populations; however, interaction tests for LRC, OS and PFS (ITT and OPC) did not demonstrate a significant interaction between p16 status and treatment effect. There were no new safety findings. **Conclusions:** p16 tumor status is strongly prognostic for pts with LASCCHN. Although the number of pts is small, these data showed that the pts benefit more from RT+cet compared with RT alone regardless of p16 status. HPV data are to be presented at the meeting. Observations in the OPC population are being evaluated in the RTOG 1016 trial. Clinical trial information: NCT00004227.

**Treatment effect.**

| | p16- | | | | p16+ | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | RT+cet | RT | HR (95% CI) | p value | RT+cet | RT | HR (95% CI) | p value | Interaction test |
| **ITT** | | | | | | | | | |
| **No. pts** | 109 | 120 | | | 44 | 39 | | | |
| **LRC median (mo)** | 12.9 | 11.3 | 0.78 (0.57–1.05) | 0.101 | NE | NE | 0.35 (0.13–0.90) | 0.023 | 0.098 |
| **OS median (mo)** | 24.4 | 20.6 | 0.90 (0.66–1.22) | 0.492 | NE | NE | 0.45 (0.19–1.06) | 0.062 | 0.134 |
| **PFS median (mo)** | 12.3 | 9.2 | 0.76 (0.57–1.03) | 0.078 | NE | NE | 0.47 (0.21–1.08) | 0.070 | 0.252 |
| **OPC** | | | | | | | | | |
| **No. pts** | 44 | 63 | | | 41 | 34 | | | |
| **LRC median (mo)** | 12.3 | 11.9 | 0.79 (0.50–1.26) | 0.319 | NE | NE | 0.31 (0.11–0.88) | 0.020 | 0.087 |
| **OS median (mo)** | 26.8 | 20.6 | 0.92 (0.58–1.46) | 0.717 | NE | NE | 0.38 (0.15–0.94) | 0.030 | 0.085 |
| **PFS median (mo)** | 11.7 | 10.1 | 0.77 (0.49–1.22) | 0.260 | NE | NE | 0.46 (0.19–1.10) | 0.073 | 0.253 |

Abbreviations: mo: months; HR: hazard ratio; NE: median not reached.

**6002 Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**Genomic profiling using targeted ultra-deep next-generation sequencing for prediction of treatment outcome after concurrent chemoradiation: Results from the German ARO-0401 trial.** *Presenting Author: Inge Tinhofer, Department of Radiooncology CCM/CVK, Charite University Hospital, Berlin, Germany*

**Background:** Genomic profiling using next-generation sequencing (NGS) has provided novel insights in the genomic landscape of squamous cell carcinoma in the head and neck region (SCCHN). This is the first report on its application within a phase III trial of concurrent chemoradiation in locally advanced SCCHN. **Methods:** Between 2004 and 2008, 364 patients with stage IV SCC of the oro- or hypopharynx were treated with hyperfractionated accelerated radiotherapy with cisplatin/5-FU or mitomycin C/5-FU. From 174 patients (48%) FFPE samples could be collected. HPV DNA PCR and p16 immunohistochemistry were carried out. From 106 cases (29%) targeted NGS was possible. Based on previous reports an SCCHN panel was designed comprised of 224 exons from 53 genes (mean coverage 3000-fold, minimum 370-fold). Only non-synonymous germline and somatic single-nucleotide polymorphisms (SNP) with an allele frequency of >5% were considered. SNP were classified according to a damage-score prediction algorithm. Kaplan-Meier-analysis, log-rank test and multivariate Cox regression analysis were performed. **Results:** The most frequent germline/somatic SNP were found in *TP53* (total 94%, disruptive mutations 22%) followed by *FAT1, PCDH15, KDR, PDGFRA* and *NOTCH1* (14%), with disruptive mutations in *TP53* and *NOTCH1* being almost mutually exclusive. Disruptive mutations in *TP53* were significantly associated with an HPV-negative status and correlated with reduced OS (HR 0.37, 95% CI 0.21-0.65, p=0.0005) and PFS (HR 0.39, 95% CI 0.23-0.69, p=0.001). In contrast, *NOTCH1* mutations were not related to HPV status, were significantly associated with improved OS (HR 2.4, 95% CI 1.1-5.7, p=0.039) and showed a trend to improved PFS (HR 2.1, 95% CI 0.9-5.1, p=0.07). Disruptive mutations in *TP53* and *NOTCH1* remained significant after correction for smoking, HPV and treatment. **Conclusions:** Targeted NGS revealed three SCCHN subgroups with distinct outcomes after chemoradiation. As discriminative factors we identified HPV, *NOTCH1* and disruptive *TP53* mutations. The functional relevance of *NOTCH1* mutations for radio-/chemosensitivity remains to be determined.

**6003 Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**Randomized phase III trial of concurrent chemoradiation with or without neoadjuvant gemcitabine, carboplatin, and paclitaxel in locally advanced nasopharyngeal cancer.** *Presenting Author: Terence Tan, National Cancer Centre Singapore, Singapore, Singapore*

**Background:** The role of neoadjuvant chemotherapy in addition to concurrent chemoradiation (CRT) in locally advanced nasopharyngeal cancer (NPC) is unclear. This trial investigates the overall survival (OS), tumor control, toxicity and quality of life (QOL) in stage III-IVB NPC patients treated with this approach. **Methods:** Patients were stratified by N-stage and randomized to neoadjuvant GCP (gemcitabine 1000mg/m$^2$, cisplatin AUC 2.5 and paclitaxel 70 mg/m$^2$) on Days 1 and 8 every three weeks for 3 cycles followed by CRT (radiotherapy 69.96 Gy (RT) with weekly 40mg/m$^2$Cisplatin), or CRT alone. The accrual (total 172) was planned to detect a 15% difference in OS with a one-sided 5% significance level and 80% power. Kaplan-Meier survival curves were compared using Peto's method. Cox regression analyses were performed. **Results:** Between September 2004 and August 2012, 180 patients were accanded, and 172 (GCP 86, CRT 86; WHO type II 7%, type III 93% ) analyzed by intention to treat. The median follow-up was 3.25 years for GCP and 2.69 years for CRT. There was no significant difference in OS between the two arms: 5-year OS 74.8% (GCP) vs 77.6% (CRT); HR =1.05; one-sided p=0.494. No significant difference was seen in the disease-free survival (HR 0.77, 95% CI 0.44–1.35, p=0.362) and distant metastases-free survival (HR 0.80, 95%CI 0.38 – 1.67, p=0.547). Treatment compliance in the neoadjuvant phase was good with relative dose intensity (RDI) between 83-85% but the RDI for concurrent Cisplatin was significantly lower in the GCP arm (75% vs 84%, p=0.003). 98% of patients received RT by intensity-modulated RT or tomotherapy. All patients completed RT except for 1 CRT patient who died during treatment. Overall, the GCP arm had higher rates of grades 3 and 4 pancytopenia (58% vs 37%), neutropenia (66% vs 12%), thrombocytopenia (14%vs 0%) and fatigue (14% vs 2%) than the CRT arm. The global QOL scores were comparable in both arms. The statistical boundary for futility was crossed at this 5$^{th}$ interim analysis and is being reported early on the recommendation of the DSMC. **Conclusions:** Neoadjuvant chemotherapy with GCP did not improve survival in locally advanced NPC and concurrent CRT remains the standard of care. Clinical trial information: CDR0000657121.

**6004** **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**Concomitant chemoradiation (CRT) or cetuximab/RT (CET/RT) versus induction Docetaxel/ Cisplatin/5-Fluorouracil (TPF) followed by CRT or CET/RT in patients with Locally Advanced Squamous Cell Carcinoma of Head and Neck (LASCCHN). A randomized phase III factorial study (NCT01086826).** *Presenting Author: Maria Grazia Ghi, Medical Oncology Department, Venezia, Italy*

**Background:** Platinum-based CRT is the standard treatment for LASCCHN. CET/RT is superior to RT alone and it is an alternative treatment to CRT. Induction TPF resulted to be superior to cisplatin/5fluorouracil but its efficacy when added to concomitant treatment is to be demonstrated. We designed this open-label multicenter 2x2 factorial study to assess 2 primary endpoints: 1) overall survival (OS) of induction vs. no induction; 2) Grade 3-4 in-field mucosal toxicity of CRT vs. CET/RT (already presented at ASCO 2013). **Methods:** 421 patients with LASCCHN of the oral cavity, oropharynx, hypopharynx, stage III-IV, ECOG PS 0-1 were randomized to one of four treatment options: Arm A1: CRT (cisplatin/5fluorouracil x 2 concomitant to standard RT fractionation); Arm A2: CET/RT; Arm B1: 3 cycles of TPF followed by the same CRT; Arm B2: 3 cycles of TPF followed by CET/RT. The superiority hypothesis of OS comparison of TPF induction vs. no induction (Arms B1+B2 vs. A1+A2), requires 204 deaths to detect a relative reduction of 33% with 2-sided 5% significance level for the log-rank test and a power of 80%. **Results:** 415 out of 421 patients (six major violations) were finally analyzed: 207 in induction and 208 in concomitant arm. By march 2014, at a median follow-up of 41.3 months (mos), 243 events for PFS and 201 deaths were observed. Radiological CR was 43.5% in induction and 28% in concomitant arm (p=0.002) Median PFS was 29.7 mos in induction vs 18.5 in concomitant arm with a 3-year PFS of 46.8% vs 36.7% (HR:0.73; 95%CI 0.57-0.94; p=0.015), respectively. Median OS was 53.7 mos in induction vs 30.3 in concomitant arm with a 3-year OS of 57.6% vs 45.7% (HR:0.72; 95%CI 0.55-0.96; p=0.025) respectively. Compliance to concomitant treatments was not affected by induction TPF. **Conclusions:** Induction TPF followed by CRT or CET/RT significantly improved PFS and OS (independently from the type of concomitant strategy) in LASCCHN patients without compromising compliance to the concomitant treatments. Clinical trial information: NCT01086826.

**6005** **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**Final analysis: A randomized, blinded, placebo (P)-controlled phase III study of adjuvant postoperative lapatinib (L) with concurrent chemotherapy and radiation therapy (CH-RT) in high-risk patients with squamous cell carcinoma of the head and neck (SCCHN).** *Presenting Author: Kevin J. Harrington, Institute of Cancer Research and Royal Marsden Hospital, London, United Kingdom*

**Background:** Epidermal growth factor receptor (EGFR) and ErbB2 are overexpressed in up to 90% and 40% of SCCHN, respectively. L, a tyrosine kinase inhibitor (TKI) of both EGFR and ErbB2, demonstrates tumor responses in SCCHN. **Methods:** Patients with resected stage II-IVA SCCHN, with a surgical margin ≤5mm and/or extracapsular extension were randomized to CT-RT with either P or L. RT was 66Gy (2Gy per day, 5 days per week).100 mg/m$^2$of cisplatin was administered on days 1, 22 and 43 of RT. P or L 1500 mg/day was given for up to one week prior to CT-RT, during CT-RT and for up to 12 months as monotherapy maintenance. Patients were stratified by nodal status, primary tumor location, geographical region and ErbB1 expression. The study had 80% power to detect a 10% absolute difference in disease free survival (DFS) rate (55% to 65%). **Results:** 688 patients were in the ITT population, 346 L and 342 P. Treatment arms were well balanced for prognostic factors. Median total doses of cisplatin (266.5 and 280 mg/m$^2$, L and P respectively) and median doses and duration of RT were similar in both arms. At the time of unblinding, recurrence/death from any cause was seen in 35% in L and 32% in P by independent review committee (IRC): Median DFS (95% CI) L: 53.6 mo (45.8, Not Reached [NR]); P: NR (54.6, NR), HR (95% CI) = 1.10 (0.85, 1.43) 2-sided p value = 0.45. Investigator results confirmed the IRC assessment: HR 1.03 (0.81, 1.30), p=0.82. No significant differences were observed in DFS for any of the pre-specified subgroups, including HPV. Death occurred in 30% L and 32% P; HR (95% CI) = 0.96 (0.73, 1.25). At least one adverse event was seen in 99% L and 98% P (SAEs 48% L/40% P, fatal AEs 7% L/5% P). AEs seen more in L were those expected with a TKI: diarrhea 42% vs 12%, rash 49% vs 30%, vomiting 46% vs 35%. Decrease in left ventricular ejection fraction SAEs were noted in 10 (3%) subjects L vs 3 (<1%) P. **Conclusions:** In patients with resected SCCHN at high risk for recurrence, L, when added to standard therapy RT/CDDP, does not extend DFS. DFS in both treatment arms exceeded adjuvant CT-RT compared with historical randomized data. Clinical trial information: NCT00424255.

**LBA6006** **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**E1308: Reduced-dose IMRT in human papilloma virus (HPV)-associated resectable oropharyngeal squamous carcinomas (OPSCC) after clinical complete response (cCR) to induction chemotherapy (IC).** *Presenting Author: Anthony Cmelak, Vanderbilt-Ingram Cancer Center, Nashville, TN*

**The full, final text of this abstract will be available at abstracts.asco.org at 2:00 PM (EDT) on Friday, May 30, 2014, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2014, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.**

**6007** **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**Randomized placebo-controlled trial (RCT) of erlotinib for prevention of oral cancer (EPOC).** *Presenting Author: William Nassib William, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Loss of heterozygosity (LOH) profiles predict oral cancer (OC) risk in patients (pts) with oral premalignant lesions (OPL). We conducted a randomized, multi-center, double-blind, placebo-controlled, personalized medicine trial of the EGFR inhibitor erlotinib in pts with OPLs defined as high risk by molecular criteria. Our primary hypothesis was that erlotinib would improve oral cancer-free survival (OCFS) in the high-risk, LOH+ population. **Methods:** Pts with histological evidence of an OPL (with or without a prior history of invasive OC) underwent LOH profiling at 3p14, 9p21, 4q, 8p, 11p, 13q, 17p. LOH+ pts were defined as those with prior OC and LOH at 3p14 and/or 9p21; or those without prior OC and LOH at 3p14 and/or 9p21 plus an additional chromosomal site. LOH- pts received no treatment. LOH+ pts were stratified by history of OC, then randomized (1:1) to erlotinib 150 mg po daily for 12 months or placebo and were assessed every 3-6 months for development of invasive OC. Primary endpoint was OCFS in the intent-to-treat (ITT) population. With a planned sample size of 150, the study had 85% power to detect a hazard ratio (HR) of 0.47 with a 5% 2-sided type I error rate (stratified logrank). **Results:** Of 375 pts evaluated for LOH, 254 were LOH+, of which 150 were randomized to erlotinib (N=75) or placebo (N=75). After a median follow up of 2.9 years, 44/179 LOH+ pts not randomized or randomized to placebo developed OC, versus 15/121 LOH- pts (HR=2.1, 95% CI 1.2-3.8, p=0.01). Among the randomized, LOH+, ITT population, 18/75 (24%) placebo-treated pts developed OC versus 22/75 (29%) erlotinib-treated pts. The HR for OCFS was 1.2 (95% CI 0.7-2.3, p=0.51) in the ITT population, 0.6 (95% CI 0.2-1.7) in 66 pts without prior OC, and 1.9 (95% CI 0.9-4.2) in 84 pts with prior OC (p=0.08 for interaction). Dose reductions were implemented in 34/75 and 1/75 erlotinib and placebo-treated pts, respectively, mostly due to expected, low-grade toxicities. **Conclusions:** EPOC is the first personalized RCT in cancer prevention and prospectively confirmed LOH as an OC risk marker. Erlotinib did not reduce OCFS in this high-risk population, although the trend of reduced OCFS in pts without prior OC suggests that the timing of this intervention may be important. Clinical trial information: NCT00402779.

**LBA6008** **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**A phase 3, multicenter, double-blind, placebo-controlled trial of lenvatinib (E7080) in patients with $^{131}$I-refractory differentiated thyroid cancer (SELECT).** *Presenting Author: Martin Schlumberger, Department of Nuclear Medicine and Endocrine Oncology,Gustave Roussy and University Paris-Sud, Villejuif, France*

**The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, May 31, 2014, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2014, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.**

**6009** **Clinical Science Symposium, Sun, 11:30 AM-1:00 PM**

**Correlation of T-cell inflamed phenotype with mesenchymal subtype, expression of PD-L1, and other immune checkpoints in head and neck cancer.** *Presenting Author: Vassiliki Saloura, University of Chicago, Chicago, IL*

**Background:** Immunotherapy with checkpoint blockade has shown encouraging activity in squamous cell carcinomas including a case report in tongue cancer (Herbst 2013). PD-L1 expression is common in HNC (Lyford-Pike 2013). In melanoma a T cell-infiltrated phenotype is common and correlates with immune inhibitory pathways. We interrogated the immune microenvironment in a large cohort of HNC in order to identify molecular correlates of an inflamed tumor microenvironment that may predict benefit from checkpoint blockade. **Methods:** We evaluated the presence of a T cell-inflamed tumor microenvironment in a cohort of 134 (Chicago HNC Genomics (CHGC)) and 424 TCGA HNC samples using a melanoma expression signature (Harlin/Gajewksi 2009). We evaluated multiple immune-related markers by IHC in a subset of CHGC tumors including CD8 tumor infiltrating lymphocytes (TIL)(N=73) and PD-L1 (N=55). Results were correlated with genetic and clinical information. **Results:** 47% of CHGC and 33% of TCGA tumors showed a T cell-inflamed phenotype (TCIP) similar to melanoma based on a gene expression signature (Harlin 2009). 75% of HPV(+) tumors showed a TCIP compared to 23% of HPV(-) tumors in both cohorts. Mesenchymal subtype (Keck 2014) strongly correlated with TCIP ($p<2.2x10^{16}$), and 90% of mesenchymal tumors showed TCIP including roughly equal numbers of HPV(+) and HPV(-) tumors in both cohorts. Basal and HPV-negative classical HNC tumors were TCIP negative. Based on IHC, 38% of CHCG tumors showed PD-L1 expression and 64% showed CD8+ TILs, both correlating with TCIP. Additional checkpoint molecules were universally co-expressed in the same TCIP tumors including CTLA4, LAG3, PDL-2, and IDO. Molecular processes enriched in non-TCIP tumors included EGFR/erbB signaling ($p=0.09$) characteristic of basal HNC, while multiple T-cell related signatures and the JAK/STAT pathway ($p<0.05$) characteristic of mesenchymal HNC were enriched in the TCIP tumors. **Conclusions:** 33-47% of HNC show a T cell-inflamed phenotype similar to melanoma. PD-L1 expression and TIL presence is common and strongly correlated with mesenchymal HNC in both HPV(+) and HPV(-) HNC and may benefit from immunotherapy.

**6010** **Clinical Science Symposium, Sun, 11:30 AM-1:00 PM**

**Distinct patterns of intratumoral immune cell infiltrates in patients with HPV-positive versus HPV-negative head and neck squamous cell carcinoma.** *Presenting Author: Simona Partlova, Department of Immunology, Charles University and University Hospital Motol, Prague, Czech Republic*

**Background:** Persistent human papillomavirus (HPV) infection is the most important etiologic agent of the oropharyngeal head and neck squamous cell carcinoma (HNSCC). Patients with HPV-positive HNSCC were reported to have a better clinical outcome than HPV-negative patients. However, little is known about the possible causes of the difference in the clinical outcome. In this study, we analyzed a detailed immune profile of tumor samples from HNSCC patients with respect to their HPV status. **Methods:** We studied the intratumoral immune cell infiltrates in 51 fresh HNSCC samples collected during the primary surgery. We analyzed the characteristics of immune cell infiltrates, including the frequency and distribution of antigen presenting cells, naïve and effector T cells, Th1/Th2/Th17 lymphocytes, regulatory T cells and cytokine and chemokine levels in the tumor tissue. **Results:** There was a profound difference in the extent and characteristics of the intratumoral immune cell infiltrates in HNSCC patients depending on their HPV status. In contrast to HPV-negative tumor tissues, HPV-positive tumor samples showed significantly higher levels of infiltrating IFN$\gamma$+ CD8+ T lymphocytes, IL-17+ CD8+ T lymphocytes, myeloid dendritic cells and proinflammatory chemokines. Furthermore, HPV positive tumors had significantly lower infiltration by exhausted CD8+ T lymphocytes characterized by high PD-1 and Tim-3 expression. **Conclusions:** The presence of strong intratumoral immune cell infiltrates might play a crucial role in the significantly better response of HPV-positive patients to standard therapy and their favorable clinical outcome. Additionally, characterization of the HNSCC immune profile may represent a valuable prognostic tool in addition to the HPV status and may help to identify novel targets for therapeutic strategies, including cancer immunotherapy.

**6011** **Clinical Science Symposium, Sun, 11:30 AM-1:00 PM**

**A phase Ib study of MK-3475 in patients with human papillomavirus (HPV)-associated and non-HPV–associated head and neck (H/N) cancer.** *Presenting Author: Tanguy Y. Seiwert, The University of Chicago Medicine and Biological Sciences, Chicago, IL*

**Background:** The PD-1 receptor-ligand pathway can be used by tumors to evade immune surveillance, thereby allowing neoplastic growth. MK-3475 is a highly selective, humanized IgG4/kappa isotype mAb designed to block PD-1 interaction with its ligands PD-L1 and PD-L2, to reactivate the immune system to eradicate the host tumor. **Methods:** Pts with recurrent/metastatic H/N cancer were enrolled in this multi-center, non-randomized trial in two cohorts (HPV and non-HPV associated). Pts were prescreened for PD-L1 expression by immunohistochemistry (22C3), and if positive allowed to proceed with treatment of single agent MK-3475 given intravenously at 10 mg/kg every 2 wks. Primary objectives are to determine (1) safety and tolerability and (2) anti-tumor activity of MK-3475 assessed by RECIST 1.1. Secondary objectives include progression-free survival, overall survival and response duration. **Results:** All results are based on preliminary, unaudited data as of Jan. 27, 2014. 77.9% of patients expressed PD-L1, defined as $\geq$1% of stained cells in the tumor microenvironment (Table). Of 60 patients (11 female, 49 male) enrolled in the study, 19 had an ECOG status of 0, and 40 had an ECOG status of 1 (1 unknown); 23 were HPV+ and 37 were HPV-; 9 had no prior systemic treatment, 10 had 1, 16 had 2, 13 had 3, and 7 had $\geq$4 prior regimens of treatment (5 unknown). Of the patients treated with MK-3475, 78.3% experienced $\geq$1 AE, and 46.7% reported a drug-related (DR) AE. The most common DR AEs reported were pruritis (6, 10%), fatigue (4, 7%), rash (4, 7%), and diarrhea (3, 5%). At least one Grade 3-5 AE was reported in 55.0% of patients, with 13.3% reporting a DR Gr 3-5 AE. Grade 3-5 AEs considered DR were hyponatremia, lymphopenia, rash, diarrhea, musculoskeletal pain, abscess (neck), and atrial fibrillation. Tumor shrinkage was observed in several patients, but protocol-specified efficacy analyses are not yet available. **Conclusions:** To date, treatment with MK-3475 has been well tolerated overall, with few serious DR AEs. Protocol-specified efficacy analyses are not yet available. Clinical trial information: NCT01848834.

**PD-L1 staining in tumors of screened patients (n=104).**

| Staining (%) | 0-10 | 11-20 | 21-30 | 31-40 | 41-50 | 51-60 | 61-70 | 71-80 | 81-90 | 91-100 |
|---|---|---|---|---|---|---|---|---|---|---|
| n | 50 | 8 | 9 | 3 | 2 | 2 | 4 | 3 | 2 | 21 |

**6012 Poster Highlights Session (Board #27), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy as treatment of unresected locally advanced head and neck cancer squamous cell cancer (HNSCC): A meta-analysis of randomized trials.** *Presenting Author: Wilfried Budach, University of Düsseldorf, Düsseldorf, Germany*

**Background:** Induction chemotherapy with docetaxel. cisplatin, and 5FU (TPF) before radiotherapy or chemoradiation (RT-CHX) has been shown to improve overall survival compared to induction chemotherapy with cisplatin and 5 FU in locally advanced HNSCC. Whether TPF induction before chemoradiation improves clinical outcome in comparison to chemoradiation is still a matter of debate. Recently, the results of 4 randomized trials addressing this question have become available. **Methods:** In the 4 trials of interest, in total 802 patients with locally advanced HNSCC were randomly assigned to receive either TPF induction chemotherapy followed by concurrent RT-CHX or concurrent RT-CHX. Platin or taxane based chemotherapy was used during radiotherapy (2x1.5 Gy and 1.8- 2 Gy in 30-35 fractions). 416 had oropharyngeal, 114 hyopharyngeal, 78 laryngeal, 143 oral cavity and 52 other HNSCC. Published hazard ratios and hazard ratios extracted from available survival curves for overall survival (OS) and progression free survival (PFS) were basis of the meta-analysis. Meta-analysis of the effect sizes on OS and PFS was performed using a random effects model based on parameter estimates of log hazard ratios in Cox models and their standard errors. **Results:** Additional induction chemotherapy with TPF before RT-CHX did not result in an improvement of overall survival (Hazard Ratio: 1.008, 95% confidence limits (CL) 0.816-1.246, p=0.940). A modest and statistically not significant benefit was observed in terms of PFS (Hazard Ratio: 0.881, 95% CL 0.723-1.073, p=0.207). **Conclusions:** Additional induction chemotherapy with TPF before RT-CHX does not improve overall survival in HNSCC.

**6013 Poster Highlights Session (Board #28), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Comparison of clinical primary tumor site (PTS) response to induction chemotherapy (IC) with APF (*nab*-paclitaxel, cisplatin, and 5-FU) or APF plus cetuximab (APF+Cetux) in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).** *Presenting Author: Jessica C. Ley, Washington University School of Medicine in St. Louis, St. Louis, MO*

**Background:** Achievement of a favorable (> PR) response (particularly CR) at the PTS to IC predicts a higher likelihood of long-term disease control after definitive chemoradiotherapy (CRT) in SCCHN. Low T classification and p16 + oropharynx [OP]SCCHN associate with favorable PTS response to IC. Based on improved tumor response rate with cetuximab added to chemotherapy in the EXTREME trial, we hypothesized a higher PTS CR rate with the addition of cetuximab to APF given as IC before CRT. **Methods:** Two consecutive prospective phase II trials (APF and APF+Cetux) were performed with the primary objective to determine the response rates (CR, PR, <PR) at the PTS. 30 patients were treated with APF (weekly *nab*-paclitaxel 100 mg/m$^2$ and every 3 week cisplatin 75 mg/m$^2$ and 5-FU 750 mg/m$^2$/dayx3) and 30 patients were treated with APF+Cetux (APF + weekly cetuximab 250 mg/m$^2$). After two cycles of IC, PTS response assessment by clinical exam was performed by experienced oncologic otolaryngologists. Patients were then scheduled for a third cycle of IC followed by definitive CRT (with cisplatin). **Results:** After two cycles of APF or APF+Cetux, CR rates at the PTS were 76.7% (23 patients) and 53% (16 patients), respectively. PR and <PR rates at the PTS after two cycles of APF were 16.7% (5 patients) and 6.7% (2 patients) and after APF+Cetux were 47% (14 patients) and 0%, respectively. CR rates at the PTS were consistently higher with APF compared to APF+Cetux when stratified for T classification and p16 status (Table). **Conclusions:** Unexpectedly, the addition of cetuximab to APF did not increase the CR rate at the PTS even when stratified for T classification and p16 status. This observation is consistent with our historical experience of TPF+Cetux (Adkins et al ASCO 2011 #5560). Validation of these findings in a randomized trial is indicated. Clinical trial information: NCT01566435 AND NCT00736944.

| | APF (n=30) | | APF+Cetux (n=30) | |
|---|---|---|---|---|
| **Characteristic** | **No.** | **%** | **No.** | **%** |
| **T2 #** | 8 | - | 8 | - |
| **CR** | 8 | 100 | 4 | 50 |
| **PR** | 0 | 0 | 4 | 50 |
| **T3 #** | 13 | - | 11 | - |
| **CR** | 9 | 69 | 6 | 55 |
| **PR** | 4 | 31 | 5 | 45 |
| **T4 #** | 9 | - | 11 | - |
| **CR** | 6 | 67 | 6 | 55 |
| **PR** | 1 | 11 | 5 | 45 |
| **<PR** | 2 | 22 | 0 | 0 |
| **P16+ OPSCC* #** | 17 | - | 17 | - |
| **CR** | 13 | 76 | 11 | 65 |
| **PR** | 3 | 18 | 6 | 35 |
| **<PR** | 1 | 6 | 0 | 0 |
| **P16- SCCHN #** | 13 | - | 12 | - |
| **CR** | 10 | 77 | 4 | 33 |
| **PR** | 2 | 15 | 8 | 67 |
| **<PR** | 1 | 8 | 0 | 0 |

* p16 not performed in 1.

**6014 Poster Highlights Session (Board #29), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Cisplatin versus cetuximab plus concomitant radiotherapy in locally advanced head and neck cancer: A meta-analysis of published trials.** *Presenting Author: Sandro Barni, Department of Medical Oncology, Treviglio and Caravaggio Hospital, Treviglio, Italy*

**Background:** Concurrent chemoradiotherapy (CTRT) or RT + cetuximab (RT + CET) are both treatment options for the treatment of locally advanced head and neck cancer (HNC). The efficacy of these two treatment modalities for patients with locoregionally advanced or inoperable HNC however has never been compared. **Methods:** We conducted a systematic review and meta-analysis by searching in PubMED, EMBASE, SCOPUS, Web of Science and The Cochrane Register of Controlled Trials, to compare CTRT and RT + CET in locally advanced HNC. Risk ratios (RRs) with 95% confidence intervals (95%CIs) were calculated for pre-specified endpoints as 2-year overall survival (OS), 2-year disease free-survival (DFS), 2-year loco-regional relapse (LRR) and 2-year distant metastases (DM). Meta-analysis was performed using the fixed- or random-effects models. **Results:** 15 trials for a total of 1,808 patients, were included. Concurrent CTRT significantly improved 2-year OS (RR=0.66, 95% CI 0.46-0.94; P=0.02), 2-year DFS (RR=0.68, 95% CI 0.53-0.87; P=0.002) and 2-year LRR (RR=0.63, 95% CI 0.45-0.87; P=0.005) compared to RT + CET. The absolute risk differences were 12%, 17% and 10%. Risk of distant metastases was identical (RR=1.01, 95%CI 0.69-1.48; P=0.94). **Conclusions:** Platinum-based CTRT is associated with a better 2-year OS and locoregional control compared to RT + CET, and still remains the standard of care in locally advanced HNC until prospective trials can demonstrate equivalence.

| **Endpoint** | **CTRT** | **RT + CET** | **Risk ratio (95% CI)** |
|---|---|---|---|
| **2-yr OS** | 71 % | 60.7 % | 0.66 (0.46-0.94) P=0.02 |
| **2-yr DFS** | 61.7 % | 43.1 % | 0.68 (0.53-0.87) P=0.002 |
| **2-yr LRR** | 19.6% | 32.3% | 0.63 (0.45-0.87) P=0.005 |

**6015 Poster Highlights Session (Board #30), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Induction chemotherapy (IC) followed by radiochemotherapy (RCT) versus radiochemotherapy alone as treatment in advanced laryngeal (LC)/ hypopharyngeal cancer (HC): Phase IIb.** *Presenting Author: Rainald Knecht, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

**Background:** Recently published long term results of the RTOG 91-11(J Clin Oncol 31:845-852) have shown that locoregional control and larynx preservation is in favour to concomitant radiochemotherapy(RCT).However there have been no differences in survival between IC, RCT and RT. RTOG 91-11 didn't use novel IC regimens like the standard IC Protocol of TPF (Tax324,Lancet Oncol 2011;12:153-59).The aim of the study was therefore to answer the question(a) if the addition of the standard IC TPF protocol to the standard RCT of the 91-11 is able to enhance the treatment efficacy(b)if TuVol and molecular markers are able to predict the outcome. **Methods:** 278 UICC Stage III/IV patients have been treated according the RTOG 91-11 protocol (concomitant arm) +/- IC TPF Tax323 induction protocol.Objective response and adverse events were assessed trough the RECIST criteria and the NCI CTCAE v2.0.Tumor assessment(endoscopy,biopsy,MRI)and EORTC QLQ C30 HN35 survey were carried out at the end of ICT and CRT and during fixed intervals after therapy. Primary endpoint was TTF assuming a 15% difference in favour of IC . **Results:** 5year Results:TPF IC+RCT vs.RCT:Completion of therapy 75%/82%; ORR 94%/87%; local 77%/64%,regional 72%/60% control(p<0.05);larynx preservation 87%/79%;distant control 94%/81%(p<0.05);OS 61%/55%(n.s);DFS 46%/37%,significant in HC(p=0.03).TTF difference in favour of IC was accepted(p=0.048).No significant differences in Grade 3-4 toxicities with the exception of neutropenia.CR after IC and IC+RCT was associated with better survival with only IC being highly significant in multivariate analysis(p<0.001).TuVol correlated with response rate(p=0.003)as well as Ki67+ and vascular density in the tumor(p<0.05). **Conclusions:** The addition of the Tax 324 TPF IC protocol to the 91-11 RCT protocol may be an appropriate approach for advanced risk for local and distant failure.The dose of cisplatin during RCT should be limted to 200mg/m$^2$.

**6016^ Poster Highlights Session (Board #31), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Induction chemotherapy (IC) docetaxel (T), cisplatin (P), 5-fluorouracil (F) (TPF), or TP followed by concomitant boost radiotherapy (R) with or without cetuximab (E) for functional organ preservation (FOP) of resectable laryngeal and hypopharyngeal cancer (LHSCC): First results of the phase II randomized DeLOS-II study.** *Presenting Author: Andreas Dietz, University of Leipzig, Leipzig, Germany*

**Background:** The DeLOS-II trial is a German multicenter randomized phase II trial (IIT) investigating IC with or without cetuximab for patients with LHSCC, followed by R assessing FOP. **Methods:** Previously untreated patients (pts) with resectable stage III/IV LHSCC indicated for total laryngectomy were randomized to three cycles (TP both 75 mg/m² day 1 and F 750 mg/m²/day on days 1-5) without (arm A) or with (arm B) standard dose of cetuximab for 16 weeks. In case of non-response after the first cycle, the study therapy was terminated and salvage laryngectomy was performed. Three cycles of IC were followed by R (69.6Gy). In this first analysis, we report rates of 6-months survival with functional larynx (FOP). Secondary endpoints included feasibility and toxicity. **Results:** 180 pts were randomized (7/2007-9/2012), 174 fulfilled ITT criteria (85.1% male, 49.4% larynx, 87.4% T3/4N2bc, equally distributed both arms). Due to 4 therapy related deaths among the first 64 pts (3 arm A, 1 B), F was omitted from IC in 2/2009. Interim analysis for response and toxicity of 126 pts in 2011 showed no efficacy differences between TPF vs TP and no more treatment related deaths. Overall, in arm A 31 pts received TPF and 55 TP, in arm B 31 TPFE and 57 TPE IC. 66.7% of pts received complete IC (4.0% two cycles; 29.3% one cycle). Dose reduction (>10%) mainly due to toxicity occurred in 27.9% arm A and 98.9% B (30.7% T, 31.8% P, 18.2% F, 98.9% E). Main early toxicity grade 3/4 was hematotoxicity (81.4% in A, 85.2% B). Early response (CR, PR) after first cycle in arm A was 67.4% (95%-CI: 56.5-77.2) and in arm B 77.3% (67.1-85.5; p=0.15). 126 pts were early responders and suitable for the complete IC and R protocol. Overall response in this group was CR/PR 81.0/8.6% in A, 77.9/5.9% in B. Endpoint (loss of FOP, death) was reached in 31.4% vs. 17.0%, favoring arm B (HR 0.502 [0.267-0.944]; p=0.0289). **Conclusions:** IC with TPFE/TPE was feasible and more effective compared to TPF/TP for Larynx preservation. TPE was less toxic and similarly effective as TPFE. Clinical trial information: NCT00508664.

**6017 Poster Highlights Session (Board #32), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**A phase II study comparing metronomic chemotherapy with chemotherapy (single-agent cisplatin), in patients with metastatic, relapsed, or inoperable squamous cell carcinoma of head and neck.** *Presenting Author: Vijay Maruti Patil, Tata Memorial Hospital, Mumbai, India*

**Background:** Cetuximab based regimen is the recommended palliative chemotherapy for head and neck squamous cell cancers. However, due to financial constraints, toxic intravenous chemotherapy with poor outcome is more commonly used in lesser developed countries. Retrospective studies have shown a role for oral metronomic therapy (MCT) in HNSCC especially in a resource poor setting. **Methods:** We conducted an open label, superiority, parallel design, randomized phase II trial comparing oral MCT [daily celecoxib (200 mg twice daily) and weekly methotrexate (15mg/m$^2$)] to intravenous single agent cisplatin (IP) (75mg/m$^2$) given 3 weekly. Patients with relapsed, metastatic and inoperable head and neck cancers meriting palliative chemotherapy,performance status 0-2, unaffordable for cetuximab and with adequate organ functions were eligible.. The primary end point was progression-free survival. The trial was powered to detect a 33% improvement in the median PFS, from 2.7 months for IP arm, with type 1 error of 5% and type 2 error of 80%. Univariate analysis of survival was performed using Kaplan Meier estimates with intention to treat analysis. Toxicity rates were compared using chi square test. **Results:** 110 patients were recruited between July 2011 to May 2013, 57 randomized to the MCT arm and 53 to the IP arm. Patients in the MCT arm had significantly longer PFS (median 101 days, 95% CI: 58.2-143.7 days) compared to the IP arm (median 66 days, 95% CI; 55.8-76.1 days) (log-rank p=0.014). The overall survival (OS) was also increased significantly in the MCT arm (median 249 days, 95% CI: 222.5 - 275.5 days) compared to the IP arm (median 152 days, 95% CI: 104.2 -199.8 days) (log-rank p=0.02). There were fewer grade 3/4 adverse effects wth MCT, which was nonsignificant.(18.9% vs. 31.4%, P = 0.14). **Conclusions:** Oral metronomic chemotherapy has significantly better PFS and OS than single agent platinum in the palliative setting. It is a viable and cost-effective treatment option in patients not affording cetuximab. Further studies are warranted to evaluate the benefit, schedule and combination of metronomic therapy. Clinical trial information: 2014/01/006359.

**6018 Poster Highlights Session (Board #33), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Cetuximab (C), fluorouracil (F), and cisplatin (P) alone or with docetaxel (D) for recurrent/metastatic (RM) head and neck cancer (HNSCC): First analysis of AIO trial # 1108.** *Presenting Author: Ulrich Keilholz, Charité Comprehensive Cancer Center, Berlin, Germany*

**Background:** This trial was based on the findings that D in addition to PF in induction treatment and C in addition to PF in RM disease both improved outcome in HNSCC. The question was, whether TPFC would be feasible and superior to PFC in patients with RM-HNSCC without limiting comorbidities. **Methods:** In an open-label randomized multicenter trial, 180 patients were assigned 1:1 to receive either (arm A) P 40 mg/sqm, D 40 mg/sqm, F 2000 mg/sqm days 1+8, C 400/250 mg/sqm days 1, 8, 15 q3w or (arm B) standard PFC (P 100 mg/sqm day 1, F 1000 mg/sqm days 1-4, C 400/250 mg/sqm days 1, 8, 15) q3w. Chemotherapy was continued for a maximum of 6 cycles in absence of disease progression or limiting toxicity, followed by C maintenance (500 mg/sqm q2w). Primary endpoint was PFS. **Results:** Accrual was completed in Nov 2013. A planned safety analysis had revealed excessive toxicity (gastrointestinal and infections) in arm A, necessitating an amendment with reduction of P to 30 and F to 1000 mg/sqm after 20 patients/arm. After the amendment, toxicity was similar in both arms, with a rate of grade 4 toxicities of 21.3% vs. 30.8% of patients in arms A vs. B. 11.2% vs. 6.6% potentially treatment related deaths were observed in arms A vs. B. Median PFS A vs. B was 5.5 vs. 5.0 mo (HR 0.78, p=0.375), and response rates 38.2% vs. 31.9%, respectively. Further follow-up is required to describe OS. **Conclusions:** Despite of the previously described advantage of both components D and C in treatment of HNSCC, the four-drug regimen was not associated with improved median PFS, the primary endpoint of the trial. There is a tail of the curve effect, which will require further follow up. Clinical trial information: 1108.

**6019^ Poster Highlights Session (Board #34), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**A phase II trial of temsirolimus plus low-dose weekly carboplatin and paclitaxel for recurrent/metastatic HNSCC.** *Presenting Author: Matthew G. Fury, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** The PI3K/mTOR pathway is commonly altered in HNSCC, but single agent activity of mTOR inhibitors is modest. Following up on encouraging results of a phase I study of temsirolimus + low dose chemotherapy (PMID 22644799), we launched this prospective phase II study. **Methods:** This was a nonrandomized, prospective, phase II study at MSKCC main campus and regional network affiliates. Eligible patients (≤ 2 prior regimens for R/M disease) received paclitaxel (80 mg/m$^2$) + carboplatin (AUC 1.5) + temsirolimus (25 mg flat dose) by vein, on days 1 and 8 of a 21 day cycle for up to 6 cycles. After 6 cycles, patients without progressive disease had the option for temsirolimus monotherapy. The primary endpoint was objective response rate, as assessed by RECIST 1.0. **Results:** Between 1/11/2012 and 5/15/2013, 30 eligible subjects were enrolled (22 M/8 F): median age 59 (range, 30 to 85 years), median KPS 80 (range, 70 to 90). 15 patients had received at least one prior systemic therapy regimen for R/M disease. Primary tumor sites were larynx (10), oropharynx (9; HPV ISH status- 6 positive, 2 negative, 1 not done), oral cavity (8), neck node with occult primary (2), and hypopharynx (1). 17 patients had tobacco history of > 10 pack-years. The most common ≥ grade 3 AEs were lymphopenia (56%), leukopenia (37%), and neutropenia, dysphagia, and low hemoglobin (each 20%). The overall radiologic response rate was 43% (13/30) with 1 CR, 10 confirmed PRs, and 2 unconfirmed PRs (Figure 1). Overall survival was 12.9 months (95% CI, 12.3 – 13.5). Correlative studies on pre-treatment pathology samples are in progress to evaluate if p-eIF4E:p-4EBP-1 ratio is associated with efficacy. **Conclusions:** This low dose weekly chemotherapy regimen demonstrates clinical activity comparable to that of standard high dose combination chemotherapy regimens, and was well tolerated after first line therapy. Acknowledgment: This study was approved and funded by the National Comprehensive Cancer Network (NCCN) from generous research support provided by Pfizer. Clinical trial information: NCT01016769.

**6021^ Poster Highlights Session (Board #36), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Platinum-based chemotherapy (CT) plus cetuximab in recurrent or metastatic squamous cell carcinoma of the head and neck cancer (R/M-SCCHN): 5-year follow-up data for the extreme trial.** *Presenting Author: Jan Baptist Vermorken, Antwerp University Hospital, Edegem, Belgium*

**Background:** The EXTREME trial demonstrated that patients with R/M-SCCHN benefit significantly from the addition of cetuximab to first-line platinum-based CT in relation to overall survival, progression-free survival (PFS) and response rate. We report the 5-year follow-up data. **Methods:** The intent-to-treat (ITT) population comprised patients (pts) randomized to receive either platinum-based CT plus cetuximab (n=222) or CT alone (n=220) for 18 weeks (6 x 3-week cycles). **Results:** A total of 100 pts in the cetuximab arm who had at least stable disease received cetuximab monotherapy until disease progression or unacceptable toxicity, with a median treatment duration of 29.9 weeks. For 77% of these pts, the relative dose intensity (RDI) of cetuximab was ≥90% during this maintenance period. Thirty-one (14%) pts in the cetuximab arm and 25 (11%) in the CT arm of the ITT population were deemed long-term survivors (>2 years). Of these, 6 (22%) and 5 (23%) pts were p16+ and 11 (35%) and 10 (40%) pts had oropharyngeal tumors, in both arms respectively. At 5-years, 6 pts treated with CT plus cetuximab and 2 pts treated with CT alone were still in the study and known to be alive. In pts in the cetuximab arm, the frequency of severe (grade 3-4) adverse events (AEs) decreased from 81% to 49% during the cetuximab maintenance period compared with the previous treatment period with CT plus cetuximab. Grade 3 skin toxicity decreased from 9% when combined with CT to 5% during cetuximab maintenance and no grade 4 skin toxicity was observed.Twelve pts (5%) in the cetuximab arm of the ITT population were long-term responders (PFS>12 months) compared with 3 pts (1%) in the CT arm, with a median treatment duration of 67.7 weeks. The RDI of cetuximab was ≥90% for all long-term responders. **Conclusions:** The addition of cetuximab to first-line platinum-based CT significantly improves outcome for patients with R/M-SCCHN. Although there are notable differences in long-term responders favoring cetuximab, the 5-year survival figures are still extremely low for both arms of the study. Cetuximab maintenance therapy proved to be feasible with manageable skin reactions. Clinical trial information: NCT00122460.

**6022 Poster Highlights Session (Board #37), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Meta-analysis of chemotherapy in nasopharyngeal carcinoma (MAC-NPC): An update on 4,798 patients.** *Presenting Author: Pierre Blanchard, Institut Gustave Roussy, Villejuif, France*

**Background:** In a previous MAC-NPC individual patient data (IPD) meta-analysis, the addition of chemotherapy (CT) to radiotherapy improved overall survival (OS) in nasopharyngeal carcinoma (NPC; Baujat IJROBP 2006). There was an interaction between the timing of CT and treatment effect, with an OS benefit restricted to the concomitant (+/- adjuvant) timing. Since other trials have been conducted, this meta-analysis was updated. **Methods:** Trials of radiotherapy (RT) with or without CT in patients with non-metastatic NPC were identified and updated IPD obtained. Both Western and Chinese medical literatures were searched. OS was the main endpoint. The fixed-effect model was used. All analyses were pre-specified. **Results:** Overall 19 trials and 4,798 pts were included. One 2x2 trial was counted twice and 5,020 pts were analyzed. Patients characteristics were well balanced (60% < 50 years, 75% male, 60% PS 0, 90% stage III-IV and 96% WHO grade 2-3). Median follow-up was 7.1 years. There was a significant benefit in favor of CT regarding OS (hazard ratio (HR) [95% confidence interval]: 0.79 [0.72;0.86], p <0.0001; absolute benefit at 5 years=6.4%). There was a significant interaction between treatment effect on OS and the timing of CT (p=0.01) in favor of concomitant CT (without adjuvant CT: HR 0.79 [0.68;0.92]; with adjuvant CT: HR 0.65 [0.56; 0.76]) compared to induction CT (HR 0.96 [0.80;1.16]) or adjuvant CT (HR 0.93 [0.70;1.24]), which explained the statistical heterogeneity. Restriction of the analysis to trials with a control arm with RT alone led to similar results. The benefit of the addition of CT was consistent for all endpoints: progression-free survival (HR 0.76 [0.70;0.82], p<0.0001), loco-regional control (HR 0.74 [0.65;0.85], p<0.0001), distant control (0.68 [0.60;0.76], p<0.0001) and NPC related mortality (0.73 [0.66; 0.81], p<0.0001). There was no significant interaction between treatment effect on OS and patient covariate (age, sex, tumor stage). **Conclusions:** The addition of concomitant chemotherapy, with or without adjuvant CT, significantly improves survival in patients with locally advanced nasopharyngeal carcinoma. Supported by PHRC and LNCC

**6023 Poster Highlights Session (Board #39), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Comparison of concurrent chemoradiation therapy with 3-weekly versus weekly cisplatin in patients with locally advanced nasopharyngeal cancer: A multicenter randomized phase II noninferiority trial (KCSG-HN10-02).** *Presenting Author: Ji Yun Lee, Department of Medicine, Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

**Background:** Concurrent chemoradiation therapy (CCRT) with every 3 week schedule of cisplatin is the standard treatment for locally advanced nasopharyngeal carcinoma (NPC), but concerns have been raised about treatment-related complications. We conducted a randomized phase II non-inferiority study of CCRT with three week versus weekly cisplatin to compare the efficacy and toxicity profiles. **Methods:** From September 2009 through August 2011, 111 patients with locally advanced NPC who have stage II-IVb were enrolled from 22 centers in Korea. Patients were randomized into treatment groups that either received cisplatin 100 mg/m$^2$ every 3 weeks for 3 cycles (arm A) or cisplatin 40 mg/m$^2$ weekly for 7 cycles (arm B) concurrently with RT. Subsequent adjuvant chemotherapy, cisplatin 80 mg/m$^2$ day 1 and fluorouracil 1,000 mg/m$^2$/day day 1-4 was administered every 3 weeks for a total of 3 cycles. **Results:** Of the 109 eligible patients, 56 were assigned to arm A, and 53 to arm B. The two arms were well-balanced in all prognostic factors and RT parameters. There was no significant difference in RT dose (67.28 Gy vs 68.30 Gy, p=0.559) or cisplatin dose (257 vs 249 mg/m$^2$, p=0.433) between two arms. About 90% of patients in both arms completed protocols of CCRT. However, 29% of patients in arm A and 45% of those in arm B received subsequent adjuvant chemotherapy (p=0.045). Overall tumor response was 97 % but no difference was noted in tumor response between two arms (96 vs 98%, p=1.000). Overall, the grade 3/4 toxicities were similar between the two arms. The most common grade 3/4 adverse events during CCRT were neutropenia (15% in arm A vs 28% in arm B), stomatitis (13% vs 15%), and nausea/vomiting (11% vs 8%). **Conclusions:** These results demonstrated that weekly regimen of cisplatin as CCRT is well tolerated and shows similar treatment efficacy compared with 3 weekly schedule of cisplatin in patients with locally advanced NPC. Longer follow-up is needed to evaluate the final results of progression free survival and overall survival.

**6024 Poster Highlights Session (Board #40), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Chemoradiotherapy regimens for locoregionally advanced nasopharyngeal carcinoma: A Bayesian network meta-analysis.** *Presenting Author: Marie Yan, University of Toronto, Toronto, ON, Canada*

**Background:** Concurrent chemoradiotherapy followed by adjuvant chemotherapy (CRT-A) is often the regimen of choice in locoregionally advanced nasopharyngeal carcinoma (LANPC). Many alternative regimens have been reported in the literature; however, it is unknown how effective these regimens are compared to each other due to the lack of direct comparisons. Our aim was to perform a network meta-analysis (NMA) to determine the relative survival benefits of these treatments in LANPC. **Methods:** We performed a systematic review following the Cochrane methodology, using MEDLINE, EMBASE, and CENTRAL to identify all randomized controlled trials (RCTs) that compared different chemoradiotherapy regimens in LANPC. Overall survival (OS) and progression-free survival (PFS) were the primary outcomes of interest. Hazard ratios (HRs) were extracted using the Parmar method. Bayesian NMAs with random effects were conducted using WinBUGS to compare all regimens simultaneously and improve precision. **Results:** Twenty-four RCTs (5,492 patients) were included in this review. All together, these trials compared seven different regimens: radiotherapy (RT), concurrent chemoradiotherapy (CRT), neoadjuvant followed by CRT (N-CRT), CRT-A, RT-A, N-RT and N-RT-A. All regimens that contained CRT performed significantly better than RT. The combined HRs for CRT-A vs. CRT were 0.96 (95% credible regions: 0.69–1.31) for OS and 0.86 (0.55–1.39) for PFS. For N-CRT vs. CRT, the HRs were 1.01 (0.65–1.46) for OS and 0.65 (0.34–1.18) for PFS. When CRT-A was compared against N-CRT, the resulting HRs were 0.96 (0.64–1.46) for OS and 1.33 (0.67–2.87) for PFS. CRT, CRT-A and N-CRT all had similar probabilities of being the best regimen (23%, 34% and 28% respectively) among all seven regimens based on OS. **Conclusions:** To our knowledge, this is the first NMA to study chemoradiotherapy regimens in LANPC. Contrary to common clinical practice, adjuvant chemotherapy does not appear to improve survival following CRT. The efficacies of CRT, CRT-A and N-CRT all appeared to be similar. Further studies are warranted to examine whether omitting additional chemotherapy phases can decrease side effects without adversely affecting survival.

**6025 Poster Highlights Session (Board #41), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**The correlation between the severity of cetuximab-induced rash and clinical outcome for patients with head and neck carcinoma treated with chemoradiotherapy (CRT) plus cetuximab: The RTOG experience.** *Presenting Author: Voichita Bar-Ad, Department of Radiation Oncology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA*

**Background:** To evaluate the severity of cetuximab-induced rash and its correlation with clinical outcome and late skin toxicity. **Methods:** The analysis included patients who received definitive CRT on RTOG 0522 (70 Gy + cisplatin and cetuximab) or postoperative CRT on RTOG 0234 (60–66 Gy + cetuximab and either docetaxel or cisplatin). Patients had to have received the loading dose and at least one concurrent dose of cetuximab. **Results:** Six hundred two patients were analyzed: 406 on RTOG 0522 and 196 on RTOG 0234; 386 patients (64.1%) developed Grade 2-4 cetuximab rash. Patients with Grade 2-4 rash had younger age ($p<0.001$), fewer pack-years smoking history ($p<0.001$), were male ($p=0.03$) and had an oropharynx primary site ($p=0.002$). Combined across treatment groups, patients with Grade 2-4 rash, when compared to those with Grade 0-1 rash, had increased OS (HR 0.58 [95%CI 0.44-0.76)], $p<0.001$), increased PFS (HR 0.76 [95%CI 0.60-0.97], $p=0.03$), and reduced incidence of distant metastasis (HR 0.63 [95%CI 0.40-0.99], $p=0.04$), but no detectable difference in loco-regional failure (HR 0.80 [95%CI 0.58-1.10], $p=0.17$). After adjustment for prognostic factors (age, Zubrod PS, primary site, TNM stage): HR 0.69 [95%CI 0.51-0.92], $p=0.01$ for OS; HR 0.87 [95%CI 0.68-1.12], $p=0.28$ for PFS; HR 0.90 [95%CI 0.65-1.25], $p=0.55$ for loco-regional failure; and HR 0.67 [95%CI 0.42-1.06], $p=0.08$ for distant metastasis. Twenty-five percent of patients with Grade 2-4 acute in-field radiation dermatitis experienced Grade 2-4 late skin fibrosis vs 14% of patients with Grade 0-1 acute in-field radiation dermatitis (Odds ratio 1.92 [95%CI 1.23-3.00], $p=0.004$). **Conclusions:** Grade 2-4 cetuximab rash was associated with increased OS, that may be due to a reduction in incidence of distant metastasis. Grade 2-4 rash was not associated with increased PFS or decreased loco-regional failure. Grade 2-4 acute in-field radiation dermatitis was associated with higher risk of late Grade 2-4 skin fibrosis. This project was supported by RTOG grant U10 CA21661, and CCOP grant U10 CA37422 from the National Cancer Institute (NCI) and Bristol-Myers Squibb.

**6026 Poster Highlights Session (Board #42), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**A multicenter international phase 2 trial of pazopanib in metastatic and progressive medullary thyroid carcinoma: MC057H.** *Presenting Author: Keith Christopher Bible, Mayo Clinic, Rochester, MN*

**Background:** Pazopanib is a small molecule inhibitor of kinases principally including vascular endothelial growth factor receptors (VEGFR)-1,-2, and -3, platelet-derived growth factor receptors (PDGFR)-$\alpha$ and $-\beta$; and c-Kit. We previously reported a tumor response rate of 49% in patients with advanced differentiated thyroid cancer and 0% in patients with advanced anaplastic thyroid cancer. The present report details results of pazopanib therapy in advanced medullary thyroid cancer (MTC). **Methods:** Having noted preclinical activity of pazopanib in MTC, patients with advanced MTC who had disease progression within the preceding 6 months were accrued to this multi-institutional international Phase II clinical trial to assess tumor response rate (by RECIST criteria) and safety of pazopanib given orally once daily at 800 mg until disease progression or intolerability. **Results:** From September 22, 2008 to December 11, 2011, 35 individuals (80% males, median age 60 years) were enrolled. All patients have been followed until treatment discontinuation or for a minimum of 4 cycles. Eight patients (23%) are still on study treatment. The median number of therapy cycles was 8. Five patients attained partial RECIST responses (14.3%; 90% CI: 5.8- 27.7%) with median progression-free survival and overall survival 9.4 and 19.9 months respectively. Side effects included treatment-requiring (new) hypertension (33%), fatigue (14%), diarrhea (9%) and abnormal liver tests (6%); three of 35 patients (8.6%) discontinued therapy due to adverse events. There was one death of a study patient after withdrawal from the trial deemed potentially treatment-related. **Conclusions:** Pazopanib has promising clinical activity in metastatic MTC with overall manageable toxicities. Supported by NCI CA15083 and CM62205. Clinical trial information: NCT00625846.

**6027 Poster Highlights Session (Board #43), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Axitinib treatment in advanced RAI-resistant differentiated thyroid cancer (DTC) and refractory medullary thyroid cancer (MTC).** *Presenting Author: Jaume Capdevila, Vall d'Hebron University Hospital, Barcelona, Spain*

**Background:** Multikinase inhibitors (MKI) have demonstrated significant activity in advanced thyroid cancer. Axitinib is a potent oral MKI targeting the three known receptors of VEGF. **Methods:** Patients (pts) with advanced RAI-refractory DTC or unresectable MTC in documented disease progression were included in a compassionate use program of axitinib 5 mg bid. Primary end point was response rate (RR) by RECIST, and secondary objectives included progression-free survival (PFS), toxicity profile and biomarker correlation analysis. The program was validated by regulatory authorities and all patients signed informed consent form. **Results:** 41 pts were enrolled (med age: 54; male: 51%; 29 DTC, 12 MTC). Axitinib was first-line MKI therapy in 39%, second-line in 36% and 24% in subsequent lines. One level dose reduction (5 mg qd) was required in 24% of pts to manage toxicity. Main side effects were grade 1-2, including fatigue (46%), mucositis (24%), diarrhea (24%) and hypertension (19%). Grade 3-4 side effects included anorexia, diarrhea and cardiac toxicity in less than 5% of pts. 32 pts were evaluable for efficacy. In DTC, RR was 41%, stable disease (SD) 18% and progression disease (PD) 41%. In MTC, RR was 30%, SD 40% and PD 30%. Regarding treatment lines, RR in first-line was 69% and SD 31%; in second and third-lines, RR was 20%, SD 30% and PD 50% ($p<0.05$). No differences in median PFS were observed between DTC and MTC ($p=0.509$). However, significant differences were found regarding treatment lines: first-line 12.6 months, second-line 8.6 months and successive lines 3.9 months. 15 pts were evaluated for biochemical response. The Kappa index correlation observed between biomarker reduction >30% and tumor growth control (RR + SD) was for thyroglobulin 0.21 (0.30-0.72), CEA 0.22 (0.19-0.64) and calcitonin 0.087 (-0.62-0.79). No correlation was observed in this small number of pts. **Conclusions:** Axitinib has showed meaningful activity and a safety toxicity profile in refractory and progressive thyroid cancer regardless tumor histology in first and second-line therapy. Efficacy significantly decreases in successive lines suggesting cumulative resistance to MKIs.

**6028 Poster Highlights Session (Board #44), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Interest of pretreatment quantification of anti-cetuximab IgE to prevent severe hypersensitivity reaction to cetuximab.** *Presenting Author: Benoit Dupont, University Hospital (CHU), Caen, France*

**Background:** Hypersensitivity reactions (HSR) are dreaded and relatively frequent adverse events associated with cetuximab (CTX). High pretreatment levels of anti-CTX IgE have been observed in patients (pts) who experienced a grade 3-4 reaction (NCI CTCAE v3.0) after CTX administration. We hypothesized that dosage of anti-CTX IgE prior to treatment in pts naive to CTX may be used for therapeutic decisions to reduce the incidence of severe HSR. Our main objective was to compare the incidence of severe HSR during the first injection of CTX among pts with low levels of anti-CTX IgE, compared to an incidence of 5.2% retrospectively observed among 213 pts previously treated in our centre. **Methods:** We conducted a multicentre prospective diagnostic trial among pts with a colon or head-and-neck cancer, candidate to a first treatment by CTX. The pre-treatment level of anti-CTX IgE was measured. An IgE level lower than 30 EAU (IgE Arbitrary Unit) did not interfere with the therapeutic decision whereas for pts with levels of 30 EAU or higher, CTX indication was either revised or maintained provided that the 2 first injections were done under closer medical monitoring. **Results:** 300 of 303 included pts were assessable. Median age was 60 years old, sex ratio was 4.3 and 77% had head-and-neck cancer. Prevalence of high levels of anti-CTX IgE was 22% (66 pts): 38 (58%) of which received CTX *vs* 208 (89%) among low level pts. Severe HSR during the first injection were noted in 8 pts (5 grade 3 and 3 grade 4). No death was observed following HSR. The incidence among low level pts was significantly lower than the retrospective one (1.4%, $p=0.03$). The incidence of severe HSR was significantly higher among pts with high levels of IgE rather than low levels (5/38 *vs* 3/208; odds ratio=10.4, $p=0.0027$) Pts with severe HSR had higher levels of anti-CTX IgE (median 45 *vs.* 5 EAU, $p=0.006$). No significant relation was noted between severe HSR and gender, age, history of allergies or tumor localization. **Conclusions:** Our findings support the role of an allergic mechanism in CTX reactions. Detection of anti-CTX IgE prior to treatment is a feasible and helpful strategy to predict HSR and adapt care. Clinical trial information: NCT01436617.

**6029 Poster Highlights Session (Board #45), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Single-nucleotide polymorphism (SNP) of excision repair cross complementation group 1 (ERCC1) in nasopharynx cancer (NPC): A companion biomarker study to Hong Kong NPC Study Group 0502 trial.** *Presenting Author: Edwin Pun Hui, Partner State Key Laboratory of Oncology in South China, Sir Y K Pao Centre for Cancer, Department of Clinical Oncology, Hong Kong Cancer Institute and Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong*

**Background:** Polymorphisms at ERCC1 has been linked to platinum sensitivity and treatment outcome. We hypothesized that ERCC1 SNP at codon 118 and C8092A is predictive of relapse free survival (RFS) in NPC, and correlates with ERCC1 protein/mRNA in paired tumor samples. **Methods:** 0502 is a multi-center prospective clinical trial to assess adjuvant chemotherapy in NPC pts with detectable plasma EBV-DNA (pEBV) following primary radiotherapy (RT) or cisplatin-RT (CRT) (NCT00370890). Eligible pts with biopsy proven NPC, AJCC stage IIB-IVB, no persistent locoregional disease or distant metastasis, ECOG 0-1, adequate organ function, were screened by pEBV at 6-8 weeks after completing RT/CRT. Post-RT pEBV -ve pts received no further treatment. pEBV +ve pts underwent work-up and randomization to adjuvant chemotherapy or observation. We tested our hypothesis using samples collected in the 0502 screening cohort. Primary endpoint is relapse free survival (RFS). ERCC1 genotyping was by TaqMan real time PCR. 450 pts is planned to detect a hazard ratio (HR) of 1.5 for the weaker ERCC1 SNP at 80% power and 2-side 5% alpha level. In subset with available tumor biopsies, we quantified ERCC1 protein expression by immunohistochemistry (IHC) or Western blot (WB) with mouse monoclonal antibody (clone 8F1), and ERCC1 mRNA by quantitative RT-PCR. **Results:** ERCC1 SNP was analyzed in peripheral blood lymphocytes from 478 pts. Median follow up was 3.61 years (90% C.I. 3.36-3.88). 31% pEBV +ve, 17% randomized. ERCC1 genotype distribution at codon 118: 54% CC, 39% CT, 7% TT; C8092A: 38% CC, 50% CA, 12% AA. There was no significant association of ERCC1 SNP with 3-year RFS or overall survival. No significant correlation was observed in ERCC1 SNP and tumor ERCC1 expression by IHC, WB or mRNA. In subset evaluated by ERCC1 IHC (n=79), pts with ERCC1+ve tumor (H-score > median) had worse RFS (HR 2.34, 95% C.I. 1.06-5.16, p=0.036). Multivariate analysis showed pEBV was the most significant adverse prognosticator for all clinical endpoints. **Conclusions:** We found no association of ERCC1 SNP with NPC survival. pEBV remained the most significant prognostic biomarker in NPC.

**6030 Poster Highlights Session (Board #46), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Proteomic profiling of HPV-positive head and neck cancer to identify new candidates for targeted therapy.** *Presenting Author: Lauren Averett Byers, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** The incidence of oropharyngeal cancer (OPC) has increased 5% per year over the past decade due to a rise in human papilloma virus (HPV)-driven OPC. HPV+ OPC is clinically and molecularly distinct from HPV- head and neck squamous cell carcinomas (HNSCC). However, there are currently no validated therapeutic targets for HPV+ HNSCC. **Methods:** Reverse phase protein array (RPPA) was performed on HNSCC tumors from The Cancer Genome Atlas to measure cancer-associated pathways and targets. Differences in individual markers and proteomic pathway scores between HPV+ and HPV– tumors were assessed by t-test in the overall group and for the subset of OPC. **Results:** Significant proteomic differences were observed in 14 HPV+ and 186 HPV- HNSCC. Of 160 proteins, the top marker overexpressed in HPV+ HNSCC was p16, an established clinical biomarker of HPV status ($p<0.0001$). Other cell cycle proteins significantly dysregulated were p27; cyclins B1, E1 and E2; and E2F1 (higher in HPV+) and pRb (lower in HPV+) ($p<0.03$). In the OPC subset, several E2F1 targets were overexpressed in HPV+ cancers, including those involved in apoptosis (Bcl2, BIM) and DNA repair (PCNA, Chk2) ($p<0.05$). Despite frequent PIK3CA mutations, no significant PI3K pathway activation was observed in PIK3CA-mutated HPV+ tumors. Interestingly, total and pEGFR were expressed at lower levels in HPV+ tumors while pSTAT3, paxillin, and FAK were elevated ($p=0.04$). Finally, consistent with previous gene signature analyses showing less EMT in HPV+ HNSCC, they expressed higher levels of E-cadherin ($p=0.04$). **Conclusions:** Proteomic profiling of HPV-positive HNSCC identified potential therapeutic targets including DNA repair proteins and Src. These results are consistent with the known role of HPV E6/E7 oncoproteins in activating DNA damage response and of paxillin/FAK activation contributing to anoikis-resistance. The activation of Src substrates (STAT3/paxillin/FAK) despite inactive EGFR suggests an alternate mechanism of Src/STAT pathway activation that may have implications for response to EGFR inhibitors. Inhibitors of CDK2, Chk2, Bcl2, and Src are in clinical development suggesting that rapid translation to clinical practice could be achieved.

**6031 Poster Highlights Session (Board #47), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Validation of two biologically distinct HPV-associated head and neck cancer subtypes and correlation with E5 expression.** *Presenting Author: Zhixiang Zuo, University of Chicago Medical Center, Chicago, IL*

**Background:** Human Papilloma Virus (HPV) is involved in the etiology of 60-80% of oropharyngeal head and neck cancers (HNC) in the US. HPV16 is the dominant HPV type present in 90% of HPV-positive HNC. We previously discovered the presence of two distinct HPV(+) HNC groups, based on gene expression profiling and consensus clustering. In this study we apply our classifier to TCGA data, and analyze viral gene expression. **Methods:** Using consensus clusteringbased on literature derived microarray gene expression profiles of 371 HNC samples we built a gene expression based classifier for HNC. We then applied the gene signature to RNA-Seq data of 424 TCGA samples and 134 Agilent array samples of the Chicago HNC Genomics Cohort (CHGC) using nearest centroid method.HPV status was determined by E6/E7 expression and confirmed with an HPV signature. We determined HPV type and the E5, E6 and E7 mRNA level for the TCGA samples using RNA-Seq data. **Results:** Three stable groups were obtained for the 371 cross-platform HNC samples. The signature for the three groups similarly classified 415 out of 424 TCGA samples, and all 134 samples in the CHGC cohort. Groups were named Mesenchymal (MS), Basal (BA), and Classical (CL), with HPV samples falling into two groups in both CHGC and TCGA cohorts supporting the presence of two distinct HPV subgroups: MS-HPV and CL-HPV. Out of 54 HPV16 positive CHGC samples, 26 were in MS group and 28 were in CL group; similarly, out of 47 HPV16 positive TCGA samples, 24 were in MS group and 23 were in CL group. MS-HPV was characterized by EMT, and high expression of immune related genes, CL-HPV by high expression of cell cycle genes. Furthermore, in the TCGA dataset, all 23 samples in MS-HPV group showed high expression level of E5, alongside E6 and E7, while all samples with low E5 fell into the CL-HPV. E5 expression differed significantly between the two groups ($P=7.763e-05$, Fisher exact test). **Conclusions**: In conclusion, we confirm the presence of two biologically distinct HPV subgroups – MS-HPV, and CL-HPV in two large, independent cohorts, with distinct biologic characteristics. Subtypes are characterized by differential E5 expression. Further study into the underlying mechanisms is indicated.

**6032 Poster Highlights Session (Board #48), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Review of pathologic diagnosis in head and neck cancer patients: Why do it?** *Presenting Author: Gefei Alex Zhu, Stanford University, Stanford, CA*

**Background:** Our hospital mandates review of outside pathology prior to treatment. Previous studies of inter-institution pathology consultations have demonstrated discordance rates of approximately 10%. We examined the overall rate of as well as predictors of discordant interpretations in patients seen at the Stanford Head and Neck Oncology program. **Methods:** The study cohort was identified using a retrospective search of the Stanford Cancer Center Research Database for head and neck cancer patients from 2005-2010 with outside pathology reviews. Discordance was manually assessed by a board-certified medical oncologist. We captured interpretation differences in histology, depth of invasion, margin positivity, presence of high-risk features, and results of special studies. The impact of tumor type (squamous, thyroid, or other), biopsy site, and type of specimen (cytology vs. histology) were assessed using chi-squared testing. **Results:** Of the 1,003 cases in the final cohort, 306 have been reviewed to date. There was an overall 18% discordance rate (56 cases), of which 68% (38 cases) were due to differences in histology. Discordance was associated with tumor type ($p = 0.004$), with lower rates for squamous (13%) and thyroid tumors (17%), and higher rates for other tumors (30%). Tumor biopsy site was also associated with discordance ($p = 0.011$), with lower rates in tumors of the oral cavity and lip (12%), oropharynx (12%), and hypopharynx (14%) and higher rates in those of the paranasal sinuses (42%), salivary glands (38%), and thyroid (26%). Fine needle aspiration specimens were not associated with discordant review ($p = 0.14$). **Conclusions:** Discordance rates of initial versus referral center diagnosis of head and neck tumor biopsies is substantial and clinically relevant. We could not identify any subset by site or initial histology where concordance exceeded 90%. Therefore we conclude that review is clinically relevant for all head and neck cancer patient specimens. Data for all 1,003 cases will be presented at the annual meeting.

**6033 Poster Highlights Session (Board #49), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Erlotinib, dasatinib, erlotinib-dasatinib versus placebo: A randomized, double-blind window study in operable head and neck squamous cell carcinoma (HNSCC).** *Presenting Author: Julie E. Bauman, University of Pittsburgh Cancer Institute, Pittsburgh, PA*

**Background:** The epidermal growth factor receptor (EGFR) and Src family kinases are upregulated in HNSCC. EGFR interacts with cSrc to activate oncogenic STAT3 signaling; dual targeting is synergistic in HNSCC cell lines. In preclinical models, phosphorylated cSrc (pSrc) mediates resistance to erlotinib (E), a small molecule EGFR inhibitor. Baseline overexpression of pSrc was associated with E resistance in our prior window trial. Here, we conducted a four-arm phase 0 trial of E; dasatinib (D), an ATP-competitive inhibitor of cSrc; E+D; vs. placebo (P). **Methods:** Patients with operable Stage II-IVa HNSCC were randomized 1:1:1:1 to 7-21 days of neoadjuvant E 150 mg daily (n=11), D 100 mg daily (n=13), E+D (n=15), or P (for E; n=14). Paired tumor specimens were collected pre- and post-treatment. The primary endpoint, percent change in RECIST-measurable index lesions, was compared among groups by 2-way ANOVA. We analyzed the relationship between tumor percent change and pharmacodynamic expression of EGFR and cSrc pathway constituents. Pre-defined, hypothesis-driven analytes included pSTAT3, pSrc, pMet, and pMAPK. **Results:** From Apr 2009-Dec 2012, 58 patients were consented, 55 randomized, and 53 treated. Rash was observed on E arms; GI toxicities were observed in all active treatment groups. There was a significant decrease in tumor size in the E arms (p=0.0014), and no additive or independent effect from D (p=0.24). Among E-treated patients, high baseline pMAPK expression was associated with reduction in tumor size (p=0.03). An E-treated patient experiencing complete clinical response harbored a somatic *MAPK1*$^{E322K}$mutation. Among D-treated patients, high baseline pSTAT3 was associated with tumor progression (p=0.03). **Conclusions:** Brief neoadjuvant treatment with E significantly decreased tumor size in operable HNSCC, with no independent or added effect from D. Baseline pMAPK expression and genomic *MAPK* alterations warrant further study as response biomarkers for anti-EGFR therapy. High basal pSTAT3 in HNSCC patients may be independent of cSrc, explain therapeutic resistance, and preclude further development of D in biomarker-unselected cohorts. Clinical trial information: NCT00779389.

**6034 Poster Highlights Session (Board #50), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Harvey ras (HRAS) mutations in head and neck cancer (HNC) and dependence on PI3K signaling and resistance to EGFR inhibition.** *Presenting Author: Katharina Endhardt, The University of Chicago, Chicago, IL*

**Background:** HRAS is significantly mutated in head and neck squamous cell carcinomas (HNC) and is a putative oncogenic driver. We studied the impact of HRAS mutations and signaling, which remains poorly defined for HNSCC. **Methods:** We evaluated HRAS expression, copy number changes, and hotspot mutations in HNSCC tumor tissues and cell lines (Chicago HNC Genomics Cohort (CHGC) (N=120), HNC TCGA (N=279), and HNC cell lines (N=50). MAPK, PI3K-AKT pathway signaling was interrogated by immunoblotting, and viability/apoptosis were determined in HRAS mutant and control cell lines (HN4(G12D), BB49(Q61L) and H357(G13S)) in presence of EGFR, and/or PI3K inhibitors. **Results:** Incidence of HRAS mutations was 4% in CHGC and TCGA cohorts, and 6.1% in HNC cell lines – with almost exclusively canonical HRAS mutations. Neither HRAS expression nor copy number aberrations were associated with mutations, and no high-level CN aberrations occurred. HRAS siRNA gene knockdown was extremely effective at inducing apoptosis and decreased viability in all three HRAS mutated cell lines, but largely ineffective in control cell lines. Interestingly immunoblotting revealed that mutant HRAS signals exclusively via PI3K-AKT and not via the MAPK pathway. EGFR inhibition had no visible effect on viability or apoptosis in these cell lines, and did not impact PI3K pathway activity. By contrast PI3K inhibition was highly effective and induced apoptosis. Combinations of PI3K and EGFR inhibition showed synergy only in wild-type cell lines. Lastly we developed HRAS mutation gene expression signature that confirmed PI3K signaling dependence. By contrast HRAS wildtype co-expression modules enrich for EGFR and MAPK signaling. **Conclusions:** Canonical HRAS mutations are strong oncogenic drivers and in-vitro associated with high-level EGFR-resistance. Unlike KRAS in other tumor types, HRAS in HNC signals exclusively via the PI3K pathway, and PI3K inhibitors are effective at inducing apoptosis and decreased viability.

**6035 Poster Highlights Session (Board #51), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Evaluation of computational tools to determine prognostic significance of *TP53* mutation in head and neck squamous cell carcinoma (HNSCC).** *Presenting Author: David Masica, The Johns Hopkins University School of Medicine, Baltimore, MD*

**Background:** *TP53* is the most commonly mutated gene in HNSCC. The specific mutations in *TP53* can be prognostic of patient survival. Thus, a framework to predict patient survival from previously uncharacterized mutation in *TP53* is valuable. There are many computational tools for predicting the phenotypic impact of genetic variation, but the overall clinical value of these algorithms remains unclear. **Methods:** Sixteen different models to predict HNSCC patient survival based on *TP53* mutations were assessed using the *TP53* mutation and clinical data from ECOG 4393 [Poeta, M. L., et al. NEJM (2007) 357(25) 2552-2561]. These models include: server-based computational tools SIFT, PolyPhen-2, and Align-GVGD; our in-house POSE and VEST algorithms; the rules devised in Poeta *et al.*[1] with and without considerations for splice-site mutations; location of mutation in the DNA-bound TP53 protein structure; and a functional assay measuring *WAF1* transactivation in *TP53*-mutated yeast. **Results:** We assessed model performance using overall survival (OS) and progression-free survival (PFS) from 420 HNSCC patients, of whom 224 had *TP53* mutations. Each mutation was categorized as "disruptive" or "non-disruptive". For each model, we compared the outcome between the predicted disruptive group vs. the non-disruptive group. The rules devised by Poeta *et al.* [1] (disruptive mutations: non-conservative mutations in the key DNA-binding domain, or stop codons vs. non-disruptive mutations: all mutations excluding the disruptive mutations) with or without our modification were observed to be superior to others. While the differences in OS (disruptive vs. non-disruptive) appear to be marginally significant (Poeta rule+modification, p=0.089; Poeta rule: p=0.053), both algorithms identified a disruptive group that has significantly worse PFS outcome (Poeta rule+modification, p=0.011; Poeta rule, p=0.027). **Conclusions:** In general, prognostic performance was low among the computational methods assessed here. Further studies are required to develop and validate computational models that can predict functional and clinical significance of *TP53*mutations in HNSCC patients.

**6036 Poster Highlights Session (Board #52), Mon, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Prevalence and outcome of mutations (mut) in the Fanconi anemia (FA) DNA repair pathway among head and neck cancer (H&N Ca) patients (pts).** *Presenting Author: Nooshin Hashemi Sadraei, University of Cincinnati Cancer Institute, Cincinnati, OH*

**Background:** Almost all survivors of FA, an inherited DNA repair deficiency syndrome, will develop H&N Ca. Preclinical data in H&N Ca cells harboring FA mut show increased sensitivity to chemo (CT) and radiation (RT) therapy. Little is known about prevalence and outcome of FA mut in general population of H&N Ca . **Methods:** Whole exome sequencing data from tumor samples of pts with H&N Ca were analyzed for 15 FA genes. Disease related characteristics and outcome data was collected. **Results:** A total of 124 pts were identified between 3/2003 - 5/2011 based on fresh frozen tissue availability. Overall, 21 (16.9%) pts had at least one mut in an FA pathway gene. For the entire cohort the median age was 59 (range 19-90), 77% were male, and 10% were HPV+ . Oral cavity was most frequent site (54%), followed by larynx (27%), oropharynx (10%), hypopharynx (8%) and sinonasal (1 %). Overall, T3-T4 and N1-3 was seen in 72% and 65%. PNI and ECS in 55% and 54%. RT was delivered in 68% and 71% received CT. Loco-regional recurrence occurred in 29 (23%). Median survival (OS) was 23 months (m) (2-89m) There were no significant differences in tumor characteristics (T, N, PNI, ECS) between FA mut and wild type pts (p> 0.48). However, recurrence occurred in only 2/19 ( 11%) HPV(-), FA mut pts compared to 34/92 ( 37%) HPV(-) wild type FA , p=0.02. No such difference was seen in the HPV(+) pts. Median OS was 22 m in the HPV + wild type vs 14 m in the HPV+FA mut pts ( p=0.1) (HR=3.4, p=0.1) **Conclusions:** Mut in FA pathway genes are detectable in a variety of H&N Ca. Recurrence and survival may be differentin FA mut and wild type H&N Ca depending on HPV status: In absence of HPV, these mut may result in a lower disease recurrence rate, which may reflect increased sensitivity to treatment. In the presence of HPV, the presence of an FA mut may negatively impact prognosis. These findings may suggest distinct biological consequences of FA mut in HPV (–) versus HPV (+) pts.

**6037 General Poster Session (Board #72), Sat, 1:15 PM-5:00 PM**

**GDF15 as a potential predictive biomarker for TPF induction chemotherapy in oral squamous cell carcinoma.** *Presenting Author: Lai-ping Zhong, Department of Oral & Maxillofacial-Head & Neck Oncology, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China*

**Background:** Randomized trials have not shown major survival benefits when induction chemotherapy plus standard therapy is compared with standard therapy alone in patients with oral squamous cell carcinoma (OSCC). Induction chemotherapy is likely to be effective for biologically distinct subgroups and biomarker development may lead to identification of patients whose tumors are likely to respond to a particular treatment. **Methods:** We evaluated immunohistochemical staining for GDF15 in pretreatment biopsy specimens of 230 out of 256 OSCC patients who were treated in a prospective, randomized, phase three trial on induction chemotherapy including docetaxel, cisplatin and 5-fluorouracil (TPF). Relationship between GDF15 intervention and cell proliferation, migration, invasion, colony formation, and tumorigenicity was analyzed using *in vitro* and *in vivo* OSCC models. **Results:** LowGDF15 expression predicts a better survival in OSCC patients, especially overall survival ($P$=0.049, HR=0.597) and distant metastasis free survival ($P$=0.031, HR=0.562). Low GDF15 expression also predicted a better clinical response to TPF induction chemotherapy in comparison to high GDF15 expression ($P$=0.004). Decreased GDF15 expression in OSCC lines significantly inhibited cell proliferation, migration, invasion, colony formation, and tumorigenesis through increased phosphorylation of AKT and ERK1/2 ($P$<0.05). Likewise, overexpression of GDF15 significantly promoted cell proliferation, migration, invasion, and colony formation through decreased phosphorylation of AKT and ERK1/2 ($P$<0.05). **Conclusions:** GDF15 expression can be used as a prognostic biomarker for OSCC. A low GDF15 expression level predicts a high clinical response rate to TPF induction chemotherapy in OSCC patients. GDF15 promotes tumorigenesis and progression through phosphorylation of AKT and ERK1/2 in OSCC.

**6038 General Poster Session (Board #73), Sat, 1:15 PM-5:00 PM**

**Prognostic significance of multifocalty in papillary thyroid carcinoma: A multivariate analysis of prognostic factors.** *Presenting Author: Ivan Markovic, Institute of Oncology and Radiology of Serbia, Belgrade, Serbia*

**Background:** The incidence of multifocality in papillary thyroid carcinoma (PTC) was refered form 18 to 87,5%. The mechanisms of multifocal spreading, corelation with tumor size and histology variants of PTC, presence of lymph node metastases, as well as prognostic significance of multifocality has not yet been clarified. **Methods:** One hundred fifty three patients with PTC were surgicaly treated. Patients with locally invasive tumors (pT4) and initial distant metastases were excluded from study. Median age 42 years at diagnosis. Sex ratio: F/M-3.9/1. Total thyroidectomy (TT) was done in all 153 patients. Dissection of central and lower jugular lymph nodes of the neck for frozen-section histology was done in 117 (76.5%) patients and modifed radical neck dissection if positive. Statistics: Kapplan-Meier, Log Rank, Cox's multivariate regresion model. **Results:** Multifocal tumors were found in 43 (28%) thyroid gland specimens. The smallest focus was 2 mm. The incidence of multifocality was significantly higher in patients above 45 years at diagnosis (p<0.05) and in tumors greater than 4 cm in diameter (p<0.01). Multifocality was not significantely corelated with gender, histology variants of PTC or presens lymph node metastases (LNM). Incidence if LNM in patients with multifocal PTC was 29% vs. 44% in patients with solitary tumors. In a median follow up of 138 months (rang =2-229) regional relaps in not dissected lymph nodes occurred in 13 (8.4%) and distant metastases in 2 (1.3%) patients, while 8 (5.2%) patients died due to PTC. Incidence of relapse was significantly higher (p<0.01), and relapse free interval and survival significantly shorter (p=0.0095, p=0.0004, respectively) in patients with multifocal PTC. According to Cox's multivariate regrresion model, multifocality was independent prognostic factor for both relapse and survival in patients with intrathyroid papillary carcinoma. **Conclusions:** Due to high incidence of multifocality, higher relapse rate and worse survival, total thyroidectomy should be consider as optimal treatment in patients with PTC, in a goal to reduce relapse rate and improve disease free and overall survival.

**6039 General Poster Session (Board #74), Sat, 1:15 PM-5:00 PM**

**Risk factors predictive for poor outcomes in patients with human papillomavirus (HPV)-initiated oropharyngeal cancer (OPC).** *Presenting Author: Tobenna Igweonu Nwizu, Cleveland Clinic Foundation, Cleveland, OH*

**Background:** Studies have demonstrated better prognosis for patients (pts) with HPV-initiated OPC when compared to OPC caused by smoking. A small subset of pts however experience disease recurrence and have poor outcomes. We report our Cleveland Clinic experience with HPV-initiated OPC in an effort to identify determinants of a poor prognosis. **Methods:** We identified pts with stage III-IVb HPV-initiated OPC treated with definitive chemoradiotherapy between 2002 and 2012 from an IRB approved registry. HPV-initiated disease was determined by positivity for p16 by immunohistochemistry or HPV DNA by fluorescent in-situ hybridization. Radiation therapy was administered to a total dose of 70-74 Gy. Chemotherapy consisted of either cisplatin and 5-Fluorouracil, cisplatin or cetuximab. Kaplan-Meier estimates of disease-free survival (DFS) and overall survival (OS) were calculated. Univariate (UVA) and multivariate analyses (MVA) using Cox proportional hazards regression were performed to identify variables associated with inferior DFS and OS. **Results:** Of the 228 patients identified, 17% had T4 disease, 40% had N2c/3 disease, 51% had a smoking history (>10 pack years) while 31% were lifetime never smokers. Median follow up was 40 months. 3-year DFS and OS was 89% and 90% respectively. UVA revealed that DFS was inferior in pts with T4 (HR = 2.525; 95% CI = 1.089 to 5.848; P = 0.03) and N2c-N3 (HR = 2.364; 95% CI = 1.062 to 5.263; P = 0.04) disease. OS was also inferior in pts with T4 disease (HR = 2.123; 95% CI = 1.042 to 4.329; P = 0.04), and pts with a smoking history (HR = 2.475; 95% = CI 1.192 to 5.128; P = 0.02). On MVA, the most important predictors for an inferior DFS were smoking history, T4 and N2c-N3 disease. Patients with 2 or more of these risk factors had a significantly worse 3 –year DFS (77% vs. 94%; HR = 4.082; 95% CI = 1.828 - 9.091; P <0.001) and OS (83% vs. 93%, HR = 2.283; 95% CI = 1.193 - 4.367; P 0.01). **Conclusions:** Patients with HPV-initiated OPC and at least two high risk features, including T4, N2c/3, or >10 pack years of smoking, had significantly inferior DFS and OS. Such patients should not be considered for treatment de-intensification strategies.

**6040 General Poster Session (Board #75), Sat, 1:15 PM-5:00 PM**

**Minocycline for reduction of patient-reported symptoms during radiation therapy for head and neck cancer: First results of a randomized trial.** *Presenting Author: Gary Brandon Gunn, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background**: Local and systemic symptoms during radiation therapy (RT) may be exacerbated by dysregulated inflammation and its downstream toxic effects. Minocycline (mino) can suppress pro-inflammatory cytokine release. We conducted this study to investigate its potential to reduce patient (pt) reported symptom severity during RT for HNC. **Methods**: Eligible pts for this blinded, placebo-controlled trial were adults with oro- or nasopharyngeal carcinoma (T0-3, N-any, M0) dispositioned to intensity-modulated RT alone (no concurrent systemic therapy or prior resection). Participants were equally randomized to receive mino (100 mg twice daily) or placebo (P) during RT course. The primary endpoint was the area under the curve (AUC) of 5 pre-specified symptoms (pain, fatigue, sleep, appetite and swallowing) during RT course as assessed by the MDASI-HN (0-10 scale). As the overall goal of this study was to determine the potential signal/benefit of mino to inform future clinical trial design, we selected a modest power (70%) to detect a large standardized effect size (ES) of 0.70 (one-sided, 5% sig. level) on the primary endpoint, requiring 20 pts per arm. **Results**: From 8/10-7/13, 82 pts were approached and 47 were enrolled (safety analyses cohort); 7 withdrew and were replaced per protocol. 20 evaluable pts in each arm formed cohort used for symptom analyses. Pt characteristics and toxicity details will be presented. There were no grade 3+ potentially study medication-related AEs. There were 2 and 7 grade 1-2 AEs for P and mino arm respectively (p=0.53). All pts completed RT (66-70 Gy); there have been no recurrences to date. 5 pts in P arm required feeding tube during RT, versus 2 in mino arm (p<.21). The average daily AUC for the 5 preselected symptoms during RT were 3.7 (SD=1.7) and 3.1 (1.0) for the P and mino group (p<.16), respectively, and equivalent to an ES of 0.37. AUC ES comparisons for several individual symptoms and interference also favored mino but were not significant. **Conclusions**: Mino during RT for HNC is feasible and achieved a positive signal in terms of patient reported symptom severity and interference to justify and direct future trial design. Clinical trial information: NCT01173692.

**6041 General Poster Session (Board #76), Sat, 1:15 PM-5:00 PM**

**Preoperative window-of-opportunity (WOO) study of dacomitinib (Dac) in patients (Pts) with resectable oral cavity squamous cell carcinoma (OCC): Generation of a gene expression signature (DGS) as a predictor of Dac activity.** *Presenting Author: Irene Brana, Princess Margaret Cancer Centre, Toronto, ON, Canada*

**Background:** Dac is a potent, irreversible oral pan-HER tyrosine kinase inhibitor (TKI) with activity demonstrated in a multi-center phase II trial as first-line treatment in pts with recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN) (NCT01449201; Razak et al. Ann Oncol 2013). No predictive biomarkers currently exist for Dac. **Methods:** WOO is a single-center, investigator-initiated study which enrolled pts with untreated resectable OCC, ECOG 0-2, and adequate organ functions. Pts were randomized 2:1 to Dac 45 mg or placebo QD for 7-11 days prior to surgery. Pre- and post-treatment (surgical specimen) samples were collected. Study objectives: (1) to evaluate a gene expression signature as a predictor of response to Dac, (2) to assess Ki67 modulation by Dac on paired tumor samples. DGS generation and validation: Using pre- and post-treatment fresh tumor biopsies from 7 pts in the NCT01449201 study as a discovery set, DASL HT12 Illumina gene expression array was performed on RNA. Genes differentially expressed in two groups were identified: pre- vs. post-treatment samples and pts with short vs. long progression-free survival ($<$ 10 weeks vs. $>$ 10 weeks). Genes commonly deregulated in both groups defined the signature DGS. DGS was then applied to pre-treatment samples from the WOO study as a validation, blinded to clinical response. Euclidean distance was used for complete-linkage clustering. **Results:** 14 pts were enrolled in the WOO study with evaluable samples from 10 pts (Dac/Placebo 8:2; response: yes/no/unknown 4/5/1). In the discovery set, a signature of 47 commonly-deregulated genes was found to be capable of dividing patients as high- or low-expressers pre-treatment. Patients clustered as high-expressers were more likely to be good-responders after treatment (RR = 3.75, 95% C.I. 0.8-21.7). No difference was observed in pre- post-treatment Ki67 between pts on Dac or placebo, nor between responders and non-responders. **Conclusions:** DGS may identity a subgroup of SCCHN pts more likely to respond to Dac; further validation in other Dac-treated SCCHN pts is ongoing. Clinical trial information: NCT01116843.

**6042 General Poster Session (Board #77), Sat, 1:15 PM-5:00 PM**

**Adjuvant radiotherapy (RDT) plus cisplatinum (Cis) and cetuximab (Cet) in resected head and neck squamous cell carcinoma.** *Presenting Author: Frederic Peyrade, Centre Antoine Lacassagne, Nice, France*

**Background:** Adjuvant RDT-chemotherapy is the standard for resected head and neck squamous cell carcinomas (SCCHN) with adverse histological prognostic factors (AHPF). Despite this treatment, half of the patients will relapse. Cet can enhance radiotherapy activity for patients (pts) with unresectable SCCHN. Thus, we conducted a phase II clinical trial to investigate a combination of Cis, Cet and RDT in resected SCCHN with AHPF. **Methods:** Pts with resected M0 SCCHN and at least one of the following (positive margin and/or N+$>$1, and/or extracapsular extension and/or vascular embolisms and/or perineural disease) were enrolled. They received a radiotherapy (2.0 Gy per day, 5 days a week for 7 weeks) with Cet (400 mg/m2 at D- 8 before RDT followed by 250 mg/m$^2$ weekly for 7 weeks) and Cis 75 mg/m$^2$ every 3 weeks. The primary objective was Disease Free Survival (DFS). **Results:** From March 2008 through January 2011, 45 pts were included. The median follow-up was 27 months (95% IC: 26-34 months). The median age was 57 years (range 28 - 71). Tumor location was oral, oropharyngeal and hypopharyngeal in 47%, 45% and 8% respectively. All of patients had at least one adverse prognostic factor mainly $>$1 N+ (82% of cases). 71% of patient received the all treatment as planned. The 2-year disease free survival was 60% [95% CI: 46-77%]. Median DFS has not been reached yet. The two-year OS was 78.9% [95% CI: 67.5-92.1%]. 86 % of patients presented at least one toxicity $>$ Grade II according to NCI-CTCAE 3.0 classification. Grade 3-4 mucositis, dermatitis inside and rash outside radiotherapy fields were observed in 52%, 50% and 29% of pts respectively. 23 pts (52%) had a grade III/IV lymphopenia. Treatment was definitively discontinued because of toxicities in 6 cases. **Conclusions:** In patients with SCHNC with AHPF, the association of treatment with Cet, Cis and RDT appears to be safe and effective, comparing favorably with conventional RDT-Cis. Further protocols clinical investigations are justified to compare these two regimens in such a setting. Clinical trial information: NCT00875849.

**6043 General Poster Session (Board #78), Sat, 1:15 PM-5:00 PM**

**Clinical dosimetry analysis of radiation-induced temporal lobe necrosis in nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy.** *Presenting Author: Jin Yi Lang, Sichuan Cancer Hospital and Institute, Chengdu, China*

**Background:** Radiation induced temporal lobe necrosis(RITLN) is one of the late complications in nasopharyngeal carcinoma patients undergoing radiotherapy.This retrospective study aims to explore the clinical dosimetry characteristcs of radiation induced temporal lobe necrosis in nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy. **Methods:** This study enrolled the patients in Sichuan cancer hospital from January,2004 to November, 2008; diagnosised as nasopharyngeal carcinoma and treated primarily with intensity-modulated radiotherapy (IMRT). Magnetic resonance imaging ( MRI) was taken for all these patients in follow-up, RITLN was diagnosised based on the T1-weight with contrast. Dosimetry parameters of bilateral temporal lobe D1cc(the 1 cubic centimeter temporal lobe received the max dose), D2cc, D3cc, D5cc, D10cc, D15cc, D20cc,Dmean, Dmax were analysised . **Results:** MRI were assessed in a total of 148 patients primarily diagnosised with nasopharyngeal carcinoma treated by IMRT, 59 cases of RITLN were found. Univariate analysis showed that all the parameters demonstrated statistically significant results ($p<0.05$). Multivariate analysis showed that D1cc ($P= 0.026 <0.05$) and Dmax ($P=0.000 <0.05$) had statistically significant. The 5 years incidence of RITLN for D1cc$\leq$61Gy and Dmax$\leq$70Gy is less than 5%, the RITLN incidence has 3.3% increasing per Gy of D1cc beyond 60Gy and 4.6% increasing per Gy of Dmax over 69Gy. **Conclusions:** The incidence of radiation induced temporal lobe necrosis has closely relationship between the dose of temporal lobe and corresponding volume, temporal lobe D1cc less than 61Gy and Dmax less than 70Gy may be the restrict dose of temporal lobe for IMRT patients.

**6044 General Poster Session (Board #79), Sat, 1:15 PM-5:00 PM**

**Phase Ib/II study of the PI3K$\alpha$ inhibitor BYL719 in combination with cetuximab in recurrent/metastatic squamous cell cancer of the head and neck (SCCHN).** *Presenting Author: Albiruni R. A. Razak, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

**Background:** Preclinical data suggest that simultaneous inhibition of PI3K and EGFR leads to synergistic antitumor activity in SCCHN. BYL719 is a potent, oral inhibitor of the $\alpha$-isoform of class I PI3K. The Phase Ib dose-escalation part of this study used a Bayesian model to identify the recommended Phase II dose (RP2D) of BYL719 combined with standard weekly doses of cetuximab (EGFR inhibitor) in patients (pts) with platinum-resistant, recurrent/metastatic SCCHN (NCT01602315). **Methods:** BYL719 was administered QD in 28-day cycles using two methods: (1) as whole tablets (Arm A) or (2) as a drinkable suspension (crushed tablets) for pts with swallowing dysfunction (Arm B). **Results:** As of Oct 28, 2013, 32 pts were treated with either BYL719 300 mg QD (n=15) or 400 mg QD (n=5) in Arm A or BYL719 300 mg QD (n=12) in Arm B. At 300 mg (Arms A+B), 4 out of 27 pts had dose-limiting toxicities (DLTs; 2 mucositis, 1 hyperglycemia, and 1 PEG tube site infection). At 400 mg (Arm A), 2 out of 5 pts had DLTs (1 fatal tumor lysis syndrome and 1 esophageal ulcer). Other frequent drug-related AEs (any grade $>$15%) were similar across arms and included hyperglycemia (55%; G3/4, 20%), acneiform dermatitis (40%; G3/4, 5%), stomatitis (40%; G3/4, 5%), dry skin (25%; G3/4, 0%), hypomagnesemia (25%; G3/4, 5%), decreased appetite (20%; G3/4, 5%), diarrhea (20%; G3/4, 0%), fatigue (20%; G3/4, 10%), and paronychia (20%; G3/4, 0%) in Arm A. Exposures (AUC) and maximal concentrations (Cmax) were similar across arms and were consistent with the PK profile of single-agent BYL719. Best overall response per RECIST v1.1 in Arm A was 1 partial response, 3 unconfirmed partial responses, 5 stable diseases (SDs), and 1 unknown at 300 mg (10 evaluable pts); 1 pt had progressive disease (PD) and 1 pt had SD (2 evaluable pts) at 400 mg.No responses were observed in Arm B. The primary reason for discontinuation was PD (28%). The RP2D of BYL719 in combination with cetuximab was declared as 300 mg QD (whole tablets). **Conclusions:** Combined inhibition of PI3K-a and EGFR by BYL719 and cetuximab was tolerated and demonstrated encouraging antitumor activity. The Phase II part of the study comparing this combination with cetuximab alone is ongoing. Clinical trial information: NCT01602315.

**6045 General Poster Session (Board #80), Sat, 1:15 PM-5:00 PM**

**Phase 2 study of dalantercept in recurrent or metastatic squamous cell carcinoma of the head and neck.** *Presenting Author: Antonio Jimeno, University of Colorado Denver, Aurora, CO*

**Background:** Limited treatments exist for patients with recurrent or metastatic squamous cell carcinoma of the head and neck (RM-SCCHN) after platinum therapy. Activin receptor-like kinase 1 (ALK1) is a member of the TGF-$\beta$ superfamily involved in blood vessel maturation that is selectively expressed on activated endothelial cells. ALK1 binds to ligands bone morphogenetic protein (BMP) 9 and 10 and results in phosphorylation of Smad 1/5/8. Dalantercept (Dal) is an ALK1 receptor fusion protein and acts as a ligand trap. In Phase 1 testing Dal had clinical activity in pts with RM-SCCHN. This study sought to determine the activity of Dal monotherapy in pts with RM-SCCHN. **Methods:** 46 pts were enrolled and received Dal at 80 mg (n=2), 0.6 mg/kg (n=13) or 1.2 mg/kg (n=31) SC Q3W. Serum, archived, and optional biopsies were collected for pharmacodynamic (PD) studies. The primary endpoint was response rate per RECIST 1.1 and secondary endpoints included progression free survival (PFS) and overall survival (OS). Key eligibility: RM-SCCHN of mucosal origin, $\geq$1 one prior platinum regimen, ECOG $\leq$1, and no prior anti-angiogenic tx. **Results:** 41 pts were evaluable (1 at 80 mg, 13 at 0.6 mg/kg, 27 at 1.2 mg/kg). The median age was 60.5 yr, 85%M/15%F, ECOG: 0 (35%)/1(65%), HPV+ 41%, HPV- 33%, HPV unk 26%. Median number of prior tx was 4. 1 pt at 1.2 mg/kg (3.7%) achieved a PR and was on study for 9 mos. 23% (n=3) at 0.6 mg/kg and 37% (n=10) at 1.2 mg/kg had SD $\geq$ 3 cycles. Of those pts with SD or better (n=16), 62% were known to be HPV+. 17% (2 at 0.6 mg/kg and 5 at 1.2 mg/kg) pts. had SD for $\geq$ 6 cycles (4.5 mos.). The median OS (n=46) was 6.3 mos. (95% CI: 5.8-10.5) and 5 pts survived beyond 1 year. Common drug-related AEs were anemia, fatigue, peripheral edema, headache, hyponatremia, and pleural effusion. The frequency of grade $\geq$ 3 related AEs was 13% and the most common were hyponatremia (n=3) and pleural effusion (n=2). There were no thromboembolic or significant bleeding events. **Conclusions:** Dal is a novel anti-angiogenic agent that inhibits ALK1 signaling. In this heavily pre-treated RM-SCCHN population, Dal monotherapy demonstrated modest dose dependent activity and a favorable safety profile. Detailed safety, efficacy, and correlative PD data will be presented. Clinical trial information: NCT01458392.

**6046 General Poster Session (Board #81), Sat, 1:15 PM-5:00 PM**

**Boron neutron capture therapy in patients with recurrent head and neck cancers who have no other treatment options.** *Presenting Author: Itsuro Kato, Oral and Maxillofacial Surgery II ,Osaka University Graduate School of Dentistry, Suita, Japan*

**Background:** Boron neutron capture therapy (BNCT) is a targeted type of radiotherapy that has a number of significant advantages over conventional external beam photon irradiation, especially in that radiation can be selectively delivered to tumor cells. We had, first in the world, treated with BNCT for a patient with recurrent head and neck Cancers (HNC) in 2001. **Methods:** From December, 2001 to February, 2013, we have treated a total of 35 patients with recurrent HNC by means of 52 applications of BNCT. Histopathologically, there were 24 patients with squamous cell carcinomas (SCC), 7 with salivary gland carcinomas and 4 with sarcomas. All of them had received standard therapy and subsequently developed recurrent disease for which there were no other treatment options. All of the patients received intravenously either a combination of two boron containing drugs, sodium borocaptate (BSH, 5g) and boronophenylalanine (BPA, 250mg/kg) or BPA (500mg/kg) alone. In this report we will summarize the clinical results and outcomes of 35 patients with HNC who had received BNCT at either the Kyoto University Research Reactor Institute (KURI) or the Japan Atomic Energy Agency (JAEA) nuclear reactor. **Results:** All of the patients had advanced disease and 17 of 35 (49%) had regional lymph node metastases and 10 out of 35 (29%) had distant metastases at the time of treatment. (1) Boron concentration ratios of tumor/normal tissue (T/N ratio), as determined by $^{18}$FBPA-PET imaging were 1.8-7.0 for SCC, 2.5-4.0 for sarcomas and 2.5-3.7 for parotid tumors. (1) Regression rates were CR: 18 patients (51%), PR: 13 (37%), PD: 3 (9%), and not evaluated (NE):1patient. The overall patient response rate was 88%. (2) The Mean Survival Time was 24.2 months and the 4 year and 7-year OS rates were 42% and 36% , respectively. (3) Survival times following BNCT ranged from 1 to 95months. (4) BNCT improved QOL, PS and survival times. (5) The primary adverse events were brain necrosis, osteomyelitis and transient mucositis and alopecia. **Conclusions:** Our results indicate that we could make sure that safety and effectiveness of BNCT and BNCT represents a new and promising treatment modality in patients for whom there are no other treatment options.

**6047 General Poster Session (Board #82), Sat, 1:15 PM-5:00 PM**

**Impact of tumor metabolic response by PET/CT on the survival after salvage re-irradiation of head and neck cancers.** *Presenting Author: Tawee Tanvetyanon, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

**Background:** Re-irradiation (Re-RT) is a treatment option for recurrent, previously irradiated head and neck cancers. Nevertheless, most patients will still develop progressive disease after Re-RT. We sought to evaluate the predictive value of metabolic response by 18F-FDG-PET/CT (PET/CT) on the survival after Re-RT. **Methods:** Patients with locally recurrent squamous cell carcinoma of head and neck treated by Re-RT at our institution during 2005-2012 who had pre- and post-treatment PET/CT were identified. Their scans were re-analyzed by a nuclear medicine physician who was unaware of patient outcome. PET/CT analysis comprised qualitative analysis and measurement of maximum standardized uptake value (SUVmax) as a semi-quantitative index of relative tissue uptake. Complete metabolic response (CR) was defined as resolution of hypermetabolism without new lesion. **Results:** Fifty-five patients were analyzed: 41 patients (76%) had definitive Re-RT and 13 patients (24%) had adjuvant Re-RT. Median radiation dose delivered was 60 Gy (40-70 Gy). Concurrent chemotherapy was cisplatin in 28, carboplatin in 13, cetuximab in 10, and none in 3 patients. Median pre- and post-treatment SUVmax were 8.5 (range 3.3-18.9) and 4.3 (range 0-15.7), respectively. At a median of 13 weeks after Re-RT, the median metabolic response was 63% (range -80-100%), with 16 patients (30%) achieving CR. Median overall survival was 38.7 months among patients with CR vs. 12.2 months among those without CR ($p<0.0001$); Median PFS was 29.3 vs. 5.6 months ($p<0.0001$); and 5-year survival rates were 37% vs. 3%, respectively. Multivariate analysis adjusting for age, duration since previous radiation, comorbidity, organ dysfunction and sum of tumor sizes showed that achieving CR was a strong, independent predictor of survival, Hazard Ratio 5.52 (95% CI: 2.3-13.5). We found no significant difference in the survival of patients with partial metabolic response ($\geq$50% reduction of SUVmax) and those without response. For the prediction of 5-year survival, the negative predictive value of achieving CR by PET/CT was 97%. **Conclusions:** Failure to achieve a complete metabolic response after Re-RT is highly predictive of disease progression or death.

**6048 General Poster Session (Board #83), Sat, 1:15 PM-5:00 PM**

**Comparison of outcomes of locoregionally advanced oropharyngeal and non-oropharyngeal SCC over two decades.** *Presenting Author: Lauren Herman, The University of Chicago Medical Center, Chicago, IL*

**Background:** Human papillomavirus (HPV) has emerged as a causative agent and positive prognostic factor for oropharyngeal (OP) head and neck squamous cell cancer (HNSCC). This prompts inquiry into whether recent improvements in HNSCC outcomes are due to therapy improvements or the increasing incidence of HPV-related HNSCC. **Methods:** We performed a review of all patients treated for locoregionally advanced HNSCC with chemotherapy and radiation at the University of Chicago on a series of prospective institutional trials. Patients were divided into three groups according to the time period during which they were treated. Groups one, two, and three were treated between 1993-1998, 1999-2003 and 2004-2010 respectively. Trends were compared for OP and non-OP. **Results:** 422 patients were identified with OP (55.7%) and non-OP (44.3%) cancers. All patients had ECOG 0-2. Median age was 57 yrs. OP overall survival (OS) improved over time with 5 yr OS of 42.3% (group 1), 72.5% (group 2), and 78.4% (group 3), $p<0.001$. There was a trend towards improved 5 yr OS for non-OP patients with 51.0% (group 1), 58.8% (group 2), and 66.3% (group 3), $p=0.16$. Similarly 5 yr progression free survival (PFS) improved for OP groups from 42.3% to 68.4% to 75.8% ($p<0.001$). The respective increase in non-OP was from 42.9% to 53.6% to 61.7% ($p=0.094$). Five year distant failure free survival (DFFS) was 42.3%, 71.1%, and 77.8% ($p<0.001$) for OP and 46.9%, 57.1%, and 66.0% ($p=0.13$) for non-OP. Trends remained statistically significant for OP groups after adjusting for baseline covariates but were diminished in the non-OP group ($p=0.51$, $p=0.30$, and $p=0.38$ for OS, PFS, and DFFS respectively). **Conclusions:** Over the past two decades, OP HNSCC outcomes (OS, PFS, DFFS) have significantly improved while non-OP HNSCC outcomes have trended toward improvement. Although our patients are not specifically stratified by HPV, it is likely that improving OP outcomes are due to the increasing incidence of HPV-related HNSCC in the OP. These data further justify trial stratification for HPV status, investigations of novel approaches for patients with carcinogen-related HNSCC, and current de-intensification approaches for HPV-related HNSCC.

**6049 General Poster Session (Board #84), Sat, 1:15 PM-5:00 PM**

**A dose-finding study of nanoparticle albumin-bound paclitaxel plus cisplatin in patients with metastatic nasophyngeal carcinomas.** *Presenting Author: Li Zhang, Sun Yat-Sen University Cancer Center, Guangzhou, China*

**Background:** Nanoparticle albumin-bound paclitaxel (Abraxane, ABX), is a novel formulation of paclitaxel that has proved superior efficacy compared with conventional paclitaxel in the treatment of several metastatic cancers. We undertook this trial to determine the optimal dose and to preliminarily aseess efficacy of ABX plus cisplatin (DDP) in nasopharyngeal carcinoma (NPC). **Methods:** This was an open-label, nonrandomized study. Patients with metastatic NPC who were previously untreated or failed the standard treatment (radiochemotherapy or first-line chemotherapy) were enrolled sequentially into three cohorts (23 patients/cohort, N=69) to receive DDP 75 mg/m2 q3w plus ABX 260mg/m$^2$ q3w (cohort 1), or 140mg/m$^2$ d1, 8 q3w (cohort 2) or weekly ABX 100mg/m$^2$(cohort 3), respectively. Recruitment of any cohort would be deceased if more than one third of patients experienced dose-limiting toxicities (DLTs). **Results:** All clinical features were balanced among cohorts, including sex, age, histology, proportion of patients with different previous treatments, etc. All cohorts completed recruitment since DLT occured only in one case from cohort 1 and cohort 3 repspetively. The most common grade 3-4 adverse events were neutropenia (50.9%), leukocytopenia (43.6%), anemia (10.9%), fatigue (5.5%) and vomitting (5.5%). The proportion of patients experienced grade 3-4 toxicity is 65.5%, not differing in each cohort (cohort 1, 63.6%; cohort 2, 61.1%; cohort 3, 73.3%; $P$=0.74). The objecive response rates (ORR) were similar among all cohorts (70.0%, 66.7%, 66.7%, $P$=0.97). Notably, we observed that patients who had received not any prior chemotherapy (23.6%) had a significantly higher ORR than those who had ever experienced (100% vs. 56.8%, $P$=0.004), without difference in grade 3-4 toxicity ($P$=0.314). **Conclusions:** ABX-DDP is a safe and efficacious regimen for advanced NPC patients. ABX 260mg/m$^2$ q3w, 140mg/m$^2$ d1, 8 q3w or weekly ABX 100mg/m$^2$ showed equivalent response and toxicity. Taking convenience into consideration, we determined ABX 260mg/m$^2$ q3w as the standard dosage in the upcoming phase III randomized controlled trial. Clinical trial information: NCT01735409.

**6050 General Poster Session (Board #85), Sat, 1:15 PM-5:00 PM**

**Preliminary testing of a patient-reported outcome measure for recurrent or metastatic head and neck cancer.** *Presenting Author: Leanne Kolnick Jackson, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN*

**Background:** There are no patient reported outcome measures developed and tested in patients with recurrent-metastatic head and neck cancer (RMHNC). Symptom (sx) burden in RMHNC is poorly described. Available tools focus on acute and late effects of primary therapy and are hypothesized to lack content specific to RMHNC. We undertook development of the Vanderbilt Head and Neck Symptom Survey - Recurrent/Metastatic (VHNSS-RM) to assess tumor related sx, residual toxicity from prior therapy and side effects from current therapy. The tool contains 35 physical sx and 12 psychosocial issues scored on a 0 (none) to 10 (severe) scale (ASTRO abstract 46, 2014). We now report preliminary testing of the tool. **Methods:** A pilot trial with 39 patients was completed 6/2013 - 1/2014. Inclusion criteria: non-curable recurrent or metastatic HNC. The tool was administered online to all patients during clinic. **Results:** No barriers to completion of the tool via computer interface were noted. Patients found the tool acceptable, with high feasibility and readability. Completion time was $\leq$15 minutes for 92.4% of patients. A full range of scores was noted for 46 of 47 questions. VHNSS-RM includes 12 novel sx questions and 7 novel psychosocial issues. Novel sx include: diet change due to mouth swelling; tongue movement affecting speech/swallowing; swelling of face/neck; cramping in neck/jaw; bad breath; drooling; wound complications: drainage/pain/odor; nasal congestion/drainage; eyes watering; numbness of face/tongue/ear/scalp; headaches and confusion. Psychosocial issues include: perception of burden to family/friends; lost independence; fear; embarrassment; mood swings; stress and boredom. Overall, sx burden was high with moderate to severe symptoms (VHNSS-RM $\geq$5) identified in >30% of patients for 33/47 questions (70.2%), of those 48.5% had severe sx (VHNSS-RM $\geq$7). **Conclusions:** The VHNSS-RM is feasible and can be completed in a timely manner. Sx experienced by patients with RMHNC are often different than at initial presentation and during primary treatment. The 19 novel questions could aid in improved palliation to these patients. There are plans to validate the VHNSS-RM and analyze its role in assessment of treatment response and impact on overall sx burden.

**6051 General Poster Session (Board #86), Sat, 1:15 PM-5:00 PM**

**Internal lymphedema correlation with subjective and objective measures of dysphagia in head and neck cancer.** *Presenting Author: Leanne Kolnick Jackson, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN*

**Background:** Tumor/treatment-related external (EL) and/or internal lymphedema (IL) are associated with functional deficits and increased symptom burden in head and neck cancer (HNC) patients. We noted an association between EL/IL and patient-reported dysphagia using the Vanderbilt Head and Neck Symptom Survey (VHNSS) version 1.0. Consequently, we studied the relationship between EL/IL with subjective and objective measures of swallow function. **Methods:** 81 HNC patients completed: (1) the VHNSS version 2.0 which included 13 swallowing or nutrition related questions grouped into three clusters: swallow solids (ss), swallow liquids (sl), nutrition(nt); (2) physical assessment of EL using Foldi scale; (3) endoscopic assessment of IL using the Patterson scale (n=56); and (4) modified-barium videofluoroscopy (MBSS) rated by the Dysphagia Outcome and Severity Scale (DOSS) and in conjunction with a swallow evaluation, by the National Outcomes Measurement System (NOMS). Examinations were performed at varied time points to assess a spectrum of lymphedema, from baseline (n=15, 18.1%) to 18 months post therapy (n=20, 24.1%). **Results:** VHNSS swallow/nutrition items scores correlated with NOMS and DOSS ratings. The highest correlation was with the NOMS: ss (-.73; p<.001); sl (-.61; p<.001); nt (-.56; p<.001). VHNSS swallow/nutrition scores correlated with maximum grade of swelling for any single structure on the Patterson scale: ss (.43; p=.001); sl (.38; p=.004); nt (.41; p=.002). IL of the aryepiglottic and pharyngoepiglottic folds, epiglottis and pyriform sinus were most strongly correlated with VHNSS swallow/nutrition items and NOMS ratings. There was no correlation with VHNSS swallow/nutrition items or NOMS/DOSS ratings and EL. **Conclusions:** IL correlated with subjective and objective measures of swallow dysfunction. Longitudinal analysis of the trajectory and impact of IL/EL on dysphagia is ongoing. Clinical trial information: NCT01187173.

**6052 General Poster Session (Board #87), Sat, 1:15 PM-5:00 PM**

**Is there a survival benefit in patients with advanced squamous cell carcinoma of the head and neck under chemoradiotherapy or radiotherapy alone after surgery administration: A systematic review and meta-analysis.** *Presenting Author: Jinbiao Shang, Zhejiang Cancer Hospital, Hangzhou, China*

**Background:** The optimal treatment strategy for patients with operable advanced squamous cell carcinoma of the head and neck is uncertain. We performed a systematic review and meta-analysis to test the hypothesis that the addition of chemotherapy to radiotherapy after surgical resection could improve the locoregional control and survival compared with postoperative radiotherapy alone. **Methods:** A comprehensive search of PubMed for relevant studies comparing patients with advanced squamous cell carcinoma of the head and neck undergoing chemoradiotherapy or radiotherapy alone after resection was conducted using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards. The endpoints were local-regional control (LRC), disease-free survival (DFS) and overall survival (OS). Hazard ratios (HRs) were extracted from these studies to give pooled estimates of the effect of chemotherapy as an adjunct to postoperative radiation therapy on DFS and OS. **Results:** Data from a total of 1,054 patients from 5 randomized trials investigating chemoradiotherapy versus radiotherapy alone after surgery were included in a meta-analysis. The meta-analysis demonstrated significant benefits from adding chemotherapy to radiotherapy in LRC (risk ratio [RR]: 0.61, 95% confidence interval [CI]: 0.49 - 0.76, $p < 0.00001$), DFS (HR: 0.76, 95% CI: 0.65 - 0.88, $p = 0.0003$) and OS (HR: 0.77, 95% CI: 0.66 – 0.90, $p = 0.001$). The adverse effects occurred more frequently and severely in chemoradiation combined treatment, but there was no significant difference compared with radiotherapy alone. **Conclusions:** Postoperative chemotherapy adding to radiotherapy is superior to radiotherapy alone. Patients with chemoradiotherapy after surgical resection can achieve the higher LRC, longer DFS and OS. But the pronounced benefits of chemoradiation combined treatment need to be weighed against the potential toxicity of treatment.

**6053 General Poster Session (Board #88), Sat, 1:15 PM-5:00 PM**

**Quality of life of patients with locally advanced head and neck cancer (LAHNC) treated with docetaxel/cisplatin/5-fluorouracil (TPF) followed by cisplatin-containing chemoradiotherapy (CRT).** *Presenting Author: Chantal Driessen, Department of Medical Oncology, Radboud University Medical Center, Nijmegen, Netherlands*

**Background:** The CONDOR study, a randomized phase II trial, investigated feasibility of TPF followed by conventional CRT with cisplatin 100 mg/m$^2$ on days 1,22,43 (cis100+RT) versus CRT with accelerated RT with weekly cisplatin 40 mg/m$^2$(cis40+ART) in LAHNC pts, PS 0-1, age 18-65. Here we report the analysis of health-related quality-of-life (HRQOL) and symptoms. **Methods:** HRQOL was assessed at baseline (BL), after 2 TPF, before start and at the end of CRT, and 1, 4, 8, and 12 months after completion of CRT using the EORTC QLQ-C30 and QLQ-H&N35. A change of >10 points on mean scores was considered clinically significant. BL scores were compared to EORTC reference values of LAHNC pts. **Results:** 62 pts started with TPF; 56 pts were randomized to cis100+RT (n=27) and cis40+ART (n=29). The study was terminated prematurely due to toxicity and inability to get the full dose of cisplatin: 22% (cis100+RT) and 41% (cis40+ART) of the pts could receive the planned cisplatin during CRT, respectively. The planned radiotherapy was given to 96% of the pts. Despite high toxicity rates, especially mucositis in cis40+ART, and not full dosed cisplatin 2-years overall and progression free survival were 72% and 65%, respectively. Compliance with the QOL questionnaires was 94% (59/62) at BL, and dropped to 61% (30/49) at 12 months. Mean global health score (GHS) at BL was 75.3 (SD 19.7) compared to the reference value of 63.1 (SD 22.4). GHS decreased after TPF, even more during CRT to 46.8 (SD 19.7) in both arms equally, but restored to BL level after approximately 12 months. Pain and swallowing dysfunction improved significantly during TPF, but deteriorated below BL levels during CRT, more in cis40+ART than in cis100+RT ($p<0.05$). Speech ameliorated not significantly during TPF, worsened during CRT below BL level, more in cis40+ART ($p<0.05$). All symptoms restored to BL within a year in both arms. **Conclusions:** The BL GHS appeared to be high in this population reflecting the good condition of these pts. After TPF, cis40+ART had a more negative impact on symptoms than cis100+RT, probably due to the ART. GHS and symptoms restored to BL levels within one year in both arms. Clinical trial information: NCT00774319.

**6054 General Poster Session (Board #89), Sat, 1:15 PM-5:00 PM**

**Gefitinib with concurrent chemoradiation in locally advanced head and neck cancers.** *Presenting Author: Charu Singh, S.M.S Medical College and Hospital, Jaipur, India*

**Background:** Squamous cell carcinomas of Head and Neck express EGFR receptors. We conducted a study to assess the efficacy and toxicity of Gefitinib along with concurrent chemoradiation in comparison to chemoradiation alone in management of locally advanced head and neck cancers. **Methods:** 86 previously untreated histologically proven patients of squamous cell carcinoma of head and neck cancer were divided into two groups- the study group (n=43) receiving gefitinib 250 mg OD along with weekly cisplatin 30 mg/m$^2$ and radiotherapy , and the control group receiving weekly ciasplatin 30mg/m$^2$along with radiotherapy. The radiotherapy dose was 70 Gy in 35 fractions, 2 Gy / fraction in both the groups. Inclusion criteria were- patients with locally advanced head and neck cancer, biopsy proven squamous cell histology, patients of both genders, between 18 and 70 yearsof age, ECOG PS 0 to 2, life expectancy of 6 months. Patients with poor performance status, known metastatic disease, uncontrolled intercurrent illness, deranged LFT, RFT and complete blood count, and histology other than squamous cell carcinoma were excluded from study. The patients were put on follow up for 6 months after completion of treatment. **Results:** The analysis was based on intent to treat. In the study group, 34 patients had complete response and 4 had partial response. Overall response was seen in 38 patients (88.37%, $p<.05$). While in control group 27 patients showed complete response and 3 patients had partial response. Overall response (CR+PR) was seen in 69.76% patients. The most common adverse affects were skin rashes and mucositis. The incidence of dermatitis was 51.16% in the study group and 39.53% in the control group , overall incidence of grade 3 dermatitis being 3%. The incidence of mucositis was 90.69% in the control group and 97.67% in the study group. **Conclusions:** Chemoradiation remains the mainstay of treatment for head and neck cancer patients. EGFR is most expressed receptor in squamous cell carcinoma of head and neck. The present study shows that targeted therapy with gefitinib and chemoradiation is well tolerated with some enhanced, but manageable toxicities and has shown to improve local control though further studies are needed.

**6055 General Poster Session (Board #90), Sat, 1:15 PM-5:00 PM**

**Surgery and definitive chemoradiation (CRT) for locally advanced oropharyngeal cancer and impact of transoral robotic surgery (TORS).** *Presenting Author: Charles Eric Wooten, University of Kentucky, Lexington, KY*

**Background:** TORS is an emerging modality for oropharyngeal cancer. However, many patients require adjuvant therapy based on high-risk pathologic findings. We compared control rates of TORS to CRT. **Methods:** A retrospective review was performed evaluating all consecutive patients treated in our department for oropharyngeal cancer from January 2010 through December 2013. All patients treated with definitive CRT or surgical resection with adjuvant RT +/- chemotherapy. **Results:** 103 total patients identified among whom 40 were resected (33/40 TORS). Majority of patients were stage IVA (86%). 92% (37/40) of patients in the surgery group were T1/T2 vs 36% (23/63) in CRT group. p16 associated with improved locoregional control (LRC) (91% vs 43%, p=0.035). 22/40 resected patients required adjuvant radiation with chemotherapy (trimodality) due to 16/40 with extracapsular extension, 5/40 with positive margins and 2/40 with both. TORS had decreased rate of positive margins (9.1%) vs radical resection (29%). T4a primaries (3/40) had significant risk of positive margins (p=0.038). At median follow up of 20 months (3 – 50), 4 year actuarial overall survival (OS) for entire cohort was 77%. 4 year actuarial OS for trimodality was 79% vs 74% with CRT. 4 year actuarial local control with trimodality was 94% vs 86% with CRT. Compliance was 79% in the surgical group and 100% in the CRT group. Non-compliance was associated with decreased LRC (p=0.049). Sites of first recurrence for surgical and CRT groups respectively were 2.5% vs 11% primary, 10% vs 7.9% regional and 7.5% vs 11% distant. OS was negatively associated with time from initial surgery to completion of adjuvant treatment (p=0.02). Distant failure was associated with retropharyngeal nodal involvement (p=0.0043). **Conclusions:** No significant difference in control between both groups despite greater percentage of advanced primary tumors with CRT. Compliance with adjuvant therapy in TORS population was lower.

**6056 General Poster Session (Board #91), Sat, 1:15 PM-5:00 PM**

**Degree of nephrotoxicity after intermediate or high-dose cisplatin-based chemoradiotherapy (CRT) in patients with locally advanced head and neck cancer (LAHNC).** *Presenting Author: Chantal Driessen, Department of Medical Oncology, Radboud University Medical Center, Nijmegen, Netherlands*

**Background:** CRT with cisplatin 100 mg/m$^2$ on days 1, 22, 43 (cis100) is standard treatment for LAHNC and nasopharyngeal cancers (NPC) patients (pts). An alternative CRT schedule consists of cisplatin 40 mg/m$^2$ weekly during six weeks (cis40). A direct prospective comparison of these 2 schedules has not been performed, yet. Data on the influence of these schedules on cisplatin-based nephrotoxicity are scarce. This study compared the occurrence of cisplatin-induced nephrotoxicity between these 2 CRT schedules. **Methods:** All pts treated with CRT for LAHNC or NPC from 2003 until 2011 in the Radboud university medical center were studied retrospectively. One hundred forty-four LAHNC/NPC pts were included, of whom 40 received cis100 and 104 received cis40. Serum creatinine at baseline and maximal rise during treatment were collected. An increase of 25% was established as clinically relevant. Nephrotoxicity was scored according to both the CTCAE version 3.0 and version 4.03. **Results:** Baseline serum creatinine was equal in both groups. During treatment with cis40, 17.3% developed an increase of ≥25% serum creatinine versus 77.5% treated with cis100 ($p<0.05$). According to the CTCAE version 4.03, nephrotoxicity grade 1 occurred in 40% and 68%, grade 2 in 53% and 7%, grade 3 in 5% and 0%, and grade 4 in 2% and 0% ($p<0.05$) in cis100 and cis40 LAHNC/NPC pts, respectively. Scoring according to CTCAE v 3.0 showed grade 1 in 42% and 5%, grade 2 in 8% and 0%, grade 3 in 2% and 0% in cis100 and cis40 pts, respectively. In the cis100 group 3/40 pts developed chronic renal dysfunction, versus 0/104 in the cis40 group. Pts treated with cis100 were admitted to the hospital more often en needed more often extra hydration ($p<0.05$). **Conclusions:** Significantly less nephrotoxicity occurs in pts treated with cis40 CRT compared to cis100 CRT. We suggest that LAHNC/NPC pts with renal impairment are treated with cis40 CRT. The CTCAE v 4.03 is more appropriate in scoring nephrotoxicity than the CTCAE v 3.0. Until recently the CTCAE v 3.0 was used, which has lead to an underscoring of nephrotoxicity in studies using cisplatin-containing CRT schedules.

**6057 General Poster Session (Board #92), Sat, 1:15 PM-5:00 PM**

**Aggressive treatment and survival outcomes in *NUT* midline carcinoma (NMC) of the head and neck (HN).** *Presenting Author: Nicole Grace Chau, Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA*

**Background:** NMC is a rare subtype of squamous cancer defined by rearrangement of the *NUT* gene. NMC is typically found in the thorax, although ~20% of cases arise in the HN. NMC is almost uniformly fatal. We report on a cohort of patients (pts) with HN NMC to identify disease characteristics, treatment and outcomes. **Methods:** A clinical database was established using demographic and outcomes data available on all known cases of HN NMC obtained from the International NMC Registry (www.NMCRegistry.org). Clinicopathologic variables were assessed for 40 pts, the largest cohort of HN NMC studied to date. Outcome data from 31 patients treated from 1990-2013 were available for survival analyses. **Results:** HN NMC incidence has increased annually since 2010. Median age was 21.9 years (range 0.1-81.7), male: female (%) was 45:55, sinonasal origin was 50%, and the *BRD4-NUT* fusion was found in 82%. At diagnosis, 36% had regional node metastases and 15% had distant metastases. Initial treatment was upfront surgery (S) +/- adjuvant chemoradiation (CRT) or adjuvant radiation (RT) (48%), upfront RT +/- chemotherapy (C) (21%), or upfront C +/- S or RT (31%). Median progression-free survival (PFS) was 7.2 months (range 6.3-8.7). Median overall survival (OS) was 9.8 months (range 6.6-15.6). The 2-year PFS was 27% (95% CI, 9-44). The 2-year OS was 31% (95% CI, 13-50). Upfront S +/- post-operative CRT or RT, and S with negative margins were significant predictors of improved PFS and OS. Initial RT or C, type of C regimen, and *NUT* translocation type were not significantly associated with improved outcome. **Conclusions:** HN NMC portends a poor prognosis. Aggressive initial surgical resection with or without post-operative CRT or RT may be associated with enhanced survival. C or RT alone is inadequate, and the development of targeted therapies is now underway.

**PFS and OS by treatment.**

| Treatment | | n | 2-year PFS (95% CI) | P value | 2-year OS (95% CI) | P value |
|---|---|---|---|---|---|---|
| Initial upfront strategy | S +/- CRT or RT | 14* | 55 (26-85) | 0.01 | 55 (26-85) | 0.01 |
| | RT +/- C | 6 | 0 | | 0 | |
| | C +/- S or RT | 8 | 0 | | 14 (1-27) | |
| Extent of surgical resection | None | 13 | 0 | 0.03 | 8 (0-24) | 0.03 |
| | Debulking | 4 | 33 (0-88) | | 33 (0-88) | |
| | Gross total | 6 | 40 (0-84) | | 40 (0-84) | |
| | Complete with negative margins | 5 | 75 (32-100) | | 75 (32-100) | |

* 12/14 had S then CRT, 1/14 had S then RT.

**6058 General Poster Session (Board #93), Sat, 1:15 PM-5:00 PM**

**Neck dissection for oral mucosal melanoma: Caution of nodular lesion.** *Presenting Author: Wei Guo, Department of Oral and Maxillofacial-Head and Neck Oncology, Shanghai Ninth Peoples Hospital, Shanghai, China*

**Background:** Oral mucosal melanoma (OMM) often metastasizes to cervical nodes. A great number of studies have been conducted to evaluate the efficacy of neck dissection in the treatment of OMM, but considerable controversy remains in this field. **Methods:** The clinical features, treatments, and outcomes of 254 OMM patients were retrospectively analyzed from Jan. 1998 to Jul. 2012. Multivariate analysis was performed to identify the variables related to overall survival (OS). **Results:** Tumor size greater than 4 cm ($p$=0.01) and nodular types ($p$<0.0001) were independent prognostic factors for OS. Patients with nodular melanomas were more likely to have distant metastases than those with macular melanomas ($p$<0.0001). 164 patients (65%) had CLN metastases. The multivariate analysis revealed that prophylactic neck dissection was an independent favorable factor for OS ($p$=0.0016) in patients with cN0 nodular melanomas; whereas radical neck dissection ($p$=0.03) in patients with positive CLN. Patients undergoing functional neck dissection were more likely to have neck recurrence (p <0.001). **Conclusions:** Nodular type is a dangerous signal to OMM. It is advisable for patients with cN0 nodular melanomas to have prophylactic neck dissection, close observation is recommended for patients with cN0 macular melanomas, and patients with positive CLN should undergo radical neck resection.

**6059 General Poster Session (Board #94), Sat, 1:15 PM-5:00 PM**

**A double-blind, randomized, placebo-controlled trial of l-glutamine for the severe oral mucositis induced by chemoradiotherapy in patients with locally advanced head and neck cancer.** *Presenting Author: Takae Tsujimoto, Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Kobe Gakuin University, Kobe, Japan*

**Background:** The incidence ofseveremucositis is high among patients with head and neck cancer receiving chemoradiotherapy, resulting in significant pain and impairment of quality of life. This study aimed to investigate whether L-glutamine (glutamine) decreases the severity of oral mucositis (OM) including an area of the pharynx and larynx induced by chemoradiotherapy. **Methods:** This double-blind, randomized, placebo-controlled trial included 40 untreated patients with squamous cell carcinoma of the nasopharynx, oropharynx, hypopharynx, or larynx between May 2010 and August 2013. The inclusion criteria of this study were that patients must be more than 20 years old, suitable for chemoradiotherapy with cisplatin and docetaxel. The exclusion criteria were the presence of serious liver and/or renal dysfunction, uncontrolled diabetes mellitus, and oral and/or throat soreness before study. Patients received 66 or 70 Gy of total radiation at the rate of 2 Gy per fraction daily and 5 fractions per week. Cisplatin (20 mg/m$^2$) and docetaxel (10 mg/m$^2$) were intravenously coadministered once a week for 6 weeks. Patients were randomized to orally receive either glutamine (group G: 20 patients) or placebo (group P: 20 patients) at a dose of 10 g 3 times a day throughout the chemoradiotherapy course. OM was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. The primary end point was oral mucositis severity. NCI CTCAE grade was analyzed using the Mann–Whitney $U$ test, and Fisher's exact test. The $p$ values were 2-sided, and a value of <0.05 was considered statistically significant. **Results:** OM developed in all patients. A maximal OM grade of G4 was observed in 0% and 25% group G and group P patients, respectively, while that of G2 was observed in 10% and 0% group G and group P patients, respectively($p$ = .023).Glutamine significantly decreased the maximal OM grade (group G: 2.9 ± 0.3, group P: 3.3 ± 0.4; $p$ = .005). **Conclusions:** Glutamine significantly decreased oral mucositis severity induced by chemoradiotherapy in patients with head and neck cancer. Clinical trial information: UMIN000003991.

**6060^ General Poster Session (Board #95), Sat, 1:15 PM-5:00 PM**

**Updated overall survival analysis of patients with locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer (RAI-rDTC) treated with sorafenib on the phase 3 DECISION trial.** *Presenting Author: Marcia S. Brose, Department of Otorhinolaryngology: Head and Neck Surgery, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA*

**Background:** The phase 3 placebo-controlled DECISION trial established that sorafenib treatment significantly improves progression-free survival for patients with RAI-rDTC. Overall survival (OS) was immature at the time of primary analysis and possibly confounded by placebo crossing over to receive open-label sorafenib at progression. We report the OS results from a planned 9-month follow up as of May 31, 2013 and possible corrections for the crossover. **Methods:** Patients with locally advanced/metastatic progressive RAI-rDTC were randomized to receive sorafenib or placebo. Placebo patients were allowed to receive sorafenib open-label (OL) upon progression. OS data were analyzed using 2 correction methods for cross over: iterative parameter estimation (IPE) and rank preserving structural failure time (RPSFT). **Results:** A total of 417 patients were randomized (207 to sorafenib and 210 to placebo). Median OS had not been reached at the time of primary analysis (August 31, 2012) at which time 70% of placebo patients had started OL sorafenib and the difference across the two arms was not significant; HR: 0.80; 95% CI: 0.539, 1.194, p=0.138, one-sided. Correction for the effect of cross-over from the placebo to sorafenib treatment was performed using two methods: RPSFT (HR 0.61; 95% CI: 0.40, 0.94) and IPE (HR 0.70; 95% CI: 0.47, 1.04). As of the May 31, 2013 cutoff, 75% of placebo patients started OL sorafenib and there have been a total of 138 events (66 sorafenib and 72 placebo), with the median OS still not having been reached in the sorafenib arm and without statistically significant difference between arms; HR 0.88; 95% CI: 0.633, 1.236, p=0.2359. Correction for cross-over was performed using the RPSFT method (HR 0.69; 95% CI: 0.49, 0.99) and the IPE method (HR 0.79; 95% CI: 0.56, 1.11). **Conclusions:** The OS results from the DECISION trial are still immature 9 months following the primary analysis. OS analysis taking into account the crossover of placebo patients to the sorafenib arm are not conclusive, but nonetheless suggest that sorafenib may have an effect on OS. Long-term follow up of OS is on-going. Clinical trial information: NCT 00895674.

**6061^ General Poster Session (Board #96), Sat, 1:15 PM-5:00 PM**

**Population PK modeling and exposure-response analyses of sorafenib in patients with radioactive iodine-refractory differentiated thyroid cancer (RAI-rDTC) in the phase III DECISION trial.** *Presenting Author: Lars Bastholt, Odense University Hospital, Odense, Denmark*

**Background:** The recently reported phase III DECISION trial in patients with RAI-rDTC demonstrated a significant improvement in progression free survival (PFS) associated with sorafenib treatment. The purpose of this exploratory analysis was to evaluate sorafenib pharmacokinetics (PK) in RAI-rDTC and to examine the relationship between exposure and both PFS and adverse events (AEs). **Methods:** In DECISION, patients with locally advanced/metastatic RAI-rDTC who progressed in the prior 14 months were randomized to sorafenib 400 mg bid po or placebo. Plasma was collected on Cycle 2 Day 1 (steady state) and sorafenib concentrations measured using LC-MS/MS. Sorafenib AUC(0-12),ss were estimated using a population PK model developed from 10 sorafenib phase I-III trials, including DECISION. **Results:** Plasma samples from 156 patients randomized to sorafenib were valid for the analysis. Sorafenib mean AUC(0-12),ss (95.7 mg*h/L) was 103% higher in DTC compared to RCC and HCC, although the ranges of AUCs were overlapping. No specific mechanism for the elevated sorafenib levels has been determined. Analyses of sorafenib AUC vs. PFS were not significant, although patients with the highest exposure (Quartile 4) had a numerically longer median PFS (509 days [95%CI: 283-623 days]) than those in the low (Q1) or medium (Q2+Q3) exposure groups (median PFS 305 days [95%CI: 162-448 days] and 293 days [95%CI: 231-451 days], respectively). There was no correlation between sorafenib AUC and incidence or severity of AEs (e.g. any AE, any SAE, any drug-related AE, hypertension, diarrhea, and hand-foot skin reaction). **Conclusions:** Sorafenib exposure was higher in DTC patients compared to patients with RCC and HCC. There was no apparent correlation between sorafenib exposure and PFS or AEs in DTC patients. This analysis is limited by the small number of subjects in each exposure subgroup and the single measurement of sorafenib AUC on Cycle 2-Day1. Clinical trial information: NCT 00895674.

**6062^ General Poster Session (Board #97), Sat, 1:15 PM-5:00 PM**

**Safety and tolerability of sorafenib for treatment of locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer (RAI-rDTC): Detailed analyses from the phase III DECISION trial.** *Presenting Author: Francis P. Worden, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI*

**Background:** The phase III DECISION trial established that sorafenib treatment improved progression-free survival in RAI-rDTC patients. We report here on the incidence and prevalence of adverse events (AEs) by severity and treatment cycle and the dose modification patterns for patients treated on the DECISION trial. **Methods:** Patients with locally advanced/metastatic progressive RAI-rDTC were randomized and received sorafenib 400 mg bid po or placebo. AEs were recorded by cycle (C) and by grade (G) during the double-blind treatment period using NCI CTCAE v 3.0 or MedDRA v 15.1. **Results:** A total of 417 patients were randomized (207 to sorafenib and 210 to placebo). Hand-foot skin reaction (HFSR; 76% any grade/20% grade 3/ - grade 4), rash (50/5/0) and hypertension (41/10/0) tended to occur early in treatment (C1 and C2). G1-G3 HFSR occurred in C1, but was primarily G1 thereafter. Diarrhea (69/5/1) and fatigue (50/5/1) had a relatively constant onset across cycles and were predominantly G1. Weight loss (47/6/-) was primarily G1 and G2 with prevalence of G2 increasing with length of treatment. G1 TSH elevation (>0.5 mU/L) necessitating an increase in thyroxine replacement was observed in 33% of sorafenib patients and 13% of placebo patients. Hypocalcemia (19/6/3) was most likely to first occur in C2. Dose reductions in the sorafenib arm started early (35% of patients in C1 were on a reduced dose then ranged 50-60% thereafter). Dose interruptions were highest in C1 and C2 (37% and 26% of patients with dose interruption, respectively) and was <10% by C5. Most AEs decreased in severity or resolved following dose modification. Treatment discontinuation due to AEs occurred in 19% of sorafenib patients and were relatively evenly distributed after C1 (4% C1 and 0-2% C2-C9); 4% of patients in the placebo arm discontinued due to AEs. **Conclusions:** The incidence and prevalence patterns of AEs by severity and treatment cycle for RAI-rDTC patients treated with sorafenib demonstrated that the majority of AEs were Grade 1-2, occurred early during the treatment course, and were typically manageable over time. Clinical trial information: NCT 00895674.

**6063 General Poster Session (Board #98), Sat, 1:15 PM-5:00 PM**

**Pharmacokinetic and pharmacogenetic analysis in patients with advanced nasopharyngeal carcinoma (NPC) treated with 5-flurouracil (5-FU) and cisplatin.** *Presenting Author: Yuxiang Ma, Cancer Center, Sun Yat-sen University, Guangzhou, China*

**Background:** Many studies have demonstrated several pharmacokinetic and pharmacogenetic factors may affect the efficacy and toxicity of 5-FU. These factors include system drug exposure (area under the concentration-time curve, AUC), thymidylate synthase (TS) and dihydropyrimidine dehydrogenase (DPD). This study is to investigate correlation of these factors and efficacy and toxicity of 5-FU and Cisplatin in NPC patients. **Methods:** 122 NPC patients with measurable lesions were enrolled and received Cisplatin (80mg/m$^2$, day1) and 5-FU (4g/m$^2$, civ120h) regimen. The blood samples were collected at steady state of 5-FU infusion. AUC of 5-FU measurement was performed using an immune-based assay (MyCare). The 5-FU AUC target range was identified by Received Operating Characteristic Curve (ROC), based on 5-FU related mucositis and treatment response. Tumor tissues were also collected for evaluation the expression of TS, DPD by using immunohistochemistry (IHC). **Results:** 108 patients were analyzed (5 not assessable, 6 withdraw and 3 invalid sample). AUC of 5FU values ranged from 15 to 103mg·h/L. The optimal target range of 5-FU AUC was 31-37 mg·h/L. 20.4% of the patients were within the target range, while 39.8% was below and 39.8% was above. Within or above target range patients had better object response rate than those below target (75.4% vs 55.8%, P=0.033), within or below target range patients had lower toxicity rate (grade3/4) than those above target (6.2% vs 67.4%, P<0.001). A nomogram model based on AUC, DPD and TS expression for predicting treatment response shown that, all as independent variables, within the target AUC range, high-DPD or low-TS tumor had better response rate. **Conclusions:** The combination of pharmacokinetic and pharmacogenetic approach may be an innovative strategy for optimizing chemotherapy in patients with advanced NPC. These findings deserve confirmation in additional prospective studies.

**6064 General Poster Session (Board #99), Sat, 1:15 PM-5:00 PM**

**Association of young patient age with high-risk pathologic features and recurrence in papillary thyroid cancer.** *Presenting Author: Iris H. Wei, University of Michigan, Ann Arbor, MI*

Background: Certain histopathologic features may be risk factors for recurrent disease after resection of papillary thyroid cancer (PTC). Age is also an important prognostic factor, with higher mortality in patients over 45. Our objective was to determine whether age was associated with these pathologic features and rates of recurrence. Methods: A retrospective analysis was performed for PTC patients who underwent anatomically complete resection at the University of Michigan between 2006 – 2012. Patients with known distant metastases were excluded. Demographics, high-risk pathologic features (capsular or vascular invasion, extrathyroidal extension, lymph node metastases, extranodal extension), and disease recurrence were examined. Results: A total of 623 PTC patients were included in the analysis; 141 (23%) were men, 482 (77%) women. Median age was 49 years (range 10–87). Twenty patients had recurrent disease, and all recurred locoregionally in the central or lateral neck, with a mean time to recurrence of 1.2 years. One patient was treated with radioactive iodine, while the rest underwent reoperation. By Kaplan-Meier analysis, there was no difference in recurrence rates between patients <45 and ≥45 years ($p = 0.92$). However, additional subgroup analysis revealed that patients ≤25 had a higher rate of recurrent disease compared to those >25 years ($HR = 8.2$, $p = 0.02$). The tumors of young patients (≤25 years) were also larger ($p = 0.001$), with higher rates of extranodal extension ($p = 0.0004$), vascular invasion ($p < 0.0001$), capsular invasion ($p < 0.0001$), and lymph node metastasis ($p = 0.007$). Overall, the presence of any aggressive pathologic features was associated with an increased risk of recurrence ($HR = 18.5$, $p = 0.004$). Using a Cox proportional hazards model, the most significant risk factors were tumor size, capsular invasion, extrathyroidal extension, and lymph node metastases. **Conclusions:** PTC patients ≤25 years old have significantly higher rates of recurrence and reoperation despite being classified as AJCC Stage I. This may be in part due to larger tumor sizes and presence of aggressive histopathologic features. Patients with these factors should be monitored with close surveillance.

**6065 General Poster Session (Board #100), Sat, 1:15 PM-5:00 PM**

**Does age impact treatment of head and neck squamous cell carcinomas? A retrospective monocentric study about 107 patients age 75 and over.** *Presenting Author: Laurence Digue, Medical Oncology, CHU Bordeaux, Bordeaux, France*

**Background:** About 30% of head and neck carcinomas occur in patients over 70, and 10% in patients over 80. There is no standard of care for this population, which is under-represented in clinical trials. How are non-metastatic patients 75 and over treated in routine practice? **Methods:** Our study is a retrospective analysis based on 107 patients aged 75 and over (median 81.4 [75-94]) with non-metastatic squamous cell head and neck carcinomas treated in Bordeaux Academic Hospital between March 2007 and March 2012. We compared, for each patient, the standard treatment proposed to younger patients as described by international recommendations (NCCN, ESMO), the treatment recommended in multidisciplinary staff, and the treatment ultimately received. **Results:** Of the 107 patients, 69 (64.5%) were males and 38 (35.5%) females. 51.4% had an oral cavity cancer, 16.8% oropharyngeal, 15.9% laryngeal, 13.1% hypopharyngeal and 2.8% prevalent cervical lymph node without primary tumor. The standard treatment was proposed by multidisciplinary staff in less than 40% of patients, because of their deteriorating performance status (PS), chronological age and/or comorbidities. The treatment recommendedby multidisciplinary staff (with patients present in ¾ of the cases) was ultimately received in more than 80% of cases. In the others, the proposed treatment was not administered because of patient's deteriorating PS or their refusal. Only 15 patients had a geriatric assessment and none of them received the standard treatment. Treatment toxicities were acceptable and similar to those found in literature for younger patients. At 5 years, overall survival of our population was 14.5%, but specific survival was 74,5%. Our population passed away more from comorbidities than from their cancer after the first 2 annual follow-ups. **Conclusions:** We recommend the systematic completion, before treatment proposal, of at least one easy screening of geriatric fragilities in order not to under or over-treat these patients, and a prompt start of treatment after decision by multidisciplinary staff because of quick deterioration of PS. We also recommend that elderly patients can be included in clinical trials.

**6066 General Poster Session (Board #101), Sat, 1:15 PM-5:00 PM**

**Survival disparities and trend of head and neck cancer in the United States: A Surveillance, Epidemiology, and End Results (SEER) database study 1973-2010.** *Presenting Author: Shahzad Raza, Ellis Fischel Cancer Center, University of Missouri Health Care, Columbia, MO*

**Background:** Despite recent advances in the management of head and neck cancer (HNC), there is little evidence of improvement in 5-year overall survival (OS) over the last few decades. Ethnicity, age, and socioeconomic status have all been associated with outcomes in HNC. We examine the survival disparities and trends of HNC in major ethnicities using the largest population based database. **Methods:** Frequency, rate and survival sessions (Kaplan-Meier, age adjusted) on demographics and survival trends were performed and compared among Non-Hispanic-White (NHW), African-American (AA), Hispanics, Asians and Pacific-Islanders (A/PI) and Asian-Indian and Alaskan-Natives (AI/AN) with SEER*Stat using SEER 1973-2010 data. **Results:** A total of 247,310 HNC patients were reported from 1973-2010 in SEER database. The primary sites were lip (11%), Tongue (27%), floor of mouth (8%), gum and other parts of mouth (16%), tonsils (15%), oropharynx (4%), nasopharynx (7%), hypopharynx (9%) and others (3%). Overall, 71% patients were male. The incidence rates per 100,000 were reported highest in AA (16.4) compare to NHW (15.3), Hispanics (9.6), A/PI (9.7), and AI/AN (7.8). There were 40% stage IV cases which were equally distributed across all ethnicities. After adjusting for age, stage and year of treatment, AA has significantly ($p<0.05$) inferior 5-year OS (41.8%) compared to NHW (60.8%), Hispanics (59.3%), A/PI (62%) and AI/AN (50.2%).The OS rates in A/PI and AI/AN have improved by 17.5% and 14.6% ($p<0.05$) over last 37 years respectively. In contrast, the AA had 6.1% decreased OS ($p<0.05$) from 1973 to 2010. In subset analysis, OS for stage IV in AA is poor (21%) compare to other ethnicities ($p<0.001$). **Conclusions:** According to SEER analysis, the OS in AA has decreased significantly from 1973 to 2010 and they continue to have dismal prognosis. The underlying causes are largely unknown. However, biologic/genetic and epigenetic factors, access to health care, socioeconomic status may play a role. Prospective studies are needed to define these factors in AA and to formulate treatment strategies that would improve survival outcome in AA.

**6067 General Poster Session (Board #102), Sat, 1:15 PM-5:00 PM**

**Postsurgical erlotinib and cisplatin concurrent chemoradiotherapy (CRT) promotes favorable outcomes in high-risk locally advanced head and neck squamous-cell cancer (LAHNSCC): A GICOR Working Group trial.** *Presenting Author: Fernando Arias, Complejo Hospitalario de Navarra, Pamplona, Spain*

**Background:** The approach to LAHNSCC including surgery, radiotherapy(RT), and chemotherapy (CT) lacks of significant improvements in long-term survival. In an attempt to explore tolerance and potentially improve outcomes, the Spanish Clinical Research Group on Radiation Oncology (GICOR) designed a phase I/II study, with a dose-finding period to determine the maximum-tolerated dose (MTD) of daily erlotinib(E) administered in combination with cisplatin(C) and RT, followed by a phase II study to evaluate the therapeutic activity and safety of the selected dose combination. **Methods:** 13 patients(pts) were enrolled in phase I. The MTD was defined at C, 40 mg/m2 and E, 150 mg, based on G3 infection and mucositis in 2 out of 3 pts at dose level III. Phase II: 56 pts from 5 institutions were assigned to receive RT, 63 Gy (35 fractions over 7 weeks) combined with C, 30 mg/m2, on days 1, 7, 15, 22 and 29 of a 7-week radiation course, and E, 150 mg once daily on a continuous basis. The trial was designed to detect a 15% increase in disease free survival (45% to 60% at 2 years) with a 0.05 significance level, and a power of 0.8. **Results:** RT, C and E were completed on schedule in 87,5%, 64,3% and 80,4% of the cases, respectively. At a median follow-up (FU) of 40,6 months(mo), the 2-year DFI, locoregional DFI and OS was: 64,9%, 72,6% and 77,9%, respectively. High-risk criteria defined by involved surgical margins, extranodal extension and/or perineural infiltration were reported in 31 pts (55,4%). Treatment-related toxicity was generally mild to moderate: G-3/4 radiation skin changes included mucositis (n=33, 59%) and erithema (n=14, 25%). C-related G-3/4 toxicities were mucositis (n=15, 11%) and neutropenia (n=4, 7%). E-associated skin toxicity ≥G3 occurred in 14 (25%) pts. No toxic death occurred during the treatment. **Conclusions:** After surgery, CRT using conventional fractionated RT, with concurrent C and E promoted remarkable 2-year DFI, locoregional control rate and 2-year OS. The addition of erlotinib to cisplatin/RT is acceptably tolerated with a manageable side-effect profile. Clinical trial information: 2005-001506-29.

**6068 General Poster Session (Board #103), Sat, 1:15 PM-5:00 PM**

**Expressions of EGFR, HER2, and HER3 and their correlations with clinical characteristics in oropharyngeal squamous cell carcinoma (OPSCC).** *Presenting Author: Nabil F. Saba, Emory University, Atlanta, GA*

**Background:** Epithelial growth factor receptor (EGFR) is overexpressed in squamous cell carcinoma of the head and neck (SCCHN) and is a therapeutic target for this disease. Since other members of the HER receptor family may be valid therapeutic targets in SCCHN we examined the expressions of EGFR, HER2, and HER3 and correlated their expression with clinical patient characteristics. **Methods:** After IRB approval 96 patients with OPSCC had tissue and clinical information collected and analyzed. Tissue microarray stained by immunofluorescence (IHF) was used to evaluate HER receptor expression. High risk HPV status and p16 status were determined by HPV DNA *in situ hybridization* (ISH) and immunohistochemistry (IHC) staining, respectively. The correlation with clinical characteristics of each receptor and their effects on disease-free survival (DFS) or overall survival (OS) were assessed. **Results:** p16 status was inversely correlated with EGFR expression ($P$=0.012), whereas no significant association between p16 status and HER2 or HER3 expression was found ($P$= 0.563 and 0.635, respectively). Current smokers had the highest EGFR expression compared to never or former smokers ($P$= 0.006). Patients with T3 and T4 disease had a higher EGFR expression compared to T1 and T2 disease ($P$= 0.040). HPV negative smokers had a significantly higher HER2 ($P$ = 0.043) and HER3 expression ($P$ = 0.019) compared to non-smokers. Among patients with low EGFR expression, HPV negative patients had a higher HER3 expression compared to HPV positive patients ($P$ = 0.048). Patients with high EGFR expression were more likely to have disease progression (HR: 1.58; 95% CI: 1.13 – 2.20; $P$= 0.007) or death (HR: 1.30; 95% CI: 1.01 – 1.68; $P$=0.042). HER2 or HER3 expression were not related to DFS or OS in OPSCC. **Conclusions:** EGFR was a prognostic factor for worse DFS and OS in OPSCC. Among patients with low EGFR expression HER3 expression was higher in HPV negative patients. These findings may point to a role for combined EGFR and HER3 targeted therapy in HPV negative disease, but will need to be confirmed in other studies. (This study was supported by a grant from Merrimack Pharmaceuticals to NFS and GZC).

**6069 General Poster Session (Board #104), Sat, 1:15 PM-5:00 PM**

**Head and neck cancer (HN) characteristics and outcomes in a human immunodeficiency virus infected (HIV+) patient cohort: A 12-year experience of the Louisiana State University Health Sciences Center (LSUHSC) and Charity Hospital in New Orleans.** *Presenting Author: J. Nicholas Bodor, LSU Health Sciences Center, New Orleans, LA*

**Background:** HIV+ patients (pts) are typically excluded from enrollment on randomized clinical trials for head and neck cancer. Data regarding clinical characteristics and outcomes for HIV+ pts with HN are limited in the medical literature. Despite lack of data, pts with HN and HIV are managed at LSUHSC in a multidisciplinary fashion according to the standards of care established for HIV negative (HIV-) pts. **Methods:** 15 HIV+ pts with AJCC Stage I (33%), Stage II (0%), Stage III (20%) and Stage IV (47%) squamous cell carcinoma of the head and neck treated from 1/1999 to 6/2011 were retrospectively reviewed. Additional data collected included: tumor primary site, age at diagnosis, gender, ethnicity, time from confirmed HIV infection to HN diagnosis and characteristics of pts HIV status. End points analyzed were progression-free survival (PFS) and overall survival (OS). **Results:** Oral tongue (26%), tonsil (20%) and larynx (13%) were most common primary sites; mean age at diagnosis was 48 years (yrs) old; 86% of pts were male, 14% were female; 47% of pts were white and 53% were black. Mean time from diagnosis of HIV to HN was 69 months and mean CD4 count nadir at any point prior to HN diagnosis was 93 cells/mm^3. 60% of pts in the cohort had been diagnosed with acquired immune deficiency syndrome (AIDS) before the HN diagnosis; the diagnosis of AIDS occurred a mean of 16 months prior to HN diagnosis. PFS at 3 yrs was 80% and OS at 3 yrs was 40%; median overall survival was 2.1 yrs. **Conclusions:** A majority of HIV+ pts in this cohort had AIDS diagnosed preceding the HN diagnosis. However, outcomes of HIV+ pts diagnosed with HN treated at our institution are favorable compared to HIV- pts. Our experience would suggest that HIV+ pts be treated according to accepted standards of care with careful management by physicians with HIV expertise.

**6070 General Poster Session (Board #105), Sat, 1:15 PM-5:00 PM**

**Docetaxel (DOC) with concurrent radiation (CRT) and bevacizumab (BEV) or erlotinib (ERL) for locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN).** *Presenting Author: Panayiotis Savvides, The James Cancer Hospital and Solove Research Institute, The Ohio State University, Columbus, OH*

**Background:** Cisplatin (CIS) may not be the optimal radiosensitizer when combined with targeted agents in CRT regimens. RTOG 0234, a randomized phase II trial of postoperative radiation (RT) plus DOC or CIS plus cetuximab for high-risk LA-HNSCC showed an impressive improvement in overall survival and disease-free survival of DOC versus CIS (79% versus 69% and 66% versus 57% respectively). DOC-based CRT backbone regimens are worth further study in the organ preservation setting. To facilitate and accelerate evaluation of additional targeted agents, we summarized our experience in DOC-based chemo-RT using two consecutive phase II clinical trials with either BEV or ERL. **Methods:** 73 patients with LA-SCCHN (stage III- IVb) treated with RT (70 or 70.2-72Gy, 1.8-2Gy/day), weekly DOC (20 mg/m$^2$) and targeted therapy [BEV (5 mg/kg/qow) or ERL (150 mg/day)] were included. DOC dose was based on a phase I clinical trial of RT + DOC + ERL (Savvides P. Phase I study of ERL, DOC and RT in LA-SCCHN. AACR 2007.). **Results:** Patients with a median age 57 (range 35-75), primary site of LA-SCCHN [oropharynx (n=49), larynx (n=17), hypopharynx (n=2) and oral cavity (n=5)]. Efficacy data have been previously presented separately for the 2 trials (Savvides P. Phase II study of ERL, DOC and RT in LA-SCCHN. AHNS 2010.), (Galanopoulos N. Phase II study of BEV, DOC and RT in LA-SCCHN. ASTRO 2011.). Delivery of planned treatment was achieved in both trials; median total radiation therapy dose 70 Gy, median duration 53 days. DOC median dose intensity (MDI) 20mg/m$^2$/qw, x8 doses; BEV MDI 5mg/kg/qow, x4 doses and ERL MDI 150mg/qd.No increased SAEs, compared to historical controls. BEV/ERL related events limited to 2 G4 bleeding episodes and 1 G3 episode of thrombosis (BEV); 4 G4 skin rash episodes and 1 G5 event (death not treatment related) (ERL). **Conclusions:** Weekly DOC at 20 mg/m$^2$/wk with RT and either BEV or ERL is feasible and safe for definitive treatment of patients with LA-SCCHN and should serve as the backbone for evaluation of novel targeted agents. Supported in part by Genentech, NIH grants CA62502 and M01 RR-000080. Clinical trial identifier: NCT00049283; NCT00281840.

**6071 General Poster Session (Board #106), Sat, 1:15 PM-5:00 PM**

**Patterns of distant metastases in HPV-positive head and neck squamous cell carcinoma.** *Presenting Author: Jennie York Law, The University of Texas Southwestern Medical Center, Dallas, TX*

**Background:** Patients with HPV-positive head and neck squamous cell carcinoma (HPV+HNSCC) demonstrate favorable outcomes compared to HPV-negative SCC. Despite loco-regional control distant metastases (DM) can occur. The pattern of DM in HPV+HNSCC is not clearly defined. **Methods:** 109 patients with HPV+HNSCC underwent treatment at our institution from 2010-2012 (HPV status not identified prior to 2010). Recurrence time and metastatic sites were compared to patients with high risk HPV-negative/unknown SCC (HR HPV-/unk) and intermediate risk HPV-negative/unknown SCC (IR HPV-/unk) from 2006-2012. **Results:** Group 1: 109 patients with HPV+HNSCC (10 never achieved initial disease control). 7/109 (6.4%) developed DM. Median time to metastases was 11 months (range 7-41 months, mean 16 months). Median follow up from diagnosis was 18 months. Predominant sites of metastases were lung (6), liver (1), bone (1), and brain (1). 5/7 patients with DM (out of 65 patients with a tobacco history and 44 without) had prior or current tobacco use. Primary sites of disease were base of tongue (4/49 total base of tongue sites), tonsil (1/27), glottis (1/9), and nasal cavity (1/1). Group 2: 546 high risk HPV-/unk patients (hypopharynx/larynx/glottis). 124 never achieved initial disease control. 25/546 (4.6%) developed DM. Median time to metastases was 15 months (range 6-52 months, mean 18 months). Median follow up was 25 months. Predominant sites of metastases were lung (10), bone (3), and CNS (3). Group 3: 839 intermediate risk HPV-/unk patients (oral cavity/oropharynx/hard palate/tonsil). 246 never achieved initial disease control. 34/839 (4.1%) developed DM. Median time to metastases was 9 months (range 3-54 months, mean 14 months). Median follow up was 24 months. Predominant sites of metastases were the lung (12), bone (2), and liver (2). **Conclusions:** At median follow up of 18-25 months, there was no difference in the overall rate of DM for HPV+HNSCC compared to HR HPV-/unk (p=0.21) and IR HPV-/unk (p=0.13) but there was a significant difference in the rate of DM to the lung in the HPV+HNSCC group compared to HR HPV-/unk (p=0.012) and IR HPV-/unk (p=0.002). In our data set, HPV+HNSCC showed a higher rate of DM to the lung compared to HPV-/unk HNSCC (p=0.002).

**6072 General Poster Session (Board #107), Sat, 1:15 PM-5:00 PM**

**Detection of novel HPV mutations and chromosomal number imbalance (CNI) in laryngeal cancer using next-generation sequencing (NGS).** *Presenting Author: Howard B. Urnovitz, Chronix Biomedical, Göttingen, Germany*

**Background:** We selected HPV-associated laryngeal papillomas and squamous cell carcinomas for genomic analysis of viral induced benign and malignant neoplasms. The nearly universal presence of HPV in Recurrent Respiratory Papillomatosis (RRP) and in certain squamous cell carcinomas provides an important model for the study of biomarkers and clinical outcomes as well as the generation of robust panels of viral and genomic mutation biomarkers that can be used to follow disease progression. **Methods:** DNA was isolated from biopsies of three patients and sequenced on a NGS Illumina HiSeq platform. The sequences were compartmentalized in 250kbp bins, normalized, and compared to the mean (+/- 3SD) of Chronix controls to identify regions of chromosomal number imbalance (CNI). Sequences were also compared to databases with known viral genomes. **Results:** Sample 1: an exophytic, focally invasive, HPV positive (PCR), squamous cell carcinoma from a never-smoker. The full genome of HVP16 was detected in low amount (~ 500 sequences/10 million sequences, average coverage=42 fold). Mismatches to the closest reference HPV16 strain isolate were found in protein (number of mismatches) E7 (1), E1 (2), E2 (4), E4 (1), L2 (3) and L1 (4). Sample 2: from a RRP patient, contained the full genome of HPV6, also in low amount (~300 sequences/10 million sequences, average coverage = 24 fold). Interestingly, the HPV long control region was a variant as yet undescribed. Sample 3: from a RRP patient whose papillomas slowly and spontaneously regressed, did not contain any detectable viral DNA. Only the HPV16 squamous cell carcinoma contained CNI with gains at chromosomes 3q and 8p, and losses at chromosomes 3p, 11q, 12p, and 21q consistent with a malignant transformation. **Conclusions:** NGS reveals the identity and copy number of viral genes directly from clinical samples. This approach has revealed new HPV mutations not described by current viral analytical procedures. The detection of novel HPV mutations and CNI analysis in a single NGS run on HPV-related diseases provides important information into viral-host dynamics while generating biomarkers that can be correlated with treatment outcomes.

**6075 General Poster Session (Board #110), Sat, 1:15 PM-5:00 PM**

**Comparison of three different induction regimen in nasopharyngeal cancer: CF versus DC versus DCF.** *Presenting Author: Neyran Kertmen, Hacettepe University Cancer Institute, Department of Medical Oncology, Ankara, Turkey*

**Background:** The standard treatment of local advanced nasopharyngeal cancer is chemoradiotherapy. There is no enough data about the induction therapy. In this study we retrospectively examined patients treated with induction therapy and chemoradiotherapy. **Methods:** Locally advanced nasopharyngeal cancers patients were included into the study who were treated between 1996-2013 in our clinic. Three different induction regimen were administered to our patients in different time periods; CF, DC and DCF. The dosage of the regimens as follows: CF regimen; cisplatin 50 mg/ m2 1-2 days , fluorouracil 500 mg/ m2 1-5 days, DC; docetaxel 75 mg/ m2 1.day, cisplatin 75 mg /m2 1.day and DCF; docetaxel 75 mg/ m2 1.day, cisplatin 75 mg / m2 1.day, 5-fu 750 mg/ m2 1-5 days. **Results:** One hundred fifty-four patients were included, 76% (n= 117) of the patients was male and 24% (n= 37) of them female. Median age at diagnosis was 47 (20-73). Most of the patients were at stage III (36.4%) and stage IV (51.7%). In terms of induction therapy, cisplatin-fluorouracil (CF) was administered to 24.7% (n= 38) of patients, docetaxel-cisplatin (DC) to 35.1% (n= 54) and docetaxel-fluorouracil (DCF) to 40.3% (n= 62). Median follow-up time was 50 months (2-201 months). Response rate to induction therapy in the CF group were 5.7% (n= 2) complete response, 82.9% (n= 29) partial response.In the DC group they were 11.4% (n= 5) complete response, 59.1% (n= 26) partial response and 10.6% (n= 5) complete response, 74.5% (n= 35) partial response in the DCF group. (p=0.20). 3- Year progression-free survival (PFS) levels was 79.3% and 5-year PFS of 72.4 % in all patients. 3-year overall survival (OS) rate were 87.4% and 5-year OS rate 76% in all patients. In terms of induction therapies, 3-year OS was 96.5% in the DCF group, 86.6% in the DC group and 76.3% in the CF group (p= 0.036). There was no statistically significant PFS difference according to the chemotherapy regimens. **Conclusions:** There was no significantly difference in response rate and PFS between three regimens. OS of the DCF group was significantly higher than the others. However, this study was retrospective and limited toxicity data were available, the findings need to be interpreted with care.

**6076 General Poster Session (Board #111), Sat, 1:15 PM-5:00 PM**

**Dynamic changes in epithelial to mesenchymal composition and prognostic relevance of circulating cancer cells (CTCs) in head and neck squamous cell carcinoma (HNSCC).** *Presenting Author: Elena Mihal Vagia, Attikon Hospital, National Kapodistrian, University of Athens, Athens, Greece*

**Background:** Epithelial-mesenchymal transtition (EMT) of adherent epithelial cells to migratory mesenchymal state has been implicated in tumor metastasis in preclinical models. To investigate its role in HNSCC, we characterized EMT in circulating tumor cells (CTCs) from HNSCC patients. **Methods:** We quantified by RT-qPCR EGFR, TWIST1, stem cell marker gene transcripts in immunomagnetically positively selected CTCs from 27 locally advanced HNSCC , 8 recurrent/metastatic HNSCC, and 20 healthy individuals. Patients with locally advanced disease were treated with cisplatin chemoradiotherapy +/- TPF induction chemotherapy. To assess the univariate differences of study parameters according to the expression of *EGFR*,*TWIST1* and $CD24^{-/low}/CD44^{+}$ and/or $CD24^{-/low}/ALDH1^{high}$ stem cell markers standard statistical procedures were used, as appropriate (Chi-square test for categorical data and Fisher's Exact test for categorical data with limited number of frequencies). Subsequently, survival curves were generated by Kaplan-Meier analysis and tested for significance using the Mantel-Cox log rank test. **Results:** Thirteen of 27 (48%) primary HNSCC and six of 8 (75%) metastatic HNSCC harbored CTCs in peripheral blood**.** Mesenchymal cells were highly enriched in CTCs. Significant correlations could be found for stem cell-like CTCs and TNM stage (p=0.046,Fisher's exact test). Detection of $EGFR^{+}$ CTCs at baseline in primary HNSCC was associated with recurrence or death (p=0.041,Fisher's exact test). **Conclusions:** These data support a role for EMT in cancer progression in human HNSCC. Liquid biopsies may identify patients at high risk for relapse in need for adjuvant therapy in locally advanced disease setting.

**6077 General Poster Session (Board #112), Sat, 1:15 PM-5:00 PM**

**Toxicities of tyrosine kinase inhibitors: Occurrence of hemoptysis and tracheo-oesophageal fistula in 150 patients with advanced thyroid cancer.** *Presenting Author: Livia Lamartina, Gustave Roussy Cancer Campus Grand Paris, Villejuif, France*

**Background:** Anti-angiogenic Tyrosine Kinase Inhibitors (TKI) represent the main systemic treatment for patients with refractory advanced thyroid cancer (TC), but may induce severe adverse events. **Methods:** The objective is to determine the incidence and risk factors of hemoptysis (H) or tracheo-oesophageal fistula (TOF) in TC patients during TKI treatment. Subjects and methods: A retrospective analysis of all advanced TC patients treated with TKI between 2004 and 2013 at Gustave Roussy, was performed. 150 patients were enrolled (94 M; median age at initiation of the first TKI treatment: 60 yr), 85 (57%) with medullary TC and 65 (43%) with differentiated TC (28 papillary, 20 follicular and 17 poorly differentiated). Total thyroidectomy was performed in 133 (89%) patients, and neck and mediastinum external beam radiation therapy (ERBT) in 44 patients (median dose 60 Gy). Tracheal invasion (TI) was present at initiation of TKI treatment in 32 (21%) cases and was evidenced in 7 patients by CT scan, in 3 by fibroscopy, in 10 with both techniques, and in 12 as an intra-operative finding. No patient disclosed H before initiation of TKI treatment (H within one month is an exclusion criteria in all trials). Patients received from 1 to 4 lines of TKI treatments (median 1). Median follow-up after the initiation of the first TKI treatment was 24 months. Occurrence of mild (grade 1 or 2) or severe (grade 3 to 5) H or TOF according to CTCAE v 4 were collected. Risk factors for H/TOF were investigated. **Results:** Grade 1-2 H occurred in 10 patients (7%) all aged ≥45 yr and was associated with TI in 7 [p 0.0008], EBRT in 7 [p 0.007], and differentiated TC in 9 [p 0.002]. Grade 3-5 events occurred in 3 (2%) patients (TOF in 1 case and fatal H in 2 cases), all with known TI. One fatal H and the TOF were preceded by grade 1-2 H. No significant relationship with age, gender, EBRT, surgery, pathology or number of TKI lines was found for grade 3-5 events. The rate of grade 3-5 event was 9% in patients with TI [p 0.0008]. **Conclusions:** Grade 3-5 H/TOF occurred during TKI treatment in 9% and grade 1-2 in 22% of patientswith known TI even in the absence of H prior to TKI treatment. This should lead to a careful use of TKI in these patients.

**6078 General Poster Session (Board #113), Sat, 1:15 PM-5:00 PM**

**Expression of interleukin-1$\alpha$ (IL1-$\alpha$) and risk of distant metastases (DM) in head and neck squamous cell carcinoma (HNSCC).** *Presenting Author: Antonio Lopez-Pousa, Hospital de La Santa Creu i Sant Pau, Barcelona, Spain*

**Background:** There is a lack of biologic predictive factors in HNSCC patients. Interleukin-1$\alpha$ is a cytokine that participates in the mechanisms of carcinogenesis in patients with HNSCC, through the induction of the expression of genes involved in angiogenesis process and metastases. The aim of our study was to evaluate the relationship between the levels of expression of IL-1$\alpha$ and clinical behaviour in patients with HNSCC **Methods:** In this retrospective study, we have included 157 consecutive HNSCC patients with complete remission after multimodal treatment, with a minimum 2-years follow-up. mRNA expression of IL-1$\alpha$ and $\beta$-actin was quantified by RT-PCR in tissue samples. Relative expression was expressed as IL-1$\alpha$/$\beta$-actin ratios. Multivariate analysis and a recursive partitioning analysis were performed. **Results:** During the follow-up period 46 p (29%) had a local failure, 23 (14.6%) regional failure and 18 (11.5%) DM. Frequency of DM in patients with low levels of IL-1$\alpha$ expression ( n = 103, 65.6%) was 5.1 %, and in patients with high levels (n = 54, 34.4%) was 23.5 . %. The 5-y DM free-survival was 93% vs 68.6% (low vs high expression). These differences are maintained regardless local and regional control. The only variables significantly associated with the risk of DM in the multivariate analysis were the presence of lymph node involvement at diagnosis (HR 3.1, 95% CI : 0.9- 9.6, p= 0.050), and elevated expression of IL-1$\alpha$ (HR 6.1 , 95% CI : 2.0-18.4, p=0.001). **Conclusions:** High levels of IL-1$\alpha$ expression is an independent factor associated with the risk of DM and survival. Although it should be validated prospectively, is a factor to be considered both clinically and in clinical trials.

**6079 General Poster Session (Board #114), Sat, 1:15 PM-5:00 PM**

**The effect of proteolytic enzyme-containing gargling agents on severe stomatitis caused by therapy for head and neck cancer.** *Presenting Author: Masatoshi Ohmae, Rinku General Medical Center, Izumisano, Osaka, Japan*

**Background:** Severe stomatitis is one of the most frequent and undesirable side effects of chemotherapy (CT) and chemoradiation therapy (CRT) for the treatment of head and neck cancer. It remarkably limits patients' quality of life, and in some cases, it becomes a dose-limiting factor. Such stomatitis is usually treated with oral care, anti-inflammatory agents, and analgesics. As for gargling agents, sodium gualenate hydrate, aspirin, and glycerin are widely used for oral care; however, they typically offer insufficient pain relief. Objective: To devise gargling agents to relieve pain and other related symptoms induced by CT or CRT for head and neck cancer. **Methods:** We focused on the necrotic tissue covering the inflammatory mucosa as an exacerbating factor for stomatitis, and we empirically applied a proteolytic enzyme to remove the necrotic coating and relieve the pain. We used 2 proteolytic enzymes, bromelain and pronase, as topical oral antiphlogistics, which are easily available as oral medicines, and established 3 gargling agent treatment groups: G, gualenate hydrate + glycerin; GB, G + bromelain; and GBP, GB + pronase. Bromelain is a general name for a family of sulfhydryl proteolytic enzymes. Thirty patients were included in this study and received CT or CRT. When they developed stomatitis during the course of CT or CRT, they were randomly assigned into 1 of the 3 above groups. Pain intensity was measured with a 100-mm visual analog scale (VAS) and degree of discomfort was estimated using the face scale (FS) at day 0 (just prior to treatment initiation) and at day 7. The effects of the gargling agents were evaluated by changes in the VAS and FS scores **Results:** The changes in the VAS score for groups G, GB, and GBP were −18, −20, and −42, respectively. The FS score for each group decreased by 1.5, 1.2, and 2.7 points, respectively. **Conclusions:** Proteolytic enzyme-containing gargling agents are beneficial for the treatment of severe stomatitis related to cancer therapy for the head and neck region.

**6080 General Poster Session (Board #115), Sat, 1:15 PM-5:00 PM**

**Molecular profiling of HPV-positive and -negative HNSCC.** *Presenting Author: Rebecca Anne Feldman-Moreno, Caris Life Sciences, Phoenix, AZ*

**Background:** Head and neck squamous cell carcinoma (HNSCC) is comprised of two subtypes: human papilloma virus (HPV)- and carcinogenic-associated (HPV-negative), both linked to inactivation of the TP53 pathway. We examined alterations in HPV positive (pos) and negative (neg) HNSCC to identify treatment options and elucidate differences in pathogenesis. **Methods:** Eighty HNSCC cases (24 HPV-pos and 33 HPV-neg) were profiled using a multiplatform (IHC, NGS, ISH) approach (Caris Life Sciences, Phoenix, AZ) aimed at identification of biomarkers of therapeutic drug responses. **Results:** HNSCC arising in the following anatomic sites were assessed: larynx, nasopharynx, oropharynx, oral cavity, tongue, and head and neck, NOS. HPV positivity was detected in: nasopharynx, oropharynx, tongue, and head and neck, NOS. Statistically significant differences between HPV-pos and HPV-neg HNSCC were observed for ER(20% (4/20) vs. 0% (0/31); p=0.02) and MGMT(75% (18/24) vs. 40% (13/32); p=0.02) expression (IHC). NGS detected variants in 69% (20/29) of HPV-neg, of which 90% (18/20) had TP53 mutations. 39% (7/18) had 2$^{nd}$ and 3$^{rd}$ hits in the following genes: APC, PTEN, PDGFRA, GNAQ, CDH1 and IDH1. Rare TP53 WT/HPV-neg (10% or 2/20) patients exhibited mutations in APC and PIK3CA. In HPV-pos cases NGS detected variants in 39% (9/23) including: APC, HNF1A , FBXW7, NRAS, PDGFRA, PIK3CA and PTEN. Co-occurrence of mutations included: PDGFRA, NRAS and FBXW7, and PIK3CA and PTEN. In patients with PTEN/PIK3CA mutations (both subgroups), 83%( 5/6) exhibit loss of PTEN expression indicating benefit of mTOR inhibitors. Novel therapies based on NGS data include Wnt pathway inhibitors, multi-kinase inhibitors (imatinib), MEK inhibitors and alkylating agents based on mutations in APC, PDGFRA, GNAQ/NRAS and IDH1, respectively. **Conclusions:** Common and HPV-specific biomarkers characterize HNSCC. ER over-expression indicates anti-hormonal therapies as a potential novel therapy option in HPV-pos, whereas alkylating agents may be of benefit in HPV-neg HNSCC. Novel therapies also include mTOR inhibitors based on alterations in PTEN/PIK3CA. Lower incidence of mutations in HPV-pos HNSCC indicates a need for a multi-platform approach in identifying theranostic biomarkers.

**6081 General Poster Session (Board #116), Sat, 1:15 PM-5:00 PM**

**Prediction of HNSCC recurrence by using kinetic and volumetric FDG-PET parameters.** *Presenting Author: Ronan Abgral, Nuclear Medicine department, University Hospital of Brest, Brest, France*

**Background:** Head and neck squamous cell carcinoma (HNSCC) are tumors with a high recurrence rate and a poor prognosis. Find pre-treatment indicators for predicting survival of patients is therefore a real challenge. Fluorodesoxyglucose positron emission tomography (FDG-PET) is a functional imaging technique used for initial staging of HNSCC. Its prognostic value has already been demonstrated using SUVmax but no threshold has been established to predict recurrence (4-10 within studies). New quantitative indexes such as volumetric (MTV=metabolic tumoral volume) or kinetic (RI=retention index) parameters have been recently suggested as prognostic factors of HNSCC. The aim of this study was to compare the prognostic interest of these parameters to predict HNSCC recurrence. **Methods:** Patients referred to our department to perform FDG-PET for HNSCC staging were included. Tumoral RI corresponding to the percentage variation of SUVmax was calculated by using a dual time point method. Tumoral MTV corresponding to the 3D contour around voxels that are equal or greater to 40% of SUVmax was measured by using a semi-automated workflow. ROC analysis was performed to determine best SUVmax, RI and MTV thresholds to predict recurrence. Univariate analysis was performed to test prognostic significance of these parameters. Kaplan–Meier method was used to estimate recurrence free survival (RFS) probabilities. Multivariate analysis using Cox proportional hazard model was performed. **Results:** Seventy (61M/9F) consecutive patients (62 ± 9yo) were included. ROC analysis revealed SUVmax=7.3 (AUC=0.67), RI=19.5% (AUC=0.76), and MTV=6,7ml (AUC=0.73) as best thresholds to predict recurrence. In univariate, besides age and T stage, SUVmax (p=0.001), RI (p<0.0001) and MTV (p<0.0001) were significantly correlated with RFS. In multivariate, RI (p=0.005) and MTV (p=0.022) persisted as independent predictive parameters of recurrence but not SUVmax (p=0.703). There was no significant correlation between RI and MTV value using a Pearson test (p=0.718). **Conclusions:** Kinetic and volumetric FDG-PET parameters are independent prognostic factors likely to provide complementary information for predicting recurrence in patients with HNSCC.

**6082 General Poster Session (Board #117), Sat, 1:15 PM-5:00 PM**

**Phase I trial of intratumoral therapy using HF10, an oncolytic HSV-1, demonstrates safety in HSV+/HSV- patients with refractory and superficial cancers.** *Presenting Author: Robert L. Ferris, University of Pittsburgh Cancer Institute, Pittsburgh, PA*

**Background:** HF10 is an oncolytic herpes simplex virus 1 (HSV-1) which can replicate in and destroy cancer cells by direct oncolysis and enhanced anti-tumor immunity. This Phase I dose escalation trial is investigating intratumoral HF10 injections in patients with refractory and superficial cancers. Objectives are to evaluate the safety, tolerability, recommended HF10 dose; viral replication in blood, urine, saliva and tumor biopsies; overall and local (injected lesion) antitumor activity; anti-HSV antibodies; and anti-tumor T cell reactivity, serum cytokines, and proteomics. **Methods:** InStage 1,1 intratumoral injection of HF10 was administered to a single lesion; in Stage 2, up to 4 injections (≥ 2 weeks apart) are administered per patient. Stage 1 patients were HSV-1 seropositive; Stage 2 patients are HSV-1 seropositive or seronegative. Adverse events (AEs) are evaluated according to NCI CTCAE v3.0. **Results:** As of 12/10/2013, 26 patients were enrolled and 24 were treated. Stages 1 and 2 have been completed; an expansion cohort (with patients receiving 4 HF10 injections at 1 x $10^7$ $TCID_{50}$/dose) is ongoing. Total accrual will be 28 patients. 18 patients reported AEs and 6 had HF10-related AE, including: chills (2 patients), and injection site discolorations, edema, and pain, malaise, pruritus, and hypotension (1 patient each). Clearance of HF10 from blood, saliva and urine was rapid. Despite rapid viral clearance, one patient formed ulcers at both the injected and the non-injected lesions after single injection. Importantly, the ulceration occurred only in tumor cells without affecting normal tissue. The observed AEs and viral clearance in HSV-1 seropositive and seronegative patients did not differ. **Conclusions:** Multiple intratumoral injections of HF10 are safe and well-tolerated in HSV+ and HSV- patients with refractory/superficial cancers. Related AEs include flu-like symptoms and injection site reactions that are also reported for other oncolytic viruses. Despite rapid clearance from blood, urine, and saliva, HF10 has the potential to provide continued viral antitumor activity, suggesting that HF10 could be a promising new oncolytic virus treatment. Clinical trial information: NCT01017185.

**6083 General Poster Session (Board #118), Sat, 1:15 PM-5:00 PM**

**Oropharyngeal cancer (OPC) and racial outcome disparities in squamous cell carcinoma of the head and neck (HNSCC): Ten-year experience at the University of Maryland Greenebaum Cancer Center (UMGCC).** *Presenting Author: Dan Paul Zandberg, University of Maryland Greenebaum Cancer Center, Baltimore, MD*

**Background:** Racial outcome disparities have been observed in head and neck cancer with diminished survival for black patients compared to whites. The etiology of this disparity appears to be multifactorial in origin. **Methods:** We retrospectively analyzed 1318 patients with primary HNSCC treated at the UMGCC from 2000 to 2010. **Results:** 65.9% of patients were white, 30.7% were black and 3.3% were other races. Black patients were far less likely to present with oral cavity cancer (15.6% of cases) and far more likely to present with laryngeal or hypopharyngeal cancers (47.9% and 65.6% of cases respectively). Whites were more likely to have early stage (I and II) disease, especially in the oral cavity. In the full cohort, overall survival (OS) for blacks was significantly worse than for whites (median 2.5 years vs. 4.8 years, $p<0.0001$). Multivariable Cox regression analysis showed black patients had significantly worse OS accounting for age, gender, stage, primary site, and tobacco and alcohol consumption. Black patients had worse OS in both oral cavity (medians 5.7 vs. 3.2 years, $p<0.0001$) and oropharynx (OPC) (medians 4.9 vs. 2.1 years $p<0.0001$). However, multivariable analysis showed that race was only significantly associated with survival in OPC. The difference in survival in oral cavity cancers resulted from the larger proportion of white patients with Stage I or II disease. White patients with oral cavity and OPC were more likely to have surgery as primary treatment than blacks reflecting the higher prevalence of early stage disease. There was no difference in OS between races in laryngeal or hypopharyngeal cancer with the majority of these patients presenting with locally advanced disease. **Conclusions:** We observed striking differences in site of disease, stage at presentation and survival comparing black and white patients. Survival disparity overall is driven by a large difference in OPC patients. This is consistent with previous reports of differences in the incidence of HPV in the two ethnic groups, but likely reflects other factors as well.

**6084 General Poster Session (Board #119), Sat, 1:15 PM-5:00 PM**

**Inferior local control for T2bN0 glottic carcinoma with impaired mobility treated with radiation alone: A need for more chemotherapy?** *Presenting Author: Priyanka Bhateja, Cleveland Clinic Foundation, Cleveland, OH*

**Background:** Radiation therapy monotherapy (RT) is standard for patients (pts) with T2N0 squamous cell cancer (SCC) of the glottis. The presence of impaired vocal cord mobility (T2b) is known to portend higher failure rates compared to cancers with supra/sub-glottic extension without impaired cord mobility (T2a). This study sought to compare the local control (LC) rates for these pts and also compare them to LC rates in pts with T2b-3N0-2 glottic cancer treated with concurrent chemoradiotherapy (CRT). **Methods:** In this IRB approved retrospective review, we identified pts with histologically confirmed T2-3N0-2 invasive SCC of the glottis, treated with definitive RT or CRT from 1986 to 2013 at our institution. RT (mean dose 70Gy) was delivered using conventional opposed lateral fields; elective nodal irradiation was used for the majority of pts. Chemotherapy consisted of a 96 hour infusion of cisplatin and 5-fluorouracil on weeks 1 and 5, or single agent cisplatin q3wks. LC, overall survival (OS) and disease free survival (DFS) rates were calculated by the Kaplan-Meier method and compared between the groups using the Log-Rank test. **Results:** Among the 84 pts identified, RT alone was administered to 27 pts with T2aN0 and 31 pts with T2bN0. CRT was delivered to 26 pts with T2b-3N0-2. With a median follow-up of 34 months, we observed a 3-year LC rate in the T2bN0 pts treated with RT alone of 72.5%, compared to 95% in the T2aN0 pts treated with RT ($p=0.01$) and 91% in the T2b-3N0-2 pts treated with CRT ($p=0.08$). There was no difference in OS and DFS rates between the 3 groups. There were 13 local failures, 10 of whom were successfully surgically salvaged. On univariate analysis, lower performance status ($p=0.04$) and T2b disease treated with RT alone ($p=0.02$) were the only factors that were significantly associated with inferior LC. Patient age, tumor bulk, anterior commissure involvement, nodal stage and the type of chemotherapy were not associated with LC. The rates of acute and late toxicities were higher in the CRT group. **Conclusions:** Pts with T2bN0 glottic cancer have a relatively high rate of local failure with RT alone. CRT should be considered to maximize the likelihood of treatment success.

**6085 General Poster Session (Board #120), Sat, 1:15 PM-5:00 PM**

**Racial disparities in the incidence and survival trends in women with squamous cell carcinoma of the oral tongue based on the Surveillance, Epidemiology, and End Results (SEER) analysis.** *Presenting Author: Lindsay Joseph, Rollins School of Public Health, Emory University, Atlanta, GA*

**Background:** The incidence of oral tongue cancer (OTC) in the United States is increasing in women. To better understand this phenomenon, we examined thetime trends and racial disparities in incidence and survival in this population. **Methods:** We identified 6,199 women diagnosed with OTC that were reported to the Surveillance, Epidemiology and End Results (SEER) Program from 1973 to 2010. Cases were categorized by age, race, and year of diagnosis. The incidence and survival rates were compared across metropolitan, urban and rural residential settings and several other demographic categories by calculating rate ratios (RRs) with the corresponding 95% confidence intervals (CIs). We examined temporal variations in incidence of OTC across racial groups using joinpoint analyses to evaluate changes since 1973. **Results:** Cases were predominantly white (85.5%), and 60-64 years of age. OTC incidence in white females demonstrated a statistically significant increase with 0.53 annual percentage change (APC) between 1973 and 2010. For African American (AA) females, on the other hand, the incidence has decreased by -2.79 APC since 1973. Overall incidence was higher among white women (1.30 cases per 100,000/year) compared to AA women (0.67 cases per 100,000/year). Comparisons across residential settings produced similar results wherein incidence rates among women living in metropolitan areas were significantly lower for AA females compared to white females (RR=0.51; 95% CI: 0.43-0.60). The 1-, 5- and 10-year relative survival estimates (RS: defined as observed survival among cancer patients divided by the expected survival in the general population) for all women with OTC were 85%, 63% and 53%, respectively. When stratified on race, the corresponding 1-, 5- and 10-year race specific RS estimates were 86%, 63% and 54% for white women, and 76%, 46% and 33% for AA women. **Conclusions:** The racial disparity in survival of women with oral tongue cancer is pronounced. Identifying the demographic characteristics of white women with OTC may lead to a better understanding of the causes behind the increased incidence in this group.

**6086 General Poster Session (Board #121), Sat, 1:15 PM-5:00 PM**

**Expression of tumor biomarkers in HIV-infected patients with head and neck cancer.** *Presenting Author: Hongzheng Zhang, Department of Hematology & Medical Oncology, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA*

**Background:** Human immunodeficiency virus (HIV)-infected individuals are at increased risk for head and neck cancer (HNC). Poor survival is associated with low CD4 counts, larynx/hypopharynx site and current tobacco use. The expression of tumor biomarkers and their correlation with risk factors has not been studied in HIV+HNC. We compared a panel of tumor oncogenic (NFkB, pAKTS473, pSTAT3tyr705 and Bcl2) and inflammatory (TGF$\beta$, IL-6 and VEGF) biomarkers in tumors from patients with HIV+ vs HIV-HNC. **Methods:** 56 HIV+HNC cases were identified at 5 US tertiary care referral centers between 1991-2011. Expression of tumor biomarkers was detected on tissue microarray by immunohistochemistry using formalin-fixed paraffin-embedded surgical specimens from primary tumors matched with anatomical site in HIV-patients with HNC (N=44/group), and scored by a pathologist. Clinical information was captured in the HIV+HNC cohort only (N=29 for biomarker analysis). **Results:** In the HIV+HNC group: median age 49 (range 28-70), median CD4 counts 298 cells/$\mu$L (range 5-1038), 78% patients were current alcohol consumers, 79% current smokers, 61% receiving highly active antiretroviral therapy at time of cancer diagnosis. Median follow up was 517 days. Tumors from the HIV- cohort tended to express greater NFkB than those from HIV+ cohort ($p=0.062$). In the HIV+HNC cohort, VEGF expression was associated with advanced tumor stage ($p<0.05$) while pSTAT3 expression was associated with early stage ($p<0.05$). Regardless of HIV status, NFkB expression was positively correlated with pAKT ($r=0.753$, $p<0.001$), both were expressed at greater levels in the oral cavity than other sites ($p<0.001$ and $p=0.003$, respectively), and both lower in current alcohol drinkers ($p<0.001$) and current smokers ($p<0.05$) than in former and/or never drinkers/smokers. Multivariate analysis indicated that high pSTAT3 ($p<0.05$) and VEGF ($p=0.061$) were associated with improved overall survival and African American race ($p<0.05$) with poor prognosis. **Conclusions:** This is the first exploratory study linking tumor biomarkers with risk factors in HIV+HNC. Tumor biomarkers are differentially expressed by HIV status, alcohol and tobacco use, and are associated with overall survival.

**6087 General Poster Session (Board #122), Sat, 1:15 PM-5:00 PM**

**Nasopharyngeal carcinoma patients with new primaries.** *Presenting Author: Musa Altun, Istanbul University Oncology Institute, Istanbul, Turkey*

**Background:** Due to improvements in treatment, the importance of new primaries in nasopharyngeal carcinoma (NPC) patients is increasing. The aim of this study is to evaluate new primaries in NPC. **Methods:** NPC patients treated between 1980 and 2008 are divided according to age at diagnosis; pediatric (≤17), and adult (> 17). In each group, new primaries (NP) are classified depending on the organ, latent period, histopathology and location (in or out of the radiation field). **Results:** 97 pediatric, 709 adult were treated between 1980 and 2008. Male: female ratio of the whole group and the patients with NP are 2:1 and 3:1, respectively. Median follow-up time was 7 years. 7 (7%) pediatric, 44 (6%) adult patients had NP. All NP were confirmed histopathologically. 6 of the 7 NP detected in pediatric patients were in-field and 4 of them were sarcomas. In the adult group, 37 metachron, 3 synchronic, 5 previous tumors were observed. 35% of metachron primaries were in the irradiated area. Larynx and lung cancers were the commonest NP in the in-field and outfield primaries. Median latent period of metachron tumors was 125 months (range 11-462) (Table). 46% of NP were located in HNC region. The incidence of radiation induced sarcoma (RIS) was significantly higher in pediatrics compared with adults (4,12% vs.0,14%, p<0,005). **Conclusions:** The significantly increased incidence of RIS in pediatric NPC patients is striking. Viral or field-cancerization relationship in NP seems not as obvious as in other HNC. Physicians should be aware of NP during follow-up for early diagnosis in this group of patients.

**The characteristics of the new primaries.**

| | | Out-field | | | In-field | | | |
|---|---|---|---|---|---|---|---|---|
| **Age** | **Timing** | **Organ** | | **Time interval (month)** | **Organ** | | **Time interval** | **Total** |
| ≤17 | **Previously to NPC** | Prostate | 1 | 30 | Larynx | 1 | 310 | 5 |
| | | Stomach | 1 | 78 | Tonsilla | 1 | 690 | |
| | | | | | HL | 1 | 209 | |
| | **Synchronic** | Lung | 1 | 0 | Larynx | 2 | 0 | 3 |
| | **Metachron** | Lung | 10 | 11,17,23,28,36,40,70,71,224 | Larynx | 5 | 11,14,88,141,162 | 36 |
| | | Breast | 3 | 23,26,56,145 | Tonsilla | 2 | 63,72 | |
| | | Colon | 2 | 13 | Oropharynx | 1 | 108 | |
| | | Stomach | 2 | 56 | Palate | 1 | 152 | |
| | | Prostate | 1 | 244 | Esophagus | 1 | 169 | |
| | | Pancreas | 1 | 41 | Parotid | 1 | 163 | |
| | | Kidney | 1 | 171 | Sarcoma | 1 | 42 | |
| | | Bladder | 1 | 22 | | | | |
| | | NHL | 1 | 42 | | | | |
| | | Tymoma | 1 | 46 | | | | |
| | | ALL | 1 | 95 | | | | |
| | | **Total** | 27 | | | 17 | | 44 |
| >17 | **Metachron** | Bladder RMS | 1 | 61 | Sarcoma | 4 | 45,462,182,213 | 7 |
| | | | | | Tongue | 1 | 240 | |
| | | | | | **HL** | 1 | 68 | |
| | | **Total** | 1 | | | 6 | | |
| | | **Total** | 28 | | | 23 | | 51 |

**6088 General Poster Session (Board #123), Sat, 1:15 PM-5:00 PM**

**Molecular predictors of response to sorafenib in patients with radioactive iodine-resistant advanced thyroid cancer.** *Presenting Author: Mark Yarchoan, Department of Internal Medicine, University of Pennsylvania, Philadelphia, PA*

**Background:** Sorafenib has demonstrated significant antitumor activity in patients with advanced iodine-refractory thyroid carcinoma. In order to identify molecular predictors of response to sorafenib, we studied tumor molecular markers and clinical responses obtained from a subset of patients entered in a phase 2 study of sorafenib in advanced thyroid cancer. **Methods:** Paraffin embedded tissues sections of the most recent tumor sample from patients were immunostained (IHC) with DAB-labeled antibodies to pERK, pAKT and pS6. Protein expression was quantified using a multispectral imaging system which allows for automated tumor segmentation, and cellular and subcellular stain localization and quantitation. Using this system, the optical density of the DAB for each immunostain on a cell by cell basis is achieved along with subcellular location. Protein expression levels were correlated with objective tumor response and progression free survival for all patients. BRAFV600E genetic mutation analysis was performed on all samples. **Results:** IHC was performed for 40 patients, of whom 17 (42.5%) achieved a partial response (PR), 21 (52.5%) achieved stable disease (SD), and 2 (5%) had disease progression as a best response. There was an inverse association between nuclear pAKT expression level and achieving a partial response to sorafenib (p=0.003). Only 2/10 patients in the highest quartile of pAKT expression achieved a partial response, as compared to 7/10 patients in the lowest quartile of pAKT expression. However, nuclear pAKT expression was not predictive of time to progression. Furthermore, there was no correlation of pERK or pS6 nuclear expression and response to sorafenib. In tumor endothelial cells, expression of pERK, pAKT and pS6 was not predictive of response to sorafenib. There was no correlation between BRAFV600E mutation status and response to sorafenib across the entire cohort or within the subset of patients with papillary thyroid cancer (n=22). **Conclusions:** These results suggest that lower nuclear pAKT expression may be a positive predictive biomarker for response to sorafenib in advanced thyroid cancer, and merits further evaluation in additional clinical trials. Clinical trial information: NCT00654238.

**6089 General Poster Session (Board #124), Sat, 1:15 PM-5:00 PM**

**Effect of the addition of temsirolimus to cetuximab in cetuximab-resistant head and neck cancers: Results of the randomized PII MAESTRO study.** *Presenting Author: Apoorva Chawla, The University of Chicago Medicine and Biological Sciences, Chicago, IL*

**Background:** Patients with cetuximab resistant HNC have a median PFS of only 1.8 months (deSouza 2012). Preclinical/computational modelling suggests synergy between mTOR and EGFR, and potential to overcome resistance and aberrations in the PI3K-MTOR pathway occur in ≥30% of HNC. A previous trial of erlotinib+everolimus was terminated early due to toxicity (Bauman 2013). **Methods:** Eligibility was PS≤1, metastatic HNC with documented progression on cetuximab. Pts were randomized to temsirolimus (T) 25 mg +/-cetuximab (C) 400/250 mg/m$^2$ weekly. Primary endpoint was PFS with a target of 80 pts to detect a 2 months increase. 2$^{nd}$ endpoints were RR, OS, toxicity. **Results:** 80 pts (40 TC, 40 T) started treatment via the Univ. of Chicago, and Mayo Phase II CTEP networks. Median age was 63 yrs; 69M, 11F. Median PFS was 89 days (TC) vs 93.5 days (T), NS. Median overall survival was 205/181 days, NS. Treatment was tolerable with fatigue, skin and hematologic toxicities being common. Hyperglycemia was seen in 17/80 patients (11 TC, 6 T). Grade 3-4 toxicities included metabolic abnormalities (17/40 TC, 10/40 T), hematologic toxicity (7/40 TC, 13/40 T), infection (4/40 TC, 3/40 T), and pulmonary toxicity (2/40 TC, 2/40 T). 5 responses (1 CR, 4 PR) were observed in the TC arm (RR 12.5%) (TC) vs 1 PR (2.5%) on T arm (one-sided $P$=0.1). Of note, all TC responders had disease control from prior C treatment (response/prolonged SD) with subsequent acquired resistance. In responders the mean interval between C failure and start of trial treatment was 3.4 months (1.1 – 6.5). In TC responders, median duration of response was 7.2 months (5.1 – 15.3). Interestingly, TC responses were maintained for up to 15 months exceeding prior benefit from C in several pts. TC responders had a median PFS of 231 days. The sole T alone response was short (89 days). **Conclusions:** T+C is safe and tolerable. The addition of T to C appears to overcome acquired C resistance in 12.5% of pts despite an overall negative trial. Responses are durable and clinically meaningful in this otherwise poor prognosis population. Single agent T is ineffective. Prior benefit from cetuximab is a candidate predictive biomarker for benefit from TC. Clinical trial information: NCI 8692.

**6090 General Poster Session (Board #125), Sat, 1:15 PM-5:00 PM**

**Phase II trial of radiotherapy (RT) with concurrent cisplatin (C) plus panitumumab (pmAb) for patients (pts) with high-risk, resected head and neck cancer (HNC).** *Presenting Author: Robert L. Ferris, Department of Otolaryngology, University of Pittsburgh School of Medicine, Pittsburgh, PA*

**Background:** Treatment intensification for human papillomavirus (HPV)-negative HNC is an active area of investigation. Targeting the epidermal growth-factor receptor pathway using the monoclonal antibody pmAb with C chemoradiation was investigated in high-risk resected, primarily HPV-HNC patients. **Methods:** Eligible were pts with ECOG performance status 0-1 with pathologic stage III or IVA squamous cell carcinoma of the oral cavity, larynx, or hypopharynx, without gross residual tumor and with high-risk factors (margins <1mm, extracapsular spread (ECS), perineural/angiolymphatic invasion, or 2 or more positive lymph nodes). Postoperative treatment started within 7 weeks of surgery, consisting of standard RT (60-66 Gy, once daily fractions in 6-7 weeks) concurrent with weekly pmAb 2.5 mg/kg IV and weekly C 30 mg/m$^2$IV. Carboplatin (AUC 1.5 weekly) substitution was allowed for certain C-associated toxicities. The primary endpoint was progression-free survival (PFS). **Results:** Of 46 pts accrued, 2 did not receive pmAb, leaving 44 for analysis. Median age was 58 (range 23-81); 16% were female. Primary sites included: oral cavity (73%), larynx (20%), hypopharynx (5%), oropharynx (2%); 86% were stage IVA. Indications for adjuvant therapy included ECS (n=23), perineural invasion (n=22), and/or positive margins (n=3). The median follow-up for 32 pts without recurrence was 27 months (range 3-67). The 2-year PFS was 73% (95% CI, 61-88%) and the 2-year overall survival (OS) was 76% (95 % CI, 64-91%). 12 pts developed recurrence; 8 of them died. An additional 5 pts died from other causes. Grade 3/4 toxicities included mucositis (41%), hyponatremia (25%), leukopenia (25%), dysphagia (18%), neutropenia (21%), nausea/vomiting (14%), anorexia (11%), rash (9%), and neutropenic fever (9%). Prophylactic gastrostomy tubes were placed in 43% of patients; 18% required tube placement during or after therapy. **Conclusions:** Preliminary analysis of adjuvant treatment intensification by adding pmAb to C chemoradiation suggests promising clinical outcome for high-risk, predominantly HPV- HNC pts. Clinical trial information: NCT00798655.

**6091 General Poster Session (Board #126), Sat, 1:15 PM-5:00 PM**

**Effect of FGFR1 on epithelial-mesenchymal transition and EGFR resistance in HNC: A systems biology approach.** *Presenting Author: Damian Rieke, The University of Chicago, Chicago, IL*

**Background:** Fibroblast Growth Factor Receptor 1 (FGFR1) plays an important role in cancer and is an emerging treatment target for squamous lung cancer and other tumor types. We determined the functional implicatiosn of FGFR1 signaling using a systems biology approach. **Methods:** 120 HNSCC tumor samples from patients treated at Univ. of Chicago were analyzed. We determined copy number alterations (Nanostring, +qPCR validation), gene expression (Agilent) as well as mutations (IIlumina)and employed in-silico modeling/published gene expression signatures (GSEA) to investigate receptor kinases as well as mechanisms correlated with FGFR1 signaling. HNC TCGA data was used for validation. Secondly we performed in-vitro validation in a panel of 12 HNSCC cell lines. Viability testing was performed with PD173074, ponatinib, gefitinib, as well as combinations of these drugs. Immunoblotting was performed for MAPK and AKT pathways, Vimentin and E-Cadherin total protein. **Results:** FGFR1 copy number gain occurred in 3% or our cohort and 8% of TCGA samples and was most prominent in laryngeal tumors. Interestingly high FGFR1 expression were identified in 20% of HNSCC and highly correlated with Epithelial-to-Mesenchymal Transition (EMT) ($p<0.001$). Several additional receptor Tyrosine Kinases (RTKs) strongly correlated with EMT including PDGFRA, PDGFRB, AXL, and ACVRL1 (TGF-beta pathway). By contrast EGFR and MET expression strongly correlated with an epithelial phenotype. We identified 6 mesenchymal-like and 6 non-mesenchymal-like cell lines out of a panel of 40 cell lines. Mesenchymal cell lines were resistant to Epidermal Growth Factor Receptor-inhibition with gefitinib, but combined FGFR and EGFR inhibition showed strong synergy in these resistant cell lines. Ponatinib showed the highest level of activity, due to evidence of co-inhibition of other EMT associated kinases. **Conclusions:** FGFR1 drives the EMT phenotype in HNC, and is a valid treatment target that may help overcome EGFR resistance when used in combination.

**6092 General Poster Session (Board #127), Sat, 1:15 PM-5:00 PM**

**Impact of lymph node ratio on survival in advanced head and neck cancer: National Cancer Data Base (NCDB).** *Presenting Author: Sukamal Saha, McLaren Regional Medical Center, Michigan State University, Flint, MI*

**Background:** Lymph node ratio (LNR), the no. of positive nodes divided by no. of nodes extracted, has prognostic importance in colon and breast cancer. We aim to evaluate the role of LNR in the treatment of head and neck cancer (HNC), as its prognostic value is unknown. **Methods:** Pts from NCDB with advanced HNC (1998-2010), including laryngeal (LC) and non laryngeal cancer (NLC), were analyzed. Pts underwent surgery of the primary site with neck dissection. Only pts with complete data of age, sex, grade, TNM staging, and LNR were included. Using the median LNR of 0.1, pts were divided into two groups: GpA (LNR $<0.1$) or GpB (LNR $>0.1$). 5yr overall survival (5yr OS) was compared using K-Meier. Multivariate analysis was performed using Cox-proportional model. An adjusted hazard ratio (aHR) was calculated for pts in both groups. **Results:** Of 81, 672 pts included, a majority were Stage III (16,562) or Stage IV (44,831) with 47,510 pts having nodal metastasis. Of these, 24,206 (51%) were in GpA and 23,304 (49%) in GpB. There were 4,564 LC pts in GpA and 4,059 in GpB. The median no. of +'ve LN were 2 and 4 while the median no. of LN extracted were 40 and 21, respectively. 5yr OS for GpA and GpB was 50% vs. 33% for Stage III and 40% vs. 24% for Stage IV. There were 19.462 NLC pts in GpA and 19,245 in GpB. The median no. of +'ve LN were 1 and 3 while the median no. of LN extracted were 36 and 17, respectively. 5yr OS for GpA and GpB was 60% vs. 57% for Stage III and 53% vs. 39% for Stage IV. The aHR of pts with LNR $>0.1$ compared to LNR $<0.1$ was 1.4 (95% CI 1.36-1.43), after adjusting for other prognostic covariates (Table 1). **Conclusions:** LNR has significant impact on the survival of pts with advanced HNC. LNR of 0.1 or higher in HNC is associated with 40% increased relative risk of death.

**Characteristics of patients in GpA (LNR < 0.1) and GpB (LNR > 0.1).**

| Variables | GpA(LNR<0.1) | GpB(LNR>0.1) | P-value |
|---|---|---|---|
| No. of patients(%) | 24,206(51%) | 23,304(49%) | |
| Median age(yrs) | 58 | 59 | |
| No. of LC(%) | 4,564(53%) | 4,059(47%) | |
| Median LN extracted | 40 | 21 | <0.001 |
| Median positive LN | 2 | 4 | <0.001 |
| 5yr OS stage III | 50% | 33% | <0.001 |
| 5yr OS stage IV | 40% | 24% | <0.001 |
| No. of NLC(%) | 19,642(50.5%) | 19,245(49.5%) | |
| Median LN extracted | 36 | 17 | <0.001 |
| Median positive LN | 1 | 3 | <0.001 |
| 5yr OS stage III | 60% | 57% | <0.001 |
| 5yr OS stage IV | 53% | 39% | <0.001 |

**6093 General Poster Session (Board #128), Sat, 1:15 PM-5:00 PM**

**Phase II study of axitinib in patients with progressive, recurrent/metastatic adenoid cystic carcinoma.** *Presenting Author: Alan Loh Ho, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Recurrent/metastatic adenoid cystic carcinoma (R/M ACC) is an incurable disease with no standard treatments. >70% of ACCs highly express the oncogenic transcription factor c-myb, which drives expression of genes that activate vascular endothelial growth factor receptor (VEGFR) and c-kit pathways. Axitinib (AG-013736; Pfizer) is a potent inhibitor of VEGFR and c-kit that we hypothesized would be an effective therapeutic for R/M ACC patients. **Methods:** For this minimax two-stage phase II trial, patients with locally advanced, recurrent, and/or metastatic ACC (any primary site) not amenable to curative surgery or radiation were enrolled. Evidence of disease progression on imaging performed within 6 months of enrollment ornew/worsening disease-related symptoms was required. Patients were treated with axitinib 5 mg orally twice daily (BID); those with ≤Grade 2 axitinib-related adverse events (AEs) for two consecutive weeks and blood pressure ≤150/90 mmHg without antihypertensive medication were eligible for dose escalation up to 10 mg BID. The primary endpoint was best overall response rate (ORR) by RECIST v1.1 criteria. The objective was to detect a difference in ORR of 5% vs. 20% (with 10% one-sided type I error and 90% power); ≥1 response among the first 18 patients had to be achieved before accruing 14 more patients in the second stage. ≥4 responses out of 32 patients would be deemed promising. **Results:** 33 patients were registered and evaluable for response. One patient included in the analysis was determined to be ineligible after one dose of axitinib and replaced. 15 of 19 eligible for dose escalation had the axitinib dose increased. 22 achieved reductions in tumor size. 3 (9.1%) had confirmed PR and 25 (75.8%) stable disease (SD) as best overall response. 11 had SD for ≥ 6 months. The most common axitinib-related AEs were hypertension, fatigue, weight loss, anorexia, diarrhea, hand-foot syndrome, nausea, and oral pain. Exploratory analyses evaluating clinicopathologic correlates to response (including c-myb expression) are ongoing. **Conclusions:** The study did not meet its primary endpoint. Axitinib does appear to achieve disease-control in a subset of progressive R/M ACC patients. Clinical trial information: NCT01558661.

**6094 General Poster Session (Board #129), Sat, 1:15 PM-5:00 PM**

**Correlation of homologous recombination deficiency in head and neck cancer with sensitivity to PARP inhibition.** *Presenting Author: Jana Heitmann, The University of Chicago, Chicago, IL*

**Background:** Cancers deficient in homologous recombination (HR) exhibit synthetic lethality when treated with poly (ADP-ribose) polymerase (PARP) inhibitors and may be more sensitive to platinum based therapies. While BRCA1/2 mutations are uncommon in head and neck cancer (HNC), we hypothesized that other mechanisms of HR deficiency occur frequently. **Methods:** We employed three methods to determine homologous recombination deficiency (HRD): (1) HRD-score, (2) Large-scale chromosomal breaks (Popova et al), (3) BRCA-like CN profile (Schouten et al) using HNC TCGA and Chicago HNC Genomic cohort (CHGC) data. We furthermore screened for HR pathway mutations in both genomic cohorts. Single agent activity of three PARP inhibitors (veliparib (non-locking), olaparib and rucaparib (locking)) was evaluated in a panel of 10 HNC cell lines (colony formation, viability) and compared with a BRCA deficient breast cancer cell line. Immunofluorescent staining for γH2AX and RAD51 was performed. A gene signature of HRD deficiency was developed. **Results:** HR deficiency was present in 25% of HNC, and was largely concordant between all three methods (1. and 2. had the highest correlation), but were not related to BRCA1/2 mutations in HNC TCGA. BRCA1/2 mutations were rare (<1%) and of unclear significance. In a panel of HNC cell lines rucaparib showed the highest potency as a single agent with three cell lines exhibiting sensitivity ($IC_{50}$: 7.0$\mu$M, 10.3$\mu$M and 11.7$\mu$M), comparable or superior to a BRCA deficient breast cancer cell line ($IC_{50}$value: 8.9$\mu$M). Seven HNC cell lines were more resistant to single agent PARP inhibition. Foci formation of the HR marker RAD51 did not serve as a reliable biomarker in those cell lines, but our newly developed gene expression signature was applicable. **Conclusions:** In conclusion, we discover that HR-deficiency is present in 25% of HNC tumors, and benefit of single agent PARP inhibition is present in pre-clinical HNC models, despite the general absence of BRCA mutations in this tumor type. HRD-score is a candidate biomarker to identify patients that may benefit from PARP inhibition, including combinations with cytotoxic chemotherapies or radiation in the future.

**6095 General Poster Session (Board #130), Sat, 1:15 PM-5:00 PM**

**Prognostic value of radiographic extracapsular extension in locally advanced head and neck squamous cell cancers.** *Presenting Author: Jerry T. Liu, Icahn School of Medicine at Mount Sinai, Department of Radiation Oncology, New York, NY*

**Background:** Previous data from our institution suggests that radiographic evidence of extracapsular extension (rECE), identified on pretreatment diagnostic CT imaging, predicts for worse outcomes for oropharyngeal cancer patients undergoing radiation therapy. We sought to validate these findings in all sites of locally advanced head and neck squamous cell cancers (LAHNC). **Methods:** From our departmental database, 224 LAHNC patients with accessible pretreatment CT scans completed definitive or adjuvant radiation therapy (± induction and/or concurrent chemotherapy) from 2005-2012. Three patients died shortly after treatment. The remaining 221 patients (nasopharynx (n=19), oral cavity (n=22), oropharynx (n=126), hypopharynx (n=15), larynx (n=21), nasal cavity/sinus (n=3), and unknown primary (n=15)) were selected and all pretreatment CTs were reviewed by our head/neck radiologist for evidence of rECE. Patients were stratified by presence of rECE, age, gender, race, smoking history, ECOG performance status (PS), disease site, cT-stage, cN-stage, and treatment type. Univariate and multivariate analyses (MVA) were performed regarding impact of these factors on locoregional control (LRC), distant control (DC), progression free survival (PFS) and overall survival (OS). **Results:** With median follow-up of 30 months (range: 3-100), 126 (57%) patients had rECE and 95 (43%) did not. These groups were well-balanced for age, gender, race, smoking history, disease site, PS, treatment type, and cT-stage. Patients with rECE were more likely to have cN2-3 disease versus those without rECE (84% vs. 77%, p=0.015). Patients with rECE had worse LRC (3yr: 78% vs. 89%, p=0.032), DC (3yr: 72% vs. 89%, p=0.017), PFS (3yr: 60% vs. 73%, p=0.011), and OS (3yr: 64% vs. 80%, p=0.011). On MVA, rECE was found to independently predict for worse LRC (HR 2.59, 95%CI 1.22-5.51), DC (HR 3.28, 95%CI 1.57-6.85), PFS (HR 1.91, 95%CI 1.16-3.15), and OS (HR 2.041, 95%CI 1.15-3.63). **Conclusions:** Presence of rECE independently predicts for worse outcomes for LAHNC patients undergoing radiation therapy. Larger studies with longer follow-up are needed to determine how rECE can guide clinical management in these patients.

**6096 General Poster Session (Board #131), Sat, 1:15 PM-5:00 PM**

**A retrospective study to determine the utility of measuring E6 and E7 antibody (Ab) levels in sera as a biomarker of recurrence in patients (pts) with locally advanced (LA), human papillomavirus-positive (HPV+) oropharyngeal squamous cell carcinoma (OPSCC).** *Presenting Author: Assuntina Gesualda Sacco, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI*

**Background:** Approximately 20% of pts with LA, HPV+ OPSCC have poor survival outcomes. To date, there is a paucity of biomarkers to predict which pts will ultimately fail standard therapy. E6/E7 viral oncoproteins are constitutively expressed in HPV+ tumors and highly immunogenic, resulting in readily detected serum Ab. The relative absence of E6/E7 Ab in healthy controls and HPV negative tumors, coupled with cervical cancer data suggesting a correlation between E6/E7 Ab levels and prognosis, warrants evaluation in HPV+ OPSCC. **Methods:** Pts with previously untreated, LA (stage III, IV), HPV+ OPSCC receiving definitive chemoradiation from 2003-2010 were included. Baseline and longitudinal (post-treatment, at recurrence and >12 months post-treatment) serum samples were obtained from our archived repository. E6/E7 serum Ab was measured using a glutathione-*S*-transferase (GST) capture ELISA. Serial dilutions of each serum sample were performed, with area under the curve analysis calculated. E6/E7 change was quantified linearly and on a multiplicative scale using ratios of post and pre-treatment levels. **Results:** 30 of 171 (18%) pts recurred (16 distant, 6 regional, 2 local, 2 locoregional, 2 local/distant, 2 regional/distant). 22 of 30 had baseline serum; 15 had serum at recurrence. This group (R) was compared to 30 pts who remained disease-free (NR). R and NR were well-balanced except for a non-significant (NS) trend toward higher T and N stage in R. At baseline, higher T stage was associated with lower E7 levels (p=0.016), whereas higher N stage had higher E7 levels (NS). Current smokers had lower baseline E7 levels (NS). NR pts cleared more proportion E7 than R pts, p=0.0016. Current smokers had higher baseline E6 levels (NS) and cleared less E6, p=0.04. Age and gender did not affect Ab patterns. **Conclusions:** Pts who recur clear less E7 Ab after treatment. Smoking impacts E6/E7 Ab patterns. Impact of pack-year tobacco use, alcohol and marijuana use will be reported. These findings merit evaluation in a prospective clinical trial.

**TPS6097^ General Poster Session (Board #132A), Sat, 1:15 PM-5:00 PM**

**A phase I/II randomized study of Debio1143 combined with concurrent chemoradiation therapy (CCRT) in patients with locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN).** *Presenting Author: Christophe Le Tourneau, Department of Medical Oncology, Institut Curie, Paris, France*

**Background:** Inhibitors of apoptosis proteins (IAPs) are negative modulators of apoptosis which represent attractive targets to overcome resistance to cancer therapy. The small molecule Debio1143 is a potent orally-active IAP antagonist able to promote apoptosis in tumour cells by restoring caspase activity, and modulating NF-κB signalling and TNFα effects. As single agent, Debio1143 inhibits cell growth and induces apoptosis in a subset of human cancer cell lines and in multiple xenograft models of human cancer, including SCCHN. Furthermore, Debio1143 potentiates the effects of cisplatin and radiotherapy in SCCHN nonclinical models (D. Viertl et al.,Radiotherapy and Oncol 106, Suppl.1, 2013; Abstract OC-19, p. 56). Debio1143 monotherapy was well toleratedin cancer patients up to 900 mg OD, resulted in rapid and sustained cIAP1 suppression in patient peripheral blood mononuclear cells and in skin biopsies, and achieved exposures that were previously shown to be active in animal models (H. Hurwitz et al., EJC 48, Suppl.6, 2012; Abstract 76, p. 25). **Methods:** This is a phase I/II, multicentre study comprising a dose-escalation Phase I part (A) and a randomised Phase II part (B) that enrols untreated LA-SCCHN patients with T≥2, N0-3, M0 disease eligible for exclusive chemoradiation. Oropharynx cancer patients have to be HPV-negative. Standard fraction radiotherapy is delivered with a daily dose of 2Gy for 5 days per week to a total dose of 70Gy. Cisplatin is administered on Day 2 of every 21-day cycle for 3 cycles at the dose of 100 mg/m². Debio1143 is orally administered OD on days 1-14 of every 21-day cycle. The starting dose is 100 mg and will be in part A escalated by 100 mg increase using a modified continual reassessment method. Extensive PK, PD, and pharmacogenomics assessments are included. Part B is a double-blind, placebo-controlled Phase II trial in which 97 patients will be randomised to receive placebo or Debio1143 at the dose recommended in part A in combination with CCRT. Primary endpoint is locoregional control at 18 months. Dose escalation started on September 2013 and it is ongoing. Clinical trial information: NCT02022098.

**TPS6098 General Poster Session (Board #132B), Sat, 1:15 PM-5:00 PM**

**A randomized, multicenter phase III clinical trial comparing gemcitabine and cisplatin with 5-fluorouracil and cisplatin in the treatment of recurrent or metastatic nasopharyngeal carcinoma.** *Presenting Author: Li Zhang, Cancer Center of Sun Yat-Sen University, Guangzhou, China*

**Background:** Nasopharyngeal carcinoma (NPC) is highly sensitive to both radiotherapy and chemotherapy. Nowadays, the regimen of 5-Fluorouracil plus cisplatin (FP) is widely used in recurrent or metastatic (R/M) NPC patients, but the response period is usually short and the adverse reaction is frequent and badly tolerant. Several small phase II trials suggest gemcitabine plus cisplatin (GP) has promising efficacy and better tolerability. Unfortunately, there is no head to head comparison study to evaluate these two regiments in this setting. This phase III trial will evaluate the efficacy and safety of GP versus FP as first-line therapy in patients with R/M NPC. **Methods:** The population consists of R/M NPC patients that failed the radical radiotherapy or chemotherapy-naïve advanced NPC (stage IV). Eligible patients will be randomized in a 1:1 ratio to receive either GP (gemcitabine 1,000 mg/m$^2$ on days 1, 8, cisplatin 80 mg/m$^2$ on day 1, every 3 weeks) or FP regimens (5-Fluorouracil 4,000 mg/m$^2$ CIV over 96 hours, cisplatin 80 mg/m$^2$ on day 1, every 3 weeks) for 4 to 6 cycles. The primary endpoint is progression free survival (PFS). Secondary endpoints include overall survival (OS), objective response rate (ORR), safety and quality of life. According to previously reported, it was assumed that the median PFS would be 4 months in the FP group and 6 months in the GP group. To detect a hazard ratio of 0.67, and a two-sided significance level of 5%, with a power of 80%, accommodating for a maximum drop-out rate of 5%, the necessary sample size was calculated to be 198 patients per group. Therefore, the trial plans to enroll 362 patients at 21 sites in China. Thus far, 203 patients have been enrolled. Clinical trial information: NCT01528618.

**TPS6099 General Poster Session (Board #133A), Sat, 1:15 PM-5:00 PM**

**Elderly Head and Neck Cancer (ELAN) study: Personalized treatment according to geriatric assessment in patients age 70 or older: First prospective trials in patients with squamous cell cancer of the head and neck (SCCHN) unsuitable for surgery.** *Presenting Author: Joel Guigay, Gustave Roussy, Villejuif at present Centre Antoine-Lacassagne, IUFC, Nice, France*

**Background:** 30% of SCCHN occur in patients (pts) >= 70y and the main challenges in these pts are to cope with the treatment benefit/risk ratio and the tumor related symptoms. However, these pts are usually not included in trials. We developed a large prospective clinical program planed to enroll 448 pts in 3 distinct trials to improve the multidisciplinary management of elderly SCCHN pts. The main objectives of this study are to demonstrate that a geriatric evaluation is feasible in daily practice for SCCHN pts and to set new standards of care in this population. **Methods:** To be included in one of the three trials, SCCHN pts aged 70 or over, not suitable for surgery, must first be enrolled in ELAN-ONCOVAL study where they are classified as fit or unfit, using a geriatric evaluation applicable to the daily practice. Comprehensive Geriatric Assessment is optional. In curative situation, unfit pts are proposed to be enrolled in the randomized non-inferiority ELAN-RT trial, comparing standard radiotherapy (RT, 70Gy, 35 fractions, 7 weeks) and hypofractionated split course schedule (30 Gy in 10 fractions, 2 weeks stop, 25 Gy in 10 fractions, total 6 weeks). Main endpoint is the rate of patients alive with local control 6 months after end of RT. 202 pts are planned to be randomized. In first line treatment of recurrent and/or metastatic (R/M) pts: - Fit pts are proposed to be enrolled in the 2-stage phase II ELAN-FIT trial, which evaluates the cetuximab-carboplatin-5FU (EXTREME) combination in terms of efficacy (objective response at 12 weeks) and safety assessed by lack of grade>=3 toxicity and lack of loss of independence. Enrollment of 82 pts is planned. - Unfit pts are proposed to be enrolled in the efficacy randomized phase III ELAN-UNFIT trial, that compares two monotherapies (cetuximab 500 mg/m$^2$ every 2 weeks versus weekly methotrexate 40 mg/m$^2$) in terms of failure free survival (failures are progression, treatment stop, loss >= 2 points in Activities in Daily Living scale or death). 164 pts are planned to be randomized. Inclusions started on June 2013. At now 23 centers are opened. Grants: INCa PAIR Clinical trial information: NCT01884623; NCT01864850; NCT01864772.

**TPS6100 General Poster Session (Board #133B), Sat, 1:15 PM-5:00 PM**

**Multicenter, randomized, controlled, open-label study of bevacizumab combined with carboplatin and paclitaxel versus carboplatin and paclitaxel in patients with metastatic nasopharyngeal carcinoma.** *Presenting Author: Li Zhang, Sun Yat-Sen University Cancer Center, Guangzhou, China*

**Background:** Nasopharyngeal carcinoma (NPC) is an endemic disease with a high incidence in South-East Asian. Standard chemotherapy for metastatic NPC is platinum-based regimen. Improvement the outcome of mNPC patients remains a high-unmet medical need. Vascular endothelial growth factor (VEGF) was over expressed in 67% of NPCs and correlated to higher rate of recurrence and less survival. Bevacizumab, an anti-tumor angiogenesis monoclonal antibody, precisely targets VEGF to inhibit angiogenesis for continuous tumor control. A phase II multi-institutional trial (RTOG0615) showed that bevacizumab plus chemoradiation is feasible, and might delay the progression of subclinical distant disease in NPC. We plan to initiate the first randomized study to evaluate the efficacy and safety of bevacizumab plus paclitaxel/carboplatin (TC) particularly in mNPC population. **Methods:** This is a multi-center, randomized phase II study. The primary end-point of the study was progression-free survival (PFS) based on independently assessment. Secondary end-point include overall survival (OS), response rate (ORR), disease control rate (DCR), health-related quality of life (HRQoL) and toxicity profiles. The study was designed to have 60% power to detect a 33% improvement of PFS in bevacizumab treated arms (from 6 month to 9 month) at a two-sided significance level of 5%. Based on these assumptions, a total of 80 patients are needed to observe 57 events. Eighty treatment naïve metastatic NPC patients will be randomly assigned (1:1) to receive TC plus bevacizumab or TC alone. TC consisted of carboplatin (AUC 5, iv) /paclitaxel (175 mg/kg, iv) on day 1 of each 3-week cycle for up to 6 cycles; bevacizumab (7.5 mg/kg, iv) was administered with carboplatin/paclitaxel on day 1 and maintenance after the finish of chemotherapy until disease progression or unacceptable toxicity. Recruitment will begin in March 2014. The duration of the trial will be 24 months (12 months recruitment and 12 months follow-up).

**TPS6101 General Poster Session (Board #134A), Sat, 1:15 PM-5:00 PM**

**Personalized cancer therapy for patients with metastatic medullary thyroid cancer (MTC).** *Presenting Author: Krzysztof Misiukiewicz, Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY*

**Background:** Standard approaches in cancer research identify new therapies based on observed benefit to average populations, but without emphasis on individual patients whose responses can vary considerably. Further, targeted therapies rarely account for the genomic complexity of patient tumors; the result is poor efficacy and rapid resistance. Ideally, we would identify drugs or drug cocktails that (1) target the details of an individual's tumor and (2) account for its complexity. Models using the fruit fly Drosophila represent a potential new paradigm in cancer therapy. We have developed fly models that can include up to 10 of a patient's driver mutations; the result is an inexpensive drug screening platform to identify drug cocktails through empirical screening. As validation flies helped identify vandetinib, now approved for treatment of metastatic MTC. **Methods:** Tumor mutations identified by deep DNA and RNA sequencing of individual tumors are screened for tumor drivers, which are then incorporated into the "personal" Drosophila model and tested against a library of FDA approved drugs. Fly mortality is used as a surrogate for toxicity and increased survival to adulthood; improvements in tumor mutation-linked eye and/or wing abnormalities serve to quantify efficacy. This allows rapid and parallel screening of up to 800 drugs and subsequent drug combinations. The most efficacious and least toxic combinations are tested in xenograft models and a multidisciplinary tumor board of experts select the best therapeutic option. The objective is to demonstrate that the personalized drosophila model approach is superior to the current standard, cabozantinib, which performed best in MTC with a 27% response rate (RR) against placebo in a phase III trial but with considerable toxicity. Using the 27% RR as a benchmark, we will apply a sequential Bayesian method for 50 MTC patients enrolled to receive personalized treatment to demonstrate that this approach has greater efficacy, or at minimum, substantially similar efficacy with reduced toxicity.

**TPS6102 General Poster Session (Board #134B), Sat, 1:15 PM-5:00 PM**

**Randomized phase II trial of weekly paclitaxel, carboplatin, cetuximab (PCC) versus cetuximab, docetaxel, cisplatin, and fluorouracil (C-TPF) in previously untreated patients with locally advanced head and neck squamous cell carcinoma.** *Presenting Author: Erminia Massarelli, Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background**: The use of induction chemotherapy in patients (pts) with locally advanced head and neck squamous cell carcinoma (HNSCC) remains controversial. The induction strategy has shown to reduce risk of distant metastases but also represents a vehicle for the evaluation of other clinical and molecular endpoints. The development of increasingly effective induction chemotherapy may eventually affect the efficacy of radiotherapy with an improvement in local disease control. To determine the efficacy of combining cetuximab with induction chemotherapy, we designed a randomized phase II trial in previously untreated pts with locally advanced HNSCC using two induction chemotherapy regimens that had previously demonstrated efficacy and acceptable toxicity, followed by definitive risk-appropriate local therapy, taking into consideration both tumor (T) stage at presentation as well as human papillomavirus (HPV) status. **Methods**: Pts with stage IV T0-4 N2b-2c/3 M0 measurable disease in either the T or nodal (N) site by RECIST criteria were included in the trial. Pts were randomized to receive 6-weekly cycles of paclitaxel 135 mg/m$^2$, carboplatin AUC 2 and cetuximab 400 mg/m$^2$ week 1 then 250 mg/m$^2$ weekly (PCC) or 3 cycles of every 3 weeks docetaxel 75 mg/m$^2$ on day 1, cisplatin 100 mg/m$^2$ on day 1, 5-fluorouracile (5-FU) 700 mg/m$^2$/day continuous infusion days 1-4 and cetuximab 400 mg/m$^2$ week 1 then 250 mg/m$^2$ weeks 2, 4, 5, 7, 8 (C-TPF). HPV status was required at study entrance. Primary objective was progression free survival of both regimens followed by definitive local therapy selected on the basis of stage and HPV status, compared to historical control docetaxel/cisplatin/5-FU (TPF). Secondary objectives were: overall survival, response rate, duration of locoregional control, patterns of tumor recurrence, toxicity and biomarker analysis by HPV status and outcome. The trial has accrued a total of 135 pts as of January 2014. Planned analyses beyond primary and secondary objectives include evaluation of tumor genotype and immune phenotype in correlation with HPV-status and outcome. Clinical trial information: NCT01154920.

**TPS6103 General Poster Session (Board #135A), Sat, 1:15 PM-5:00 PM**

**A phase I/II clinical trial of sorafenib in combination with cisplatin and docetaxel in patients with recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN).** *Presenting Author: Panayiotis Savvides, The James Cancer Hospital and Solove Research Institute, The Ohio State University, Columbus, OH*

**Background:** There is rapid accumulation of data pointing to a potential role of sorafenib in the setting of recurrent/metastatic SCCHN. The combination of sorafenib to a cisplatin-docetaxel doublet backbone was chosen for further development for many reasons, including that cisplatin-containing combination regimens have been associated with higher response rates when compared with carboplatin ones and cisplatin containing regimens remain the first choice for firstline treatment and taxane-cisplatin combination regimens appear to be preferable to 5FU-cisplatin combination regimens given equal efficacy and better toxicity profile. In addition, we have generated preclinical data suggesting that sorafenib enhances the antitumor effect of chemotherapy and radiation by downregulating ERCC-1 and XRCC-1 DNA repair proteins. If validated in the clinical setting, ERCC-1 downregulation by sorafenib has the potential to improve cisplatin efficacy not only in patients with SCCHN, but across multiple tumor types, as high ERCC1 expression has been associated with shortened survival outcomes in numerous primary tumors. **Methods:** A short Phase I followed by a phase II single arm clinical trial as first line in patients with recurrent/metastatic SCCHN. A total of 3-18 and 29 patients might be needed for the phase I and II portions of the trial, respectively. Correlative studies: A total of three biopsies (blood and tumor samples) will be obtained. 1) Pre-treatment biopsy; 2) Research biopsy obtained at the end of a two week period of sorafenib monotherapy; 3) Research biopsy obtained at the end of two chemotherapy cycles. Proposed correlative studies include: a) Sorafenib target proteins analysis by Immunohistochemistry (IHC) for: 1) pERK1/2 (activated form of ERK1/2); 2) ERCC-1 (DNA repair protein); 3) pVEGFR2 (activated form of VEGFR2); 4) CD31 staining (tumor angiogenesis); 5) Activated caspase-3 staining for apoptotic cells; b) ERCC-1 gene expression analysis by RT-PCR; c) VEGF and IL-6 analysis by ELISA. Clinical trial information: NCT02035527.

**Phase I dose levels.**

| | Cisplatin ($mg/m^2$/21 days)* | Docetaxel ($mg/m^2$/21 days)* | Sorafenib (mg /bid)** |
|---|---|---|---|
| **DL-2** | 75 | 50 | 200 |
| **DL-1** | 75 | 50 | 400 |
| **DL 1** | 75 | 75 | 400 |

**TPS6104 General Poster Session (Board #135B), Sat, 1:15 PM-5:00 PM**

**Phase I trial of cetuximab, intensity modulated radiotherapy (IMRT), and the anti-CTLA-4 monoclonal antibody (mAb) ipilimumab in previously untreated, locally advanced head and neck squamous cell carcinoma (PULA HNSCC).** *Presenting Author: Julie E. Bauman, University of Pittsburgh Cancer Institute, Pittsburgh, PA*

**Background:** Concurrent therapy for PULA HNSCC using the EGFR-specific mAb cetuximab (C) plus IMRT is an accepted standard, however disease control in intermediate or high risk disease could be improved. Our recent data indicate that C induces Ab-dependent, cell-mediated cytotoxicity and cross-priming of cytotoxic T lymphocytes. However, C also induces immunosuppressive regulatory T cells (Treg) expressing the checkpoint receptor CTLA-4; Treg correlate negatively with clinical outcomes to C. We hypothesize enhanced C-induced antitumor cellular immunity and clinical activity by targeting Treg with the anti-CTLA-4 mAb ipilimumab (ipi). We are conducting a phase I study adding ipi to C-IMRT in patients (pts) with intermediate or high risk PULA HNSCC. **Methods:** Eligible pts have stage III-IVb PULA HNSCC (pharynx, larynx). "High risk" pts are HPV(-). "Intermediate risk" pts are HPV(+) and have either: 1) $\geq$ 10 pack-year tobacco and $\geq$N2 disease; or 2) T4 or N3 disease, irrespective of tobacco status. A phase I (3+3) dose escalation trial is evaluating the addition of ipi to standard concurrent C (250 $mg/m^2$weekly after loading dose) + IMRT (66-70 Gy daily fractionation over 7 weeks). See table for dose cohorts and schedule. Dose limiting toxicity (DLT) is defined as any grade 4 toxicity (except in-field radiation dermatitis or asymptomatic, correctable lab abnormality), or any toxicity which delays IMRT $\geq$ 10 fractions. The DLT observation period ends 4 weeks after completing IMRT. As of Jan 2014, 3 pts have enrolled in the first cohort, receiving ipi at 3mg/kg. The next dose tier, assuming no DLTs, will increase ipi to 10 mg/kg. In the event of DLT at 10 mg/kg, ipi dosing will de-escalate to 6 mg/kg. Extensive immune monitoring is underway using baseline tumor tissue, including characterization of tumor-infiltrating lymphocytes, and serial monitoring of circulating lymphocytes and cytokines. Clinical trial information: NCT01935921.

| | Week of Treatment | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 11 | 14 |
| **IMRT** | | X | X | X | X | X | X | X | | |
| **Cetuximab** | X | X | X | X | X | X | X | X | | |
| **Ipilimumab** | | | | | X | | | X | X | X |
| **Cohort -1: 1 mg/kg** | | | | | | | | | | |
| **Cohort 1 (start): 3 mg/kg** | | | | | | | | | | |
| **Cohort 2 (de-escalation only): 6 mg/kg** | | | | | | | | | | |
| **Cohort 3: 10 mg/kg** | | | | | | | | | | |
| **Immune Biomarkers** | X | | | | X | | | X | X | X |

**TPS6105 General Poster Session (Board #136A), Sat, 1:15 PM-5:00 PM**

**Predictor: Randomized phase II study of preoperative afatinib in untreated nonmetastatic head and neck squamous cell carcinoma patients (HNSCC) aiming at identifying predictive and pharmacodynamic biomarkers of efficacy.** *Presenting Author: Christophe Le Tourneau, Department of Medical Oncology, Institut Curie, Paris, France*

**Background:** Identification of efficacy predictive biological biomarkers in HNSCC patients treated with anti-EGFR targeted therapy is still a challenge. In the recurrent/metastatic setting, sequential biopsies allowed correlating potential predictive and pharmacodynamic biomarkers with the outcome of patients treated with erlotinib (Agulnik M et al. J Clin Oncol. 2007;25:2184). Afatinib is an Erb-B family blocker that irreversibly blocks signaling from all relevant Erb-B family dimers and may overcome limitations of current EGFR-targeted treatment in HNSCC. We conduct a randomized phase II study with afatinib **Methods:** PREDICTOR is a UNICANCER sponsored multi-centre randomized phase II study of preoperative afatinib aiming at identifying predictive and pharmacodynamic biomarkers of biological activity and efficacy in untreated non-metastatic HNSCC patients. Key eligibility criteria: confirmed non-metastatic HNSCC; T2-4N0-2 tumors (except T2N0 endolaryngeal tumors); planned date of surgery allowing the patient to receive 14 to 28 days of afatinib treatment; ECOG status 0-2. Target enrolment is 60 pts. Randomization is stratified on the site of primary tumor (oropharynx versus non-oropharynx). Pts are randomized 2:1 to receive afatinib (40mg/qd) OR no treatment (control arm). Dose adjustments are permitted according to the ocurrence of drug-related AEs (reduction to 30mg/qd). The primary endpoint is to identify predictive and pharmacodynamics biomarkers.Tumor samples are collected before treatment (biopsy) and after surgery (surgical specimen). Several molecules involved in the resistance to EGFR will be analyzed through different technics (Immunohistochemistry, High throughput protein analysis, FISH, PCR sequencing and qRT-PCR). Secondary endpoints include efficacy (tumor shrinkage), pathological response, metabolic response (FDG PET/CT scan assessment) and safety. Completion of pt recruitment and data analyses are awaited. Clinical trial information: NCT01415674.

**TPS6106 General Poster Session (Board #136B), Sat, 1:15 PM-5:00 PM**

**PAZOTHYR: A randomized, multicenter, open-label, phase II study of the optimal scheme of pazopanib in radioactive iodine-refractory differentiated thyroid carcinoma (RAIR-DTC).** *Presenting Author: Christelle De La Fouchardiere, Centre Léon Bérard, Lyon, France*

**Background:** Patients with locally advanced/metastatic progressive RAIR-DTC usually have a poor prognosis and may receive tyrosine kinase inhibitors (TKI) as first line therapy. Pazopanib (P) emerged as a promising alternative in a phase II study, with high Objective Response Rates (ORR) (49%; n=18/37) and prolonged Progression-Free Survival (PFS) (mPFS = 11.7 months) (Bible et al. Lancet Oncol. 2010). However, as with other tyrosine kinase inhibitors, the toxicity profile of P leads physicians to consider dose modifications (dose reductions, temporary and/or permanent discontinuation) that may jeopardize the clinical outcome. In addition, the probability of severe toxicity and the difficulty for patients to tolerate mild to moderate events increases with the treatment duration. We decided to investigate an alternative scheme of P preserving clinical benefits for patients and their well-being. **Methods:** A randomized, multicenter, open-label phase II study is ongoing in French patients with advanced RAIR-DTC to identify the optimal treatment strategy, through a new approach. After a 6-month period of continuous P treatment following inclusion, patients with controlled disease (CR, PR or SD) are randomized between a standard strategy (daily P maintained until disease progression (PD) or unacceptable toxicity) and an experimental sequential scheme in which P is temporarily stopped every 6 cycles, and reintroduced as soon as the patient experience PD (RECIST 1.1). This sequential scheme is followed until a PD occurs under P. The primary objective of the study is to compare the two arms in terms of Time to Treatment Failure, defined as the time from randomization to permanent discontinuation of treatment due to any cause. Secondary endpoints of the study include ORR and duration of response, disease control rate, PFS and overall survival. Quality of Life Questionnaire C30 will provide precious complementary data on the potential impact of the proposed strategy on patients' quality of daily living. To date, 13 of the planned 168 patients have been enrolled and 2 patients have been randomized. Clinical trial information: NCT01813136.

**6500 Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**Impact of state-specific Medicaid policies on timely receipt of breast cancer surgery.** *Presenting Author: Michael T. Halpern, RTI International, Washington, DC*

**Background:** Reports have demonstrated barriers in access to and quality of care for Medicaid enrollees, including enrollees with cancer. State-specific Medicaid eligibility policies and low reimbursements for medical care services provided to enrollees with cancer may hinder receipt of high-quality cancer treatment. This study examined how eligibility and reimbursement policies affect timely receipt of breast cancer surgery among Medicaid enrollees diagnosed with breast cancer. **Methods:** The study utilized 2006-2008 Medicaid data for all women 21-64 years of age diagnosed with breast cancer and enrolled in fee-for-service Medicaid for at least 4 months. We examined the association of state-specific Medicaid breast surgery reimbursements, Medicaid income eligibility requirements, and frequency of Medicaid eligibility renewal on time from diagnosis to receipt of breast cancer surgery. Analyses used multivariate logistic regressions controlling for correlation between beneficiaries within a state. **Results:** We identified 10,968 Medicaid enrollees with breast cancer. Lower reimbursements for breast cancer surgery were associated with greater delays for breast conserving surgery, mastectomy, and all breast cancer surgery combined. Shorter time periods for Medicaid eligibility renewal were also associated with greater surgery delays. Income eligibility thresholds did not affect delays. Black, Hispanic, and blind/disabled patients had greater delays, while older patients were less likely to experience delays. **Conclusions:** Low reimbursements were associated with less timely surgery for Medicaid enrollees with breast cancer. In addition, within the Medicaid population, disparities in timeliness of surgery based on patient race, age, and eligibility category were observed. With substantial expansion of Medicaid expected as part of the Affordable Care Act, state legislators and health policy makers need to consider how reimbursements affect receipt of high quality care and develop programs to address disparities within this vulnerable population.

**6501 Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**Low-dose computed tomography lung cancer screening in the Medicare program: Projected clinical, resource, and budget impact.** *Presenting Author: Joshua A. Roth, Fred Hutchinson Cancer Research Center, Seattle, WA*

**Background:** Based on evidence from the National Lung Cancer Screening Trial (NLST), the U.S. Preventive Services Task Force (USPSTF) recently recommended annual low dose computed tomography (LDCT) lung cancer screening in patients age 55-80 with a 30 pack-year smoking history who currently smoke or quit in the past 15 years. Under the terms of the Affordable Care Act, Medicare will cover this screening procedure. We project the clinical, resource, and budget impact of this policy. **Methods:** We developed a model to forecast the 5-year incremental outcomes of implementing USPSTF LDCT screening recommendations vs. no screening. The model simulates a Medicare cohort consistent with 2013 enrollment and age distribution statistics. Lung cancer detection rates and stage at diagnosis were derived from the NLST. Included costs were LDCT screening/follow up, confirmatory bronchoscopy/biopsy, and stage specific lung cancer treatment (initial, continuing, terminal care). We estimated lung cancers detected, LDCT scans, and the total and per member per month (PMPM) budget impact in two scenarios: 1) complete implementation, with all eligible patients offered screening in all years, and 2) phased implementation, with an additional 20% of eligible patients offered screening each year. **Results:** In the complete and phased implementation scenarios, screening resulted in 141,000 and 101,000 more lung cancers detected (mostly Stage I), 37.5 million and 22.4 million more LDCT scans, and increased overall expenditure of $27.4 billion (PMPM $8.80) and $17.6 billion (PMPM $5.70), respectively. The most influential inputs were the proportion of eligible patients electing to undergo screening, initial treatment cost of early-stage lung cancer, and the proportion of stage IV diagnoses in the no screening strategy. **Conclusions:** Our analyses suggest that LDCT screening is will increase lung cancer diagnoses, result in a greater proportion of cases diagnosed at an early stage, and substantially increase Medicare expenditure. Forthcoming analyses will evaluate the resource demands of complete and phased screening implementation relative to existing LDCT facility and health professional supply.

**6502 Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**Cost-effectiveness analysis (CEA) of bevacizumab (Bev) in first- and second-line treatment of metastatic colorectal cancer (mCRC).** *Presenting Author: Daniel A. Goldstein, Winship Cancer Institute of Emory University, Atlanta, GA*

**Background:** The addition of Bev to 5-Fluorouracil (5-FU)-based chemotherapy is the standard of care for previously untreated mCRC. A recent randomized trial demonstrated a 1.4 month increase in median overall survival (OS) when Bev is continued beyond the first progression, thus making it standard practice to use Bev with 5-FU based chemotherapy in both first- and second-line. International CEAs have evaluated Bev in the 1st-line setting. The objective of this study is to determine the cost effectiveness of Bev in the 1st line setting and when continued beyond progression from the US-payer perspective. **Methods:** We developed two Markov models to compare the cost and effectiveness of 5-FU, leucovorin and oxaliplatin (FOLFOX) with or without Bev in the first-line treatment, and subsequent chemotherapy with or without Bev in the second-line treatment of mCRC. Weibull models were fitted to the published survival curves, and were used to extrapolate the cause-specific mortality and progression risks. Costs for administration and management of adverse events were based on Medicare reimbursement rates for hospital and physician services, and drug costs based on the Medicare average sale prices (all in 2013 US $). Health outcomes were measured in life years (LY) and quality-adjusted life years (QALYS). The simulated OS and progression free survival (PFS) were validated by the fitted survival models. Model robustness was addressed by univariate and probabilistic sensitivity analyses (PSA). **Results:** Using Bev in first-line therapy provided an additional 0.289 QALYs (0.412 LYs) at a cost of $69,381. The incremental cost-effectiveness ratio (ICER) was $240,195/QALY. Continuing Bev beyond progression provided an additional 0.108 QALYs (0.167 LYs) at a cost of $23,788. The ICER was $219,742/QALY. In all one way sensitivity analyses, the ICER of Bev was > $100,000/QALY. The ICER of Bev was greater than $100,000/QALY in > 99.9% of PSAs. **Conclusions:** This is the first US based CEA of Bev in mCRC. Bev provides minimal incremental benefit at high incremental cost per QALY in both the first and second-line setting. The ICER of Bev could be improved by use of an effective biomarker to select patients most likely to benefit.

**6503 Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**Is advanced imaging in early-stage breast cancer ever warranted? Exploring benchmarks for an ASCO Choosing Wisely quality measure.** *Presenting Author: Tian Zhang, Duke University Medical Center, Durham, NC*

**Background:** ASCO's Choosing Wisely initiative recommends reducing certain low value services, including advanced imaging in early-stage (ES) breast cancer (BC). Few have explored baseline frequency of, or documented clinical reasons for, advanced imaging in ES BC. We analyzed data at an NCI comprehensive cancer center to characterize pt scenarios in which advanced imaging was ordered. **Methods:** We analyzed all pts with ES BC from January 2010 to June 2012 at the Duke Cancer Institute (DCI). We used the Choosing Wisely criteria for ES BC (clinical Stage IIb or less) and advanced imaging (nuclear bone scan, computed tomography (CT), positron emission tomography (PET), and brain magnetic resonance imaging). We then searched an administrative database for advanced imaging performed in the Duke Health System within 60 days after diagnosis. Three independent reviewers abstracted the medical charts of 40% of cases, randomly selected, to explore reasons for image ordering. Descriptive statistics and the chi-square test were performed. **Results:** Of 1,143 ES BC cases identified, 20.6% (235 pts) had at least one advanced imaging procedure performed. Imaging type varied widely (41% CT, 22% PET, and 36% bone scans, $p<0.001$). Pts with advanced imaging were more likely hormone receptor negative, HER2-negative, younger (age$<$50), and with higher stage (Stage IIb vs. Stage IIa or less) disease (all $p<0.001$). Of the 95 abstracted cases with imaging, 62% (59 pts) were obtained for further staging, 17% to evaluate a major concurrent disease (6 oncologic, 10 non-oncologic), and 19% for exam or history findings worrisome for distant disease. 15% (9/59 pts) of images ordered for staging were abnormal. Overall, 45% (43/95 pts) of advanced imaging ordered were for a major concurrent disease, worrisome findings, or staging which ultimately revealed an abnormality. **Conclusions:** Advanced imaging is ordered in a minority of ES BC cases. When ordered, almost half of images aid in clarifying a complex clinical decision. Our data highlight the benefit of quality measures in reducing low value services, while also acknowledging that allowances for measure non-adherence are needed to promote patient-centered cancer care.

**6504 Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**Relationship between surgical oncologic outcomes and publically reported hospital quality measures.** *Presenting Author: Jason Dennis Wright, Columbia University College of Physicians and Surgeons, New York, NY*

**Background:** Hospital-level measures of patient satisfaction and process measures of quality are now reported publically by the Centers for Medicare and Medicaid Services. There are currently no metrics specific to cancer patients. We examined whether publically reported hospital satisfaction and quality data correlate with surgical oncologic outcomes. **Methods:** The Nationwide Inpatient Sample was utilized to identify patients with solid tumors who underwent surgical resection in 2009-2010. The hospitals in which patients were treated were then linked to: 1) publically reported measures of patient satisfaction (Hospital Consumer Assessment of Healthcare Providers and Systems, HCAHPS), 2) perioperative quality (Surgical Care Improvement Project, SCIP), and 3) mortality measures for medical conditions (risk adjusted mortality for pneumonia, MI, and CHF). The risk-adjusted hospital-level rates of morbidity and mortality were then calculated for each hospital and the means compared between the highest and lowest performing hospital quartiles for each of the measures. Data is reported as absolute reduction in risk (ARR) for each outcome. **Results:** A total of 63,197 patients treated at 448 hospitals were identified. The ARR in perioperative morbidity was 0.0020 for patients at high vs. low performing hospitals based on the overall HCHPS score of hospital satisfaction. Similarly, the ARR for mortality based on the same measure was 0.0038 for high vs. low performing centers. High performance on perioperative quality measures based on SCIP resulted in an ARR of 0.0056 for perioperative morbidity and 0.0049. Lastly hospitals with the lowest mortality for myocardial infarction, heart failure, and pneumonia and ARR for perioperative mortality of 0.0054, 0.0062, and 0.0011 compared to higher mortality hospitals for the respective conditions. **Conclusions:** Currently available measures of patient satisfaction and quality are poor predictors of outcomes for cancer patients undergoing surgery. Specific metrics for oncologic outcomes and quality are needed.

**6505 Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**Measuring compliance to oral antineoplastic agents: A comparison between administrative data and medical records.** *Presenting Author: Winson Y. Cheung, British Columbia Cancer Agency, Vancouver, BC, Canada*

**Background:** With increasing use of oral drugs in oncology, recent studies of administrative data indicate that compliance with these agents is suboptimal. Using a population-based cohort of colon cancer to test our hypothesis, our aim was to evaluate the proportion of patients deemed non-compliant that actually had a reasonable indication for not adhering to their prescribed oral systemic therapy regimen. **Methods:** Consecutive patients diagnosed with stage III colon cancer from 2008 to 2010, referred to any 1 of 5 regional cancer centers in British Columbia, and who initiated at least 1 cycle of oral adjuvant capecitabine within 12 weeks of curative resection were included. Administrative data from the provincial oncology pharmacy were analyzed to assess for non-compliance, which was defined as any prescription refill delays of >/= 1 week from the end date of the preceding cycle. Electronic medical record abstraction was conducted to examine the factors, if any, which contributed to non-compliance. We compared administrative vs. medical record data to determine the level of concordance. **Results:** We included 752 patients: median age was 70 years (IQR 35-87), 56% were men, and 86% had ECOG 0/1. Administrative data showed that 413 patients were non-compliant: 230 (56%) and 183 (44%) had 1 and >/=2 late refills, respectively. In this group, a total of 2095 cycles of capecitabine were delivered among which 688 (33%) treatment deviations occurred. No differences in baseline characteristics were observed between individuals who were compliant and those who were not (all $p>0.05$). Of the 688 prescription delays that were ascertained from administrative data, medical records demonstrated that 30 (4%) were misclassified. From the remainder, the majority were attributable to valid reasons, including: 340 (50%) toxicities necessitating time off therapy; 171 (25%) physician discretion; 23 (3%) patient refusal; and 41 (6%) travel requiring adjustment to treatment schedule. Only 83 (12%) cases were considered as true non-compliance. **Conclusions:** Using administrative data alone to measure oral oncology drug compliance without corroborating with clinical records may overestimate the degree of non-adherence.

**6506 Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**MD Anderson's Oncology Expert Advisor powered by IBM Watson: A Web-based cognitive clinical decision support tool.** *Presenting Author: Koichi Takahashi, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Application of cognitive computing technology in cancer has potential to democratize expert knowledge and enable personalized evidenced based oncology care. **Methods:** We developed a web based prototype of MD Anderson's Oncology Expert Advisor (OEA), a cognitive clinical decision support tool powered by IBM Watson. The Watson technology is IBM's third generation cognitive computing system based on its unique capabilities in natural language processing and deep QA (question-answer). OEA is built with four core capabilities: 1) Patient Evaluation through interpretation of structured and unstructured clinical data to create a dynamic case summary with longitudinal view of the pertinent events 2) Treatment and Management suggestions based on patient profile weighed against consensus guidelines, relevant literature, and MD Anderson expertise, which will include approved therapies, genomic based therapies as well as automatic matching to eligibility criteria of clinical trials at MD Anderson, 3) Care Pathway Advisory that supports management of patients by alerting adverse events and/or suggesting proactive care support, and 4) Patient-oriented Research functionalities for identification of patient cohorts and generation of hypothesis. **Results:** We trained OEA by loading 400 cases of historical patient cases and assessed the accuracy of OEA treatment suggestions using MD Anderson's physicians' decisions as benchmark. False positive result was defined when OEA recommends a non-correct answer with high confidence, whereas false negative was defined when OEA recommends a correct answer with low confidence. When 200 leukemia cases were tested to assess accuracy of standard-of-care (SOC) treatment recommendation, false positive rate was 2.9%, whereas false negative rate was 0.4%. Overall accuracy of SOC treatment recommendation by OEA was 82.6%. **Conclusions:** OEA is able to generate dynamic patient case summary by interpreting structured and unstructured clinical data and suggest personalized treatment options with reasonably high accuracy. Live system evaluation of OEA is ongoing and application of OEA in clinical practice is expected to be piloted at our institution.

**6508 Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**Initial utilization of Oncotype DX in the Medicare population between 2005 and 2007.** *Presenting Author: Michaela Ann Dinan, Duke Clinical Research Institute, Durham, NC*

**Background:** In 2005 the Centers for Medicaid and Medicare Services approved reimbursement for the Oncotype DX (ODX) 21-gene assay in women with early stage ER-positive, node negative breast cancers to help guide recommendations for adjuvant chemotherapy. This analysis provides the first nationally representative examination of the adoption of ODX in Medicare beneficiaries with breast cancer. **Methods:** Retrospective analysis of SEER-Medicare linked data for breast cancer patients diagnosed between 2004 and 2007 was used to characterize overall utilization of ODX and identify demographic and clinical factors associated with receipt of ODX. **Results:** A total of 46,084 Medicare beneficiaries diagnosed with breast cancer in the SEER registries met study criteria. Utilization of ODX testing among newly diagnosed Medicare breast cancer patients increased from 1.2% to 5.2% among all stages and subtypes and from 1.9% to 7.5% among women with localized, ER positive, node negative disease from 2005 to 2007. As compared to patients who did not receive ODX testing, beneficiaries who received ODX testing were more likely to have higher baseline histologic grade, larger tumor sizes, and be ER and PR positive. Increasing age category (71-75, 76-80, 80 or older) and number of comorbidities (1, 2 or more) conditions were associated with a decreased odds of receiving ODX, whereas being married was associated with increased odds of receiving ODX testing in multivariable analysis (all $P<0.001$). Relative to patients with stage 1 disease, patients with stage 0, II, III, and IV disease all had decreased odds of receiving ODX (OR 0.02, 0.55, 0.04, 0.04, all $P<0.001$). We found no significant difference in regional ODX utilization. **Conclusions:** Following the approval of ODX coverage by CMS in 2005, the utilization of ODX has significantly increased. Utilization was largely limited to patients in whom testing is considered medically necessary by CMS and is supported by current guidelines, and in younger and healthier patients in whom chemotherapy would be more likely to be a clinically appropriate management option. The impact and utilization of ODX adoption on the care of breast cancer patients in the future remains an important area of health policy research.

**6509 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

**Discussions about clinical trials among patients with lung and colorectal cancer.** *Presenting Author: Kenneth L. Kehl, Brigham and Women's Hospital, Boston, MA*

**Background:** Clinical trials are essential for evaluating new cancer therapies, but less than 5% of adults with cancer enroll in trials. Barriers to enrollment may include patient-provider communication factors, such as lack of patient awareness or understanding about the option of participation. **Methods:** We surveyed a population- and practice-based sample of patients (or their surrogates) 3 to 6 months after diagnoses of lung or colorectal cancer. We assessed whether respondents learned that clinical trial participation might be an option, and if so, with whom they first discussed this possibility. We used multivariable logistic regression to assess the association of patient characteristics with clinical trial discussions and enrollment. **Results:** Of 7,887 respondents, 1,114 (14.1%) reported discussing clinical trial participation. Most (92.7% of participants, 75.8% of nonparticipants) learned about trials from their physicians. 287 patients (3.6% of all patients, 25.8% of trial discussants) enrolled. Among 2,173 patients who received chemotherapy for advanced (stage III/IV lung or stage IV colorectal) cancer, 25.7% discussed trials, and 7.6% (29.5% of discussants) enrolled. In adjusted analyses among all patients, discussion of clinical trials was more common among college-educated patients (OR 1.9, 95% CI 1.5-2.5 vs <high school education) and those with incomes >$60,000/year (OR 1.7, 95% CI 1.4-2.2 vs <$20,000/year), and less common among older patients (OR 0.96, 95% CI 0.95-0.97/year). These factors were not significantly associated with enrollment among patients discussing trials. Enrollment was higher among patients reporting shared vs. physician–driven decisions ($P<0.05$). **Conclusions:** In this population-based cohort, less than one-sixth of cancer patients discussed clinical trials. Discussions were more frequent in the setting of advanced disease but were still reported by a minority of patients. Older age and lower education and income levels were associated with less discussion of clinical trials but not with enrollment in trials following discussions. Strategies to broaden access to trials and facilitate patient-provider communication about participation may improve enrollment rates.

**6510 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

**Clinical trial subjects compared to "real world" patients: Generalizability of renal cell carcinoma trials.** *Presenting Author: Aaron Philip Mitchell, Duke Cancer Institute, Durham, NC*

**Background:** While narrow eligibility criteria improve the internal validity of clinical trials, they threaten the generalizability of study findings to real-world populations. How similar is the population of patients receiving treatment for metastatic renal cell cancer (mRCC) to subjects enrolled in pivotal trials? **Methods:** A retrospective registry of academic (Duke University Health System) and community (ACORN Network) practices was used to compare real world mRCC patients to study subjects in the landmark phase III clinical trials of the new, targeted therapies. Patients were compared to subjects who were treated with the same agent. **Results:** Of 633 patients in the registry, 438 received sunitinib, sorafenib, temsirolimus, or pazopanib; everolimus and axitinib were not included due to small patient numbers. Registry patients were a mean of 4.6 years older than clinical trial subjects ($p<0.0001$). With the exception of temsirolimus-treated patients, registry patients had poorer risk disease by MSKCC model (poor: 7.4% vs 2.9%, $p<0.0001$; favorable: 30.6% vs 43.8%, $p=0.0004$) and were more likely to have impaired functional status (ECOG >1, 8.4% vs 0.6%, $p<0.0001$). Applying the eligibility criteria described in the clinical trial manuscripts, 40.0% of patients failed inclusion criteria for the phase III clinical trial testing the drug they received (Table), 9.9% due solely to non-clear cell histology. **Conclusions:** mRCC patients in "real world" clinical practice are older and sicker than those enrolled in pivotal clinical trials. Over one third of mRCC patients would not have met eligibility criteria for the phase III clinical trial that led to approval of the agent they received. Application of clinical trial findings to dissimilar populations may result in patient harm. Research of mRCC drugs in general populations is needed to guide real world clinical practice.

| Agent used to treat mRCC cohort patients | N | Clinical trial used for comparison | Patients meeting exclusion criteria (%) |
|---|---|---|---|
| **Sunitinib** | 289 | Motzer et al, NEJM 2007 | 98 (33.9) |
| **Sorafenib** | 59 | Escudier et al, NEJM 2007 | 20 (33.9) |
| **Temsirolimus** | 59 | Hudes et al, NEJM 2007 | 44 (74.6) |
| **Pazopanib** | 31 | Sternberg et al, JCO 2010 | 13 (41.9) |
| **Total** | 438 | | 175 (40.0) |

**6511 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

**Impact of the NCI Community Cancer Centers Program (NCCCP) on clinical trial (CT) activities in a community cancer center in rural Nebraska.** *Presenting Author: Mehmet Sitki Copur, Saint Francis Cancer Treatment Center, Grand Island, NE*

**Background:** 85% of cancer patients (pts) are diagnosed/treated in the community, but only 3-5% are enrolled on CTs. Community oncologists lack adequate time, resource, infrastructure, reimbursement to engage in CTs. In July 2007, a 5-yr NCCCP contract was awarded to 16 pilot sites in diverse communities across the United States to support CTs and cancer care delivery. **Methods:** 5-yr prior and 5-yr after NCCCP, Saint Francis Cancer Center CT activities data, which included number/percent (pts) on CTs, percent underserved on CTs, number/type CTs available, staffing, collection/storage of tissue samples, organizational infrastructure/linkage to NCI designated cancer centers, availability of new cancer care services were gathered and compared. **Results:** Number/percent pts on CTs before/after NCCCP increased from 127 (5%) to 630 (23%), ($p<0.001$, Chi-square). All pts were rural Nebraskans, with 70% older than age 60. Number of available CTs increased four-fold with more prevention, quality of life, supportive care, cancer care delivery, biospecimen and treatment type trials after NCCCP. Non-treatment/treatment type trials both increased from an average 3/yr to 12/yr and 8/yr to 28/yr respectively ($p=0.012$, Wilcoxon). Average accrual per clinical trial was 13.2 before and 15.8 after NCCCP ($p=0.5$, Wilcoxon). CT staffing increased from an average of 1.2 to 3.9 FTEs ($p=0.012$, Wilcoxon). Two nurse navigators/genetic counselors, one smoking cessation counselor/outreach project coordinator were hired. Collection/storage of tissue samples increased from 24 (19%) to 330 (52%), ($p<0.001$, Chi-square). Affiliation with NCI designated Eppley Cancer Institute enhanced linkage to NCI programs. **Conclusions:** Participation in NCCCP positively impacted CT related activities with enhanced access to expanded types of CTs and cancer care services. Our data demonstrate the feasibility of implementing an expanded spectrum of CTs and programs within the rural community setting.

| Year | Staff | # Trials | # Cases | # Accruals | % Accrual |
|---|---|---|---|---|---|
| **2002** | 1 | 5 | 503 | 14 | 3 |
| **2003** | 1 | 8 | 521 | 21 | 4 |
| **2004** | 1 | 8 | 454 | 23 | 5 |
| **2005** | 1 | 12 | 542 | 22 | 4 |
| **2006** | 2 | 16 | 515 | 47 | 9 |
| **2007** | 2 | 19 | 541 | 56 | 10 |
| **2008** | 3 | 38 | 540 | 103 | 19 |
| **2009** | 5 | 51 | 528 | 143 | 27 |
| **2010** | 5 | 51 | 548 | 132 | 24 |
| **2011** | 5 | 40 | 562 | 196 | 35 |

**6512 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

**The clinical trial assessment of infrastructure matrix tool (CT AIM) to improve the quality of research conduct in the community.** *Presenting Author: Eileen P. Dimond, National Cancer Institute, Rockville, MD*

**Background:** ASCO described minimum standards and exemplary attributes for CT sites to improve research quality (Zon et al *JCO* 2008, *JOP* 2011; Baer et al *JOP* 2010). Based on these attributes, the NCI Community Cancer Centers Program (NCCCP) developed and piloted the CT AIM Tool to facilitate research program improvements through self-assessment and benchmarking. The tool identified 9 attributes (see Table) each with 3 progressive levels for research sites to "score" their program from less (Level 1) to more (Level 3) exemplary CT infrastructure (e.g. Level 1- only phase 3 treatment trials open vs. Level 3 – Phase 1/2/3, cancer control and prevention trials open). **Methods:** From 2011-13, 21 NCCCP sites self assessed their CT programs annually using the tool. **Results:** See Table. **Conclusions:** Statistically significant increases ($p<0.0001$) occurred in Level 3 (more exemplary) infrastructure ratings from 2011 to 2013 across all 9 attribute categories assessed at the 21 sites. Statistically significant gains were seen in two attributes: CT Portfolio – increases in site early phase and cancer control trial implementation; CT Communication /Awareness - shifts observed from institutionally focused CT education to broader community outreach/engagement. The tool showed utility across the sites for promoting quality improvement, benchmarking research performance, progress reporting and providing metrics for communicating infrastructure needs. Use in research beyond oncology and outside the community setting is plausible. NCI Contract HHSN261200800001E.

| Attribute and year | Level (1-3) and No. of sites (n=21) | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| **CT communication/awareness* p 0.0281** | | | |
| 2011 | 6 | 11 | 4 |
| 2012 | 2 | 10 | 9 |
| 2013 | 1 | 10 | 10 |
| **Accrual** | | | |
| 2011 | 5 | 10 | 6 |
| 2012 | 4 | 6 | 11 |
| 2013 | 4 | 5 | 12 |
| **Education standards** | | | |
| 2011 | 3 | 12 | 6 |
| 2012 | 3 | 7 | 11 |
| 2013 | 3 | 5 | 13 |
| **Multidisc. involvement** | | | |
| 2011 | 2 | 8 | 11 |
| 2012 | 3 | 3 | 15 |
| 2013 | 2 | 4 | 15 |
| **Participation in CT process** | | | |
| 2011 | 1 | 11 | 9 |
| 2012 | 2 | 6 | 13 |
| 2013 | 2 | 6 | 13 |
| **Physician CT engagement** | | | |
| 2011 | 1 | 10 | 10 |
| 2012 | 1 | 5 | 15 |
| 2013 | 1 | 3 | 17 |
| **CT portfolio * p 0.0228** | | | |
| 2011 | 1 | 12 | 8 |
| 2012 | 1 | 6 | 14 |
| 2013 | 1 | 3 | 17 |
| **QA** | | | |
| 2011 | 4 | 11 | 6 |
| 2012 | 3 | 8 | 10 |
| 2013 | 3 | 4 | 14 |
| **Community outreach/underserved accrual** | | | |
| 2011 | 8 | 6 | 7 |
| 2012 | 6 | 6 | 9 |
| 2013 | 4 | 7 | 10 |
| **Level 3 scores for ALL attribute categories from 2011 to 2013* p < 0.0001** | | | |
| | 67 | 107 | 121 |

* Significant p value for change over time.

### 6513 Poster Highlights Session (Board #1), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM

**Impact of duration of adjuvant therapy (AT) on cancer survival.** *Presenting Author: Aalok Kumar, British Columbia Cancer Agency, Vancouver, BC, Canada*

**Background:** Trials demonstrate that patients (pts) with specific cancers who complete AT experience better outcomes than those who do not. However, the magnitude of benefit in pts who discontinue AT early is poorly defined. Using a population-based cohort of stage III colon cancer (CC) pts, our aims were to (1) examine the rate of receiving all planned AT, (2) determine the factors associated with AT completion, and (3) explore the relationship between early AT discontinuation and survival. **Methods:** We analyzed pts diagnosed with stage III CC from 2006 to 2010 and initiated at least 1 cycle of adjuvant FOLFOX at any 1 of 5 regional cancer centers in British Columbia. Logistic regression models were constructed to determine the factors associated with AT completion, which was defined as receipt of >/= 10 cycles of FOLFOX. Kaplan-Meier methods and Cox regression that accounted for prognostic factors were used to evaluate the relationship between early AT discontinuation and disease-free (DFS) and overall survival (OS). **Results:** We identified 616 patients: median age 62 years (range 26-80), 52% men, 87% T3/4 tumors, and 40% N2 disease. Among them, 183 (30%) received < 10 and 433 (70%) underwent >/= 10 cycles. Adjusting for confounders, men and those with obstruction/perforation were more likely to discontinue AT early (OR for AT completion 0.62, 95%CI 0.43-0.89, p=0.01 and 0.55, 95%CI 0.33-0.92, p=0.02, respectively). In terms of survival, T3/4 stage, N2 disease and long post-operative recovery of >/= 1 week were correlated with worse DFS, while T4 stage and N2 disease were also associated with inferior OS. However, early discontinuation of AT did not impact DFS and OS (Table). Sensitivity analyses using different definitions for AT completion produced similar findings. **Conclusions:** Early discontinuation of adjuvant FOLFOX was not associated with significant survival differences, lending support to trials that are underway evaluating the utility of shorter durations of AT.

| | DFS | | OS | |
|---|---|---|---|---|
| | HR | p | HR | p |
| >/=10 cycles | 1.0 | .40 | 1.0 | .76 |
| <10 cycles | 1.15 | | 1.07 | |
| No obstruction/perforation | 1.0 | <.001 | 1.0 | .13 |
| Obstruction/perforation | 1.95 | | 1.47 | |
| T1/2 | 1.0 | .02 | 1.0 | .09 |
| T3 | 2.31 | <.001 | 2.19 | .002 |
| T4 | 3.72 | | 4.44 | |
| N1 | 1.0 | <.001 | 1.0 | .002 |
| N2 | 1.95 | | 1.83 | |
| <7 days post-op stay | 1.0 | .049 | 1.0 | .49 |
| >/=7 days post-op stay | 1.47 | | 1.19 | |

### 6514 Poster Highlights Session (Board #2), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM

**Does routine symptom screening with the Edmonton Symptom Assessment System (ESAS) decrease emergency department visits in breast cancer patients undergoing adjuvant chemotherapy?** *Presenting Author: Lisa Catherine Barbera, Odette Cancer Centre, Toronto, ON, Canada*

**Background:** In 2007 the provincial cancer agency in Ontario, Canada initiated a wide scale program to screen for symptoms in the cancer population using the Edmonton Symptom Assessment Scale (ESAS). The purpose of this study is to evaluate the impact of screening with ESAS on emergency department (ED) visit rates in women with breast cancer receiving adjuvant chemotherapy (CT). **Methods:** This retrospective cohort study used linked administrative health care data from across the province of Ontario, Canada. The cohort included all women aged ≥18 who were diagnosed with stage I-III breast cancer between January 2007 and December 2009 and received adjuvant CT within 6 months of diagnosis. Using a recurrent event model to adjust for covariates, we examined the association of screening with ESAS at a clinic visit on the ED visit rate. **Results:** 8,359 women were included. Approximately one third were screened with ≥1 ESAS during their chemotherapy. The rate of ED visits was 35% lower among patients screened with ESAS compared to those not screened. For each additional ESAS assessment there was a 19% decreased rate of ED visits. **Conclusions:** Our results demonstrate that screening with ESAS is associated with decreased ED visits. To our knowledge this is the first report on the effectiveness of routinely documenting patient-reported symptoms on ED visits, in a real world setting. Adjusted model results showing relative rate (RR) of ED visits for exposure to ESAS during chemotherapy either as a dichotomous or continuous variable (also adjusted for region and number of clinic visits).

| | | Adjusted | | | | | |
|---|---|---|---|---|---|---|---|
| | | ESAS (Y/N) | | | ESAS (Continuous) | | |
| Variable | Value | RR | LCL | UCL | RR | LCL | UCL |
| Age | Continuous | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Income quintile | 1 | 1.04 | 0.97 | 1.11 | 1.04 | 0.97 | 1.11 |
| | 2 | 1.03 | 0.97 | 1.10 | 1.03 | 0.97 | 1.10 |
| | 3 | 1.04 | 0.97 | 1.10 | 1.04 | 0.97 | 1.10 |
| | 4 | 1.02 | 0.96 | 1.08 | 1.02 | 0.96 | 1.08 |
| | 5 | 1 | | 1 | | | |
| Charlson | 0 | 1 | | 1 | | | |
| | 1 | 1.04 | 0.97 | 1.11 | 1.04 | 0.97 | 1.12 |
| Stage | I | 1 | | | 1 | | |
| | II | 1.02 | 0.96 | 1.07 | 1.02 | 0.96 | 1.07 |
| | II | 1.06 | 0.99 | 1.13 | 1.05 | 0.99 | 1.13 |
| | Unknown | 1.12 | 1.01 | 1.24 | 1.12 | 1.01 | 1.23 |
| Docetaxol regimen | Yes | 1.41 | 1.32 | 1.51 | 1.40 | 1.31 | 1.50 |
| | No | | 1 | | 1 | | |
| ESAS exposure | Yes | 0.65 | 0.61 | 0.70 | - | - | - |
| | No continuous | - | - | - | 0.81 | 0.77 | 0.84 |

Abbreivations: LCL, lower confidence limit; UCL, upper confidence limit.

### 6515 Poster Highlights Session (Board #3), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM

**Can we accurately identify chemotherapy-related acute care visits in administrative data?** *Presenting Author: Monika K. Krzyzanowska, Division of Medical Oncology & Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada*

**Background:** Administrative data is increasingly being used to study treatment related complications that lead to acute care visits such as emergency department visits or hospitalizations (ED+H). We evaluated the accuracy of billing codes for identifying chemotherapy related acute care visits (CRVs) among women with breast cancer. **Methods:** We prospectively developed an algorithm to identify CRVs from administrative data in women receiving adjuvant chemotherapy for breast cancer in Ontario, Canada. Sensitivity (SN) and specificity (SP) were calculated for 3 scenarios: chemotherapy related ED visit, chemotherapy related H, and febrile neutropenia (FN) related visit using the chart as the gold standard. Since there is no specific billing code for FN, three different definitions of FN were considered: liberal (defined as fever or infection or neutropenia as main reason for visit), moderate (neutropenia as main reason for visit) or strict (fever or infection plus neutropenia). The population based cohort was generated by linking several health databases to identify women who had at least one ED+H during adjuvant chemotherapy for breast cancer between 2007-2009. The validation cohort consisted of 496 randomly selected cases from this cohort. **Results:** The population-based cohort consisted of 8,359 patients of whom 43.4% had at least one ED+H including 1496 women who had multiple visits resulting in 6293 unique ED+H. Of these, 73.1% were considered CRVs based on our algorithm. The algorithm performed well in identifying CRVs that included an H either from ED (SN 90%, SP 100%) or directly from home (SN 91%, SP 93%) but less well for ED visits that did not result in H (SN 65%, SP 80%). Depending on which FN algorithm was used, 4.8-24% of visits were considered FN related. The liberal FN algorithm had excellent SN regardless of whether the visit involved H (94-98%) but SP was moderate (64-80%). The strict FN algorithm had good SP (79-99%) but SN was highly variable (13-89%). The moderate FN algorithm provided the best tradeoff between SN (69-97%) and SP (83-98%). **Conclusions:** CRVs can be identified from administrative data with reasonable confidence, obviating the need for chart abstraction to evaluate chemotherapy related serious events.

### 6516 Poster Highlights Session (Board #4), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM

**Clinical outcomes of elderly patients receiving neoadjuvant chemoradiation for locally advanced rectal cancer.** *Presenting Author: Maria Jiang, University of Ottawa, Ottawa, ON, Canada*

**Background:** There are limited studies assessing the outcomes of elderly patients treated with neoadjuvant chemoradiation (nCRT) for locally advanced rectal cancer. Our aim was to assess the impact of age on clinical outcomes in a large multi-institutional database. **Methods:** Data from patients across Canada with locally advanced rectal cancer who received nCRT and had curative intent surgery from 2005 to 2012 were collected from Tom Baker Cancer Center, Cross Cancer Institute, BC Cancer Agency, Ottawa Hospital Cancer Centre and Dr. H. Bliss Murphy Cancer Centre. Age was analyzed as both a continuous and a dichotomous variable (<70 v ≥ 70 yrs) and correlated with time free of recurrence (TFR where death without recurrence is censored), disease free survival (DFS), and overall survival (OS). Multivariable analyses (MVA) controlled for sex, ECOG, circumferential resection margins, radiation dose, distance from anal verge, pre-treatment anemia, clinical stage, pathologic stage and completion of neoadjuvant chemotherapy. **Results:** A total of 1,172 patients were included with a mean age of 62 years (SE±0.33) and a mean follow-up of 3.8 yrs (SE±0.05). Among them, 295 (25%) patients were ≥ 70 years. Elderly patients were less likely to receive adjuvant chemotherapy (ACT) (57% v 77%, p<0.0001), oxaliplatin-based ACT (12% v 31%, p<0.0001). They were also less likely to complete neoadjuvant chemotherapy (76% v 86%, p<0.001) but more likely to be anemic at initiation of nCRT (42% v 31%, p=0.0004). In the MVA, elderly patients had improved TFR (HR 0.65, 95% CI 0.45 – 0.95, p = 0.02), similar DFS (HR 0.928, 95% CI 0.68 – 1.26, p = 0.63) and similar OS (HR 1.28, 95% CI 0.88 – 1.86, p =0.2) compared to younger patients. As a continuous variable, age was not significantly associated with TFR (HR 0.99, 95% CI 0.98 – 1.01, p = 0.47) or DFS (HR 1.00 95% CI 0.99 – 1.02, p =0.49). However, it was significantly associated with inferior OS (HR 1.02, 95% CI 1.00 – 1.03, p =0.04) in the MVA. **Conclusions:** Elderly patients (≥ 70 yrs) who receive nCRT followed by surgery appear to have similar cancer related outcomes compared to younger patients. Decisions regarding eligibility for nCRT and surgery should not be based on age alone.

**6517 Poster Highlights Session (Board #5), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Population-based analysis of treatment receipt in prostate cancer patients who initially pursued active surveillance (AS).** *Presenting Author: Nathan Christopher Sheets, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

**Background:** Active surveillance for early prostate cancer may reduce over-treatment based on publications of patients managed in clinical trials or at high volume academic centers. In these selected reports, up to 30% of AS patients receive treatment (prostatectomy, radiation, hormone therapy) within 3 years due to cancer progression or patient anxiety. However, no study has examined receipt of treatment in AS patients in the community. **Methods:** Patients diagnosed from 2004-7 in the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database with low or intermediate risk prostate cancer were included; claims were available through 2010. AS was defined as a repeat prostate biopsy between 2-24 months after diagnosis with no treatment prior to repeat biopsy. We report the proportion of AS patients who received treatment within 3 years. Logistic regression examined factors associated with treatment receipt. **Results:** 737 low-risk and 618 intermediate-risk prostate cancer patients were analyzed. At 3 years, 64% of low-risk and 76% of intermediate-risk patients received treatment (Table). On multivariate analysis, being married (odds ratio [OR]=1.45; 95% CI 1.1-1.9), later year of diagnosis (2007 vs 2004, OR=1.73; 95% CI 1.2-2.5) and intermediate risk disease (vs. low-risk, OR=2.0; 95% CI 1.5-2.5) were associated with increased odds of treatment. Older patients had lower odds of treatment (age 76-79 vs 66-69, OR=0.6; 95% CI 0.4-0.9). **Conclusions:** On a population level, two-thirds (low-risk) to three-fourths (intermediate-risk) of early prostate cancer patients who initially chose AS converted to treatment within 3 years. These rates are twice that of published studies from trials or academic centers. This information may be informative to patients and physicians in the treatment decision-making process. Studies are needed to discern the reasons for this high rate of treatment, potentially due to suboptimal patient selection for AS or anxiety.

**Treatment by 3 years in AS patients.**

| | Low risk N (%) | Intermediate risk N (%) |
|---|---|---|
| **Prostatectomy** | 61 (8) | 76 (12) |
| **External beam RT** | 174 (24) | 152 (25) |
| **Brachytherapy** | 219 (30) | 204 (33) |
| **Hormone** | 14 (2) | 39 (6) |
| **No treatment** | 269 (36) | 147 (24) |

**6518 Poster Highlights Session (Board #6), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Prolonged radiation duration in women with cervical cancer: A population-based analysis of associated factors and impact on survival.** *Presenting Author: Ana Isabel Tergas, Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, New York, NY*

**Background:** The National Comprehensive Cancer Network recommends that radiotherapy (RT) for treatment of locally advanced cervical cancer (LACC) finish within 8 weeks (wks). Although RT duration is a proposed national quality metric, there is little data supporting this in the era of concurrent chemotherapy. We examined factors associated with prolonged RT duration and its impact on survival in women with LACC treated with primary chemoradiation. **Methods:** Women reported in the National Cancer Database with stage IB2-IVA cervical cancer from 2003-2011 who received external beam RT, brachytherapy, and chemotherapy were analyzed. RT duration was modeled dichotomously (≤ or > 8 wks) and categorically (6-8, 9-10, >10 wks). Multivariable logistic regression was used to determine factors associated with prolonged RT duration (defined as >8 wks). Impact of RT duration on survival was examined using Kaplan-Meier analysis and Cox proportional hazards models. **Results:** Of the 7,209 women identified, 3,401 (47.1%) completed RT within 8 wks; 2,159 (29.9%) and 1,649 (22.9%) completed RT in 9-10 and >10 wks, respectively. Stage, race, insurance, comorbidity, diagnosis year, facility location, and neighborhood rurality/urbanicity were associated with prolonged RT on multivariable analysis. Black women (OR 1.22; 95% CI 1.07– 1.40), Medicaid recipients (OR 1.20; 95% CI 1.06 - 1.35), and rural residents (OR 1.84; 95% CI 1.24 - 2.73) were more likely to have prolonged RT. There was no survival difference for RT duration ≤8 vs. >8 wks. However, RT duration >10 wks was associated with inferior survival times (log rank p-value 0.002). Compared to those completing RT within 8 wks, adjusted hazard ratios for death for the 9-10 wks group and the >10 wks group were 0.90 (95% CI 0.78 – 1.03) and 1.1 (95% CI 0.95 - 1.26), respectively. **Conclusions:** Sociodemographic factors are important predictors of radiotherapy duration for cervical cancer. Impact of radiation duration on survival is marginal and only seen with duration >10 wks, bringing to question its use as a quality metric. Further research is needed to support the recommendation of radiation duration to not exceed 8 weeks in the era of concurrent chemoradiation.

**6519 Poster Highlights Session (Board #7), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**The toxicity gap: Do real-life patients get hospitalized more during chemotherapy compared to trial patients?** *Presenting Author: Rebecca Michelle Prince, Princess Margaret Hospital, Toronto, ON, Canada*

**Background:** Toxicity related hospitalizations during chemotherapy are poorly reported in the literature. We sought to compare "real world" versus clinical trial rates of hospitalizations among patients with metastatic non-small cell lung cancer (mNSCLC) receiving chemotherapy. We hypothesised that hospitalization rates in real life patients would be significantly higher. **Methods:** We conducted a systematic review of Medline and EMBASE (1946-June 2013) to identify articles reporting hospitalization rates during chemotherapy in patients with cancer. Both observational studies and clinical trials were eligible. This report focuses on patients with mNSCLC receiving palliative chemotherapy as data was available for this clinical scenario in both the observational and clinical trial setting, allowing comparison. Study results were abstracted using a standardised form. Summary statistics were used to describe results and the chi-square test used to compare hospitalization rates. **Results:** The search identified 64 articles (all published after 1987), of which 19 were clinical trials and 45 were observational ("real world") studies. Nine studies examined chemotherapy in mNSCLC - four observational studies and five randomised trials. The four observational studies included 7,456 patients; three included patients on any chemotherapy while the other focused on doublet regimens. Of the five randomised trials which included 3,556 patients, three treated patients with platinum doublets and two used single agent chemotherapy. The real life cohort was older (69.2 years vs. 62 years). The aggregate hospitalization rate among real life patients was significantly higher than among trial patients (57.5% vs. 14.8%, OR=7.7, 95% CI 6.9-8.5, p-value < 0.0001). Performance status and type of chemotherapy were associated with hospitalization during chemotherapy in clinical trials. The observational studies did not report risk factors for hospitalization. **Conclusions:** Clinical trials in mNSCLC consistently report lower rates of hospitalization than real life cohorts of patients undergoing similar therapies but very few clinical trials report this information.

**6520 Poster Highlights Session (Board #8), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Comparison of results between the first and updated reports of phase III clinical trials (RCTs).** *Presenting Author: Elena Elimova, MD Anderson Cancer Center, Houston, TX*

**Background:** Updated results of RCTs may differ from those initially reported due to the longer follow-up. The primary aim of the present study is to compare efficacy and toxicity of experimental anticancer agents between the first and updated published reports of RCTs. **Methods**: Reports of RCTs evaluating systemic therapies in lung, breast, and prostate cancer, which were published between 1990 and 2010 in *JAMA*, NEJM, JCO, *Annals of Oncology*, *Lancet*, and *Lancet Oncology* were eligible. Either first or updated report had to be published in one of these major journals. Hazard ratios (HRs) of the primary and secondary time-to event outcomes and the occurrence of adverse events (AEs) were compared between the first and the corresponding updated reports of the eligible RCTs. **Results:** We included 311 initial and 64 updated reports of RCTs into our analysis. Adjuvant and metastatic trials were equally likely to be updated for efficacy outcomes (56.3% vs 43.8%; p=0.38) and 28% of the updated reports had no update on AEs. Only 30% of the first and 27% of the updated reports used overall survival (OS) for the primary outcome. Definitions of primary, secondary or both outcomes were discordant between the first and updated report in 11.3% of RCTs. When comparing reports of RCTs with the concordant primary outcomes we found that the median hazard ratio (HR) of the primary endpoint increased from 0.75 to 0.83 in updated reports (p=0.003). However, decrease in this treatment effect occurred exclusively in the early setting trials (p<0.001). Both low- and high- grade AEs occurred significantly more often in the updated reports (p=0.01) (Table). **Conclusions**: Efficacy of anticancer agents in the first reports of RCTs for early lung, breast and prostate cancer is over-estimated. Over-estimated efficacy and under-reported toxicity of anticancer agents may lead to their overly enthusiastic prescribing in the every-day clinical practice.

**Comparison of effect size and toxicity between the first and updated reports.**

| | | Publication | | |
|---|---|---|---|---|
| **Median** | | **First** | **Updated** | **P value** |
| **HR by outcome** | Primary | 0.75 | 0.83 | 0.003 |
| | Secondary | 0.83 | 0.89 | 0.35 |
| **HR by setting (primary)** | Early | 0.74 | 0.84 | <0.001 |
| | Advanced | 0.77 | 0.81 | 0.975 |
| **AEs by grade (proportion)** | 1,2 | 25.6 | 27.8 | 0.012 |
| | 3,4 | 8.5 | 9.5 | 0.001 |

**6521 Poster Highlights Session (Board #9), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Impact of chemotherapy dose and schedule on progression and survival in metastatic breast cancer: A systematic review.** *Presenting Author: Marek S. Poniewierski, Duke University, Durham, NC*

**Background**: Metastatic breast cancer (MBC) is a responsive but heterogeneous disease with generally a poor prognosis. The clinical importance of chemotherapy dosing and schedule in this setting has been questioned. **Methods**: A systematic review of randomized control trials (RCTs) of chemotherapy in MBC was conducted via searching PubMed (1990-2013) and meetings abstracts (2010-2012). RCTs comparing regimens that utilized the same agents or those studying impact of addition of agents were eligible. Relative risks of progression and mortality were based on event rates at 6, 12, 24 months. Heterogeneity was assessed by inconsistency index $I^2$. Meta-analyses were based on fixed effects models. **Results**: Among 2626 studies identified, 70 eligible RCTs involving 15,181 patients were analyzed. Average median time to progression and overall survival were 7.5 and 19.8 months, respectively. RCTs were divided into four a priori defined groups based on trial design: higher vs lower dose intensity (DI) (n=30), addition of ≥1 agents (n=26), continuation of treatment vs observation (n=7), and sequential (A→B) vs concurrent (AB) schedule (n=7). More intense regimens were associated with reduced progression at 6 and, to a lesser extent, 12 months, as well as reduced mortality at 1 year with the greatest effect in the added drug group. At 2 years, a trend for reduced mortality was observed with the greatest reduction in sequentially treated patients (Table). **Conclusions:** Chemotherapy can be an effective treatment for MBC with results suggesting better efficacy with higher DI and multidrug regimens, with stronger early effects diminishing by 2 years. The question of optimal treatment in MBC requires additional studies.

**Relative risk and 95% confidence interval.**

| Groups | Progression 6 months | Progression 1 year | Mortality 1 year | Mortality 2 years |
|---|---|---|---|---|
| Higher vs lower DI | 0.89 (0.84-0.94) | 0.97 (0.94-1.00) | 0.94 (0.87-1.01) | 0.96 (0.92-1.01) |
| Continued tx. vs observation | 0.68 (0.61-0.76) | 0.89 (0.85-0.94) | 0.91 (0.77-1.08) | 0.93 (0.85-1.01) |
| More vs fewer agents | 0.74 (0.70-0.78) | 0.91 (0.88-0.93) | 0.86 (0.81-0.92) | 0.97 (0.94-1.01) |
| Sequential vs concurrent | 1.00 (0.85-1.19) | 0.98 (0.92-1.06) | 0.96 (0.77-1.20) | 0.88 (0.79-0.98) |

**6522 Poster Highlights Session (Board #10), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Adoption of hypofractionated radiotherapy for early-stage invasive breast cancer after publication of randomized trials.** *Presenting Author: Ronald C. Chen, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

**Background:** Large randomized trials have established the non-inferiority of shorter courses of "hypofractionated" radiotherapy to the whole breast (HyRT) vs conventional courses using smaller daily doses (CRT). HyRT is more convenient and less costly, so we sought to document its uptake as randomized trial evidence accumulated. **Methods:** In SEER-Medicare, we identified 15,781 women with pT1-2, node negative breast cancer who received lumpectomy followed by external beam RT from 2004-10. Number of RT treatments was obtained from Medicare claims, and grouped into partial breast RT (PBI, ≤12 treatments), HyRT (13-24), or CRT (≥25). We evaluated patterns and correlates of HyRT receipt on bivariable and multivariable analyses. **Results:** HyRT steadily increased after 2006 (3.6%): 5.3% (2007), 9.3% (2008), 13.7% (2009-10), with corresponding decrease in CRT from 92.6% to 83.5%. HyRT was more common in older women in all T-stage subgroups (4.0-5.9% for age 66-69 vs 6.0-8.2% age 76-79 vs 11.6-13.3% for age 80+). Multivariable analysis showed increased HyRT in recent years; in patients with older age, smaller tumors (T1a-b), increased comorbidity; and in regions with higher educational levels (Table). **Conclusions:** HyRT use increased in a low-risk population-based sample of older US women with publication of randomized trials, but overall use (13.7%) of this cost-saving approach remained low.

**Logistic regression for receipt of HyRT (vs. CRT; PBI excluded).**

| | OR (95% CI) | p-value |
|---|---|---|
| **RT year (REF=2004)*** | | |
| 2005 | 1.0 (.7-1.4) | .98 |
| 2006 | 1.0 (.7-1.4) | .96 |
| 2007 | 1.5 (1.1-2.0) | <.01 |
| 2008 | 2.8 (2.2-3.7) | <.01 |
| 2009-10 | 4.4 (3.4-5.6) | <.01 |
| **Age (yrs) (REF=66-69)** | | |
| 70-75 | 1.1 (.9-1.3) | .47 |
| 76-79 | 1.5 (1.2-1.9) | <.01 |
| 80+ | 2.8 (2.4-3.4) | <.01 |
| **Path stage (REF=T1a-b)** | | |
| T1c | .91 (.8-1.0) | .18 |
| T2 | .77 (.63-.93) | <.01 |
| **Tumor grade (REF=1-2)** | | |
| 3 | 1.1 (.96-1.3) | .16 |
| **Laterality (REF=right)** | | |
| Left | 1.0 (.88-1.1) | .97 |
| **NCI comorbidity (REF=0)** | | |
| >0 | 1.2 (1.1-1.4) | <.01 |
| **Regional education quartile (REF=Q1)** | | |
| Q2 | .74 (.61-.90) | .<.01 |
| Q3 | .76 (.61-.94) | .01 |
| Q4 (worst) | .58 (.45-.75) | <.01 |

Covariates: race (ns), urban/rural (ns), marital status, SEER region. *Canadian trial published 5-yr results in 2002 & long-term results in 2010; UK START trials published 2008.

**6523 Poster Highlights Session (Board #11), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**A randomized, controlled study comparing NCI's original and revised informed consent templates.** *Presenting Author: Holly A Massett, National Cancer Institute, Rockville, MD*

**Background:** In 1997, the National Cancer Institute (NCI) began using a standardized template to develop Informed Consent Documents (ICD) for its clinical trials. NCI recently revised the template based on expert input from five working groups to reduce its complexity and length. We report findings from a study comparing the application of the original and the revised, concise template to a Phase 3 colon cancer treatment trial. **Methods:** Two ICDs for the same trial were compared using a randomized, controlled design. Participants were randomly assigned to Group 1 (the control) which reviewed the original ICD (O-ICD) or Group 2, which reviewed the concise ICD (C-ICD). We hypothesized that viewing the C-ICD would result in higher knowledge and satisfaction scores than viewing the O-ICD. Participants' likelihood to consider a clinical trial (CT) after seeing the ICD was assessed. Participants were adult colorectal cancer survivors who completed treatment in the past 10 years and had never taken part in a CT. Pre- and post-test responses were collected via an online survey. **Results:** The groups (O-ICD, N=72; C-ICD, N=81) did not differ on age, gender, education, income or prior CT knowledge. No group differences were found on number of knowledge items correct (O-ICD: avg=20.3/24 total; C-ICD: avg=21/24; p=.20) or satisfaction (O-ICD: avg=4.23/5.0; C-ICD: avg=4.16/5; p=.23 [1 low; 5 high]). Higher education predicted greater number correct (p=.04). Less education and more prior CT knowledge predicted higher satisfaction with the ICDs (p=.01). All respondents reported lower intentions to participate in a CT after viewing the ICDs. **Conclusions:** The C-ICD's format applied plain language principles and was shorter by two pages (11 vs. 13 pgs for O-ICD). Although the C-ICD did not prove superior, it maintained high knowledge and satisfaction scores similar to the O-ICD. This study allowed unlimited time to read the ICDs and did not carry the same emotional implication as an actual CT situation where brevity may have greater impact. Finally, education about CTs appears beneficial as those reporting prior CT knowledge had significantly increased satisfaction scores and were more likely to consider a clinical trial in the future.

**6524 Poster Highlights Session (Board #12), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**The use of health-related quality of life outcomes in oncology practice: An international study.** *Presenting Author: Julie Rouette, Queen's University, Kingston, ON, Canada*

**Background:** Although health-related quality of life (HRQL) outcomes are often reported in randomized controlled trials (RCTs), research has identified challenges to their clinical application. The current perspectives of experienced oncologists on the use of HRQL outcomes, and how these perspectives vary between countries and specialties, are unknown. **Methods:** A cross-sectional e-survey of oncologist members of the NCIC Clinical Trials Group in Canada, the UK National Cancer Research Institute Clinical Studies Groups, and the network of the Australia/NZ cancer clinical trials groups was conducted. Respondents reported their perceptions of the usefulness of HRQL outcomes, use of HRQL outcomes in clinical practice, barriers/facilitators to their use in practice, and preferences for presentation of HRQL data in RCT publications. Chi-square tests were used to compare responses between countries and specialties. **Results:** Of the 396 participating oncologists (est. r. rate: 31%), 53% were medical oncologists in Canada and the UK and 61% were radiation oncologists in Australia. HRQL outcomes were reported to be useful in all types of trials (range 76-97%), particularly non-inferiority (89%) and palliative (97%) trials. More than 50% of oncologists reported not using HRQL outcomes with the majority of their patients to guide clinical decisions. Perceived barriers were lack of time (67%) and understanding (57%), and concerns about generalizability of results (68%). Identified facilitators included a summary of clinical implications of the HRQL results in RCT publications (76%), clear description of missing data (86%) and joint publication of HRQL and clinical outcomes (96%). Use of HRQL outcomes in practice, perceived barriers/facilitators, and presentation preferences did not differ by country or specialty. **Conclusions:** Oncologists support HRQL outcomes but perceive important barriers to their use in clinical practice, regardless of their country or specialty. Publishing HRQL and clinical outcomes jointly or simultaneously in the same journal, a clear description of missing data, and a clear summary of the clinical implications of the HRQL results, may facilitate the clinical application of HRQL outcomes.

**6525 Poster Highlights Session (Board #14), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Are new drugs more expensive than old ones? Trends in the benefit-adjusted launch prices of anticancer drugs, 1995-2013.** *Presenting Author: David H. Howard, Emory University Department of Health Policy and Management, Atlanta, GA*

**Background:** Media reports have fueled the perception that anticancer drugs' launch prices have increased over time, but these typically rely on inaccurate measures of prices, focus on a few high-profile drugs, and do not adjust for benefits. We evaluate trends in drugs' benefit-adjusted launch prices. **Methods:** We hand-collected data on 56 anticancer drugs newly approved between 1995 and 2013. We measured launch prices using Medicare reimbursement formulae for oral and IV drugs. Prices represent the cost of a course of therapy for the typical patient. We obtained information on survival benefits from phase III trials and modeling studies. We evaluated the relationship between drugs' prices, survival benefits, and approval year. We adjusted prices for inflation using the Consumer Price Index. **Results:** We find that there have been economically and statistically significant increases in launch prices over time. The price of an additional month of survival time increased by $600 per year (95% CI: $100-$1,100; p = 0.02). Our model predicts that the launch price of a drug that extends median survival by 5 months would be $37,000 in 1995. If the same drug were launched in 2010, the price would have been $84,000. Results are robust to the inclusion of controls for side effect rates, administration route, and other drug attributes. **Conclusions:** Our results confirm what many suspect: newer anticancer drugs are more expensive than older agents. We explain pricing trends using "reference price" models of demand. Physicians are reluctant to prescribe drugs with prices they perceive as unreasonable. However, perceptions of reasonableness are malleable and influenced by the prices of previously-approved drugs, giving manufacturers leeway to increase launch prices over time.

**6526 Poster Highlights Session (Board #15), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Cost-utility analysis of routine surveillance imaging of patients in first remission after treatment for diffuse large B-cell lymphoma.** *Presenting Author: Scott F. Huntington, Division of Hematology/Oncology, University of Pennsylvania, Philadelphia, PA*

**Background:** Surveillance imaging of patients (pts) with DLBCL in first remission (CR1) remains controversial. NCCN guidelines recommend CT scans in asymptomatic pts no more often than every 6 months for 2 years post treatment. A decision-analytic Markov model was developed to evaluate follow up (f/u) strategies for pts in CR1 after rituximab-containing treatment. **Methods:** Three strategies were compared in 55 year old pt cohorts: standard f/u without routine imaging, routine f/u with biannual CT scans for 2 years, or routine f/u with biannual PET/CT for 2 years. Our transition state model used 6 month length cycles with transition probabilities and clinical utilities derived from published studies. Costs were based on the Medicare fee schedule and future cost/benefits were discounted at a rate of 3% annually. The baseline model was biased to favor imaging strategies by associating asymptomatic imaging-detected relapses with improved clinical outcome. Quality-adjusted utility, lifetime costs, and incremental cost-effectiveness ratios (ICERs) were calculated for each f/u strategy. Conclusions were tested by multi-way sensitivity analyses that varied the rate of asymptomatic relapse detection, likelihood of favorable International Prognostic Index (IPI) with asymptomatic relapse, and the impact of IPI on salvage therapy outcome. **Results:** Surveillance strategies utilizing 2 years of routine CT or PET/CT scans were associated with minimal survival benefit versus f/u without routine imaging (mean OS, routine: 261.6 mos, CT: 261.8 mos, PET/CT: 262.1 mos). The benefit of imaging-based f/u remained small after quality-of-life adjustments (CT: 0.017 QALY, PET/CT: 0.023 QALY). Costs associated with imaging based surveillance strategies are considerable and ICERs were $202,300/QALY and $312,600/QALY for CT and PET/CT strategies respectively. ICERs for imaging strategies remained >$100,000/QALY or were dominated by routine f/u in multi-way sensitivity analyses over clinically relevant ranges. **Conclusions:** Our analysis suggests surveillance imaging of asymptomatic pts in CR1 following treatment for DLBCL offers little clinical benefit at substantial economic cost.

**6527 Poster Highlights Session (Board #16), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Cost-effectiveness analysis of pharmacokinetic-guided (PK) 5-fluorouracil (5FU) when combined with leucovorin and oxaliplatin (FOLFOX) chemotherapy for metastatic colorectal cancer (mCRC).** *Presenting Author: Daniel A. Goldstein, Winship Cancer Institute of Emory University, Atlanta, GA*

**Background:** Dosing chemotherapy based on body surface area (BSA) results in marked variability in inter-individual drug exposure. An immunoassay for 5FU has been developed that assists in PK-guided dose adjustments. A randomized trial showed increased overall survival (OS) and decreased toxicity with PK 5FU/Leucovorin compared to BSA 5FU/Leucovorin in patients with mCRC. Similar results were achieved in a non-randomized trial comparing PK FOLFOX with BSA FOLFOX. The objective of this study is to compare the cost effectiveness of PK FOLFOX with BSA FOLFOX in patients with mCRC. **Methods:** We developed a Markov model to evaluate the cost-effectiveness of PK FOLFOX compared with BSA FOLFOX. Published progression-free survival (PFS) and OS curves were fitted with Weibull models. Progression risks and cause-specific mortality were extrapolated from the fitted survival models. Costs for administration and management of adverse events were estimated based on Medicare reimbursement rates for hospital and physician services, and drug costs based on the Medicare average sale prices, (all in 2013 US $). Primary outcomes were incremental cost per quality adjusted life-year (QALY) gained. We performed univariate and probabilistic sensitivity analyses (PSA) to address parameter uncertainties. **Results:** PK FOLFOX provided 2.03 QALYs at a cost of $50,205 compared to BSA FOLFOX with 1.46 QALYs at a cost of $37,173. The incremental cost per QALY was $22,694/QALY. In all one-way and 99.7% of PSA, the incremental cost-effectiveness ratio of PK remained below $50,000/QALY. **Conclusions:** At a $50,000/QALY threshold, PK FOLFOX is cost-effective for mCRC. The main cost driver was the PK test ($400) that was used for 4 cycles to establish the optimal dose. The main driver of benefit was improved PFS and OS. Given the cost-effectiveness profile and OS advantage with PK FOLFOX, it should be evaluated further in comparative effectiveness studies.

**6528 Poster Highlights Session (Board #17), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Comparative health care (HC) costs and quality of care in five cancer types by physician office (PO) and hospital outpatient (HOP) settings.** *Presenting Author: Maxine Fisher, HealthCore, Inc., Wilmington, DE*

**Background:** This study compares HC costs, resource utilization (RU), and select quality of care measures in cancer pts receiving treatment (tx) in PO or HOP. **Methods:** This retrospective study used medical & pharmacy claims (1/2006 - 8/2012) from 14 US health plans to identify early breast cancer (eBC), metastatic BC (mBC), metastatic lung cancer (mLC), metastatic colorectal cancer (mCRC), and non-Hodgkin's lymphoma (NHL) or chronic lymphocytic leukemia (CLL) pts initiating IV chemotherapy (ctx) or biologic tx. Death date was confirmed by Social Security Administration Death Master File (SSDI). RU, quality measures of ctx and hospitalization 30 days prior to death & GCSF use were compared using T-test or chi-square test. Multivariate analyses assessed differences in mean annual HC costs. **Results:** 18,740 pts were identified (69% PO vs. 41% HOP) with mean age 51.6 yrs, Deyo-Charlson score of 5.37, and follow-up of 2.2 yrs. PO had higher mean outpatient visits (21.8 PO vs. 21.2 HOP), other outpatient services (50.8 PO vs. 48.5 HOP), and pharmacy claims (35.1 PO vs. 33.6 HOP), but lower inpatient hospitalizations (0.7 PO vs. 0.8 HOP) and ER visits (0.3 PO vs. 0.4 HOP) [p<0.001]. Proportion of pts using GCSF was significantly lower in HOP (PO 73.3% vs 57.2% HOP, p<0.001). There were no differences in ctx or hospitalizations 30 days prior to death. Mean (median) annual HC cost in HOP was higher than PO ($122,473 [$123,075] vs. $82,773 [82,424] p<0.001). In multivariate analyses, mean annual cost was 8.3% higher in HOP (95% CI: 6.3-10.3%) **Conclusions:** Pts receiving care in PO were associated with lower HC costs than HOP. Chart review and pt satisfaction studies are ongoing to further characterize the care received in PO and HOP settings.

| | | PO (N=12,899) | | | HOP (N=5,841) | | |
|---|---|---|---|---|---|---|---|
| Cancer type | N (%) | Mean | S.D | Median | Mean | S.D | Median |
| eBC* | 8896 (47.5%) | $54,092 | $45,789 | $40,691 | $81,352 | $76,929 | $58,070 |
| mBC* | 4145 (22.1%) | $93,725 | $72,560 | $76,119 | $119,211 | $103,118 | $90,061 |
| mLC* | 1890 (10.1%) | $143,290 | $94,335 | $126,453 | $196,288 | $154,921 | $166,281 |
| mCRC* | 1581 (8.4%) | $166,950 | $104,804 | $152,644 | $238,095 | $162,490 | $216,686 |
| NHL/CLL* | 2228 (11.9%) | $76,148 | $113,660 | $50,864 | $123,773 | $144,962 | $75,974 |

*Statistically significant at p-value=0.01.

**6529 Poster Highlights Session (Board #18), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Association between CT utilization and radiation therapy at the end of life (EOL) in elderly breast and prostate cancer patients.** *Presenting Author: Michaela Ann Dinan, Duke Clinical Research Institute, Durham, NC*

**Background:** High cost imaging can inform prognosis for cancer patients and potentially de-escalate unnecessary treatment at the EOL, but it may also be associated with increased health care expenditures. We investigated the association between hospital referral region (HRR)-level utilization of CT imaging and radiation therapy at the EOL. **Methods:** Retrospective, patient-level analysis of SEER-Medicare patients who died from breast and prostate cancer between 2002 and 2007. HRR-level utilization of CT scans was categorized into tertiles for each cancer type. HRRs were assigned where patients received the majority of inpatient care during the last 6 months of life. Multivariable logistic regression models were constructed to correlate tertile of imaging use with receipt, type, and overall cost of radiation therapy. **Results:** A total of 5,980 breast and 7,538 prostate cancer patients met study criteria, of which 22.2% and 28.3% received radiation therapy in the last year of life and 3.6% and 4.4% received radiation therapy in the last 30 days, respectively. The average number of CT scans in the last 6 months of life per patient varied by HRR from 0.79 to 1.74 scans for breast and 0.80 to 1.70 for prostate cancer. Treatment within a high vs. low CT utilizing HRR for either cancer type was not associated with increased use of radiotherapy in the last year or 30 days of life. Patients undergoing radiotherapy within high CT utilizing HRRs were more likely to undergo intensity modulated radiotherapy (breast; 4% vs. < 1%; prostate 5.5% vs. 3.8%, both $\chi^2$ $P < 0.05$). Mean costs of direct radiation therapy among patients undergoing radiotherapy in the last year of life were similar across HRR imaging tertiles, and averaged $5,009 in breast and $4,501 in prostate cancer patients. In contrast, overall costs were higher in both breast ($48,705 vs. $32,438) and prostate ($46,283 vs. $32,411) cancer patients in high vs. low CT utilizing HRRs (both $P<$ 0.001). **Conclusions:** Treatment within a high CT utilizing HRR for EOL patients with breast or prostate cancer was not associated with increased utilization or costs of radiation therapy at the EOL, but was associated with significantly higher overall medical expenditures.

**6530 Poster Highlights Session (Board #19), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Patient demand for care: How much does this contribute to inappropriate tests and treatments?** *Presenting Author: Keerthi Gogineni, Hospital of the University of Pennsylvania, Philadelphia, PA*

**Background:** There are many calls for physicians to provide more cost-effective care. Physicians sometimes claim that patients demand high cost or low value tests and treatments. How frequently do patients demand medical services? **Methods:** We surveyed oncologists and nurse practioners immediately after patient encounters to determine the frequency of patient requests or demands for tests and treatments, whether the request was appropriate, whether it was granted, and why. **Results:** Of the 2050 encounters, 73.1% of patients were white with a mean age of 60. Overall 42.0% had Stage IV or refractory disease and 66.3% were undergoing active treatment; 49.5% with palliative intent. Of the 26 clinicians surveyed, 97.0% were white, 54% were female and had a median of 14 years of post-training experience. In the table below, we report the key results of this survey. Providers declined granting a patient's request 18.1% (32/177) of the time; in 84.4% (27/32) of these cases this was because the test or treatment was felt to be inappropriate or had no evidence for clinical benefit. In less than 1% of encounters (4/2050) did the provider order a test or treatment deemed inappropriate. **Conclusions:** Inappropriate patient demands for tests or treatments are very uncommon among cancer patients and probably do not drive high utilization of high cost or low value medical services.

| Survey measure | Percentage |
|---|---|
| Patient encounters with requests or demands | 8.6% (177/2050) |
| Requests or demands were inappropriate based on clinician judgment | 13.6% (24/177) |
| Requests or demands were appropriate based on clinician judgment | 79.7% (141/177) |
| Clinician complied with patient request or demand | 81.9% (145/177) |
| Clinician ordered an inappropriate test or treatment based on patient demand | 0.2% (4/2050) |

**6531 Poster Highlights Session (Board #20), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Place of readmission and outcomes after major cancer surgery.** *Presenting Author: Karyn Beth Stitzenberg, Division of Surgical Oncology and Endocrine Surgery, University of North Carolina School of Medicine, Chapel Hill, NC*

**Background:** Readmission rates after major cancer surgery are high (20-45%). Many patients are readmitted to a hospital different than where surgery was performed. We hypothesize that readmission to a different hospital is associated with poorer outcomes and higher costs. **Methods:** We used SEER-Medicare to examine 2001-6 incident cases of bladder, esophagus, lung and pancreas cancer. Claims data were used to identify any hospital readmissions during the 90-days post-discharge from the surgical admission (index hospitalization). Pearson chi-square and multiple logistic regression were used for all tumor sites together and individually to compare location of readmission based on various patient and hospital factors. Cox proportional hazard models were constructed to examine the association between the location of readmission and survival. **Results:** Of the 24,412 patients who had surgery, 6,552 (27%) were readmitted at least once, and 2,133 (33%) were initially readmitted to a hospital other than the index hospital. There were no significant differences in demographics between patients readmitted to the index vs. different hospital. Patients who had surgery at the highest volume centers were the most likely to be readmitted to a different hospital ($p<.001$ for all). Patients readmitted to a different hospital lived farther from the index hospital than those readmitted to index hospital (median 24-33 vs. 6-11 miles, $p< .001$ for all). The association with volume persisted after accounting for distance. Patients readmitted to a different hospital were more likely to be transferred to another hospital (9-10% vs. 2-3%, $p<0.05$ for all). Total 90 day costs of care differed significantly only for esophagus cancer (index $69K vs. different hosp $62K, $p=0.005$). Survival was associated with location of readmission only for bladder cancer (index hosp HR=1.22; 95% CI=1.067-1.401). **Conclusions:** From a broad perspective, initial readmission to a hospital other than the index hospital after major cancer surgery is not associated with substantially poorer long-term survival or higher costs for Medicare patients. However, more detailed studies are needed to determine the impact on fragmentation of care and other patient-level outcomes.

**6532 Poster Highlights Session (Board #21), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Oral chemotherapy performance indicators: Early results from three rounds of Quality Oncology Practice Initiative (QOPI) data.** *Presenting Author: Jessica A. Zerillo, Beth Israel Deaconess Medical Center, Boston, MA*

**Background:** While use of oral chemotherapy is becoming more and more prevalent, little is known about the quality of care patients currently receive when these agents are prescribed. Moreover, few practice-level systems are in place to ensure safe utilization of oral chemotherapy. **Methods**: We analyzed results from 151 practices that voluntarily provided data to the American Society of Clinical Oncology's (ASCO's) QOPI program on 17 test measures of oral chemotherapy administration and management in at least one of three collection periods: spring or fall 2012, or spring 2013. The 17 test measures cover three domains—treatment plan documentation, patient education, and adherence/toxicity monitoring. We defined composite scores for each of the three domains. We analyzed the individual measures and composite scores by secular trend and tested the difference in composite scores for the three domains, excluding practices that had fewer than five charts for each analysis. Additionally, we tested change in scores over time among practices that participated at least twice. **Results**: The majority of data was provided by QOPI-certified practices. Overall, mean practice scores ranged from 66-68% for treatment plan documentation, 51-57% for patient education and 75-81% for adherence/toxicity monitoring ($p<.0001$ for all collection periods). Composite scores for practices that participated more than once did not improve significantly. **Conclusions**: The collection of oral chemotherapy test measures was feasible. Practices generally scored better on adherence/toxicity monitoring compared to plan documentation and patient education. Participation in subsequent rounds was not associated with an improvement in scores. These findings highlight opportunities for improvement in care for patients taking oral chemotherapy.

**Composite measures by collection round.**

| | Spring 2012 Mean (SD) | Fall 2012 Mean (SD) | Spring 2013 Mean (SD) | Trend P value |
|---|---|---|---|---|
| Plan documentation | 65.80 (19.95) | 65.85 (19.20) | 68.47 (18.36) | .3938 |
| Patient education | 50.63 (25.10) | 54.02 (26.52) | 56.64 (24.87) | .5237 |
| Adherence/toxicity monitoring | 75.16 (17.15) | 78.00 (14.09) | 81.07 (14.01) | .2015 |
| P value | <.0001 | <.0001 | <.0001 | |

**6533 Poster Highlights Session (Board #22), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Decisions about cancer treatment: Matching of actual to preferred roles and patient ratings of care.** *Presenting Author: Kenneth L. Kehl, Brigham and Women's Hospital, Boston, MA*

**Background:** Shared decision-making in cancer treatment is an important aspect of high-quality care and is associated with improved outcomes. However, patients have different preferences regarding roles they want to play in treatment decisions. We assessed the association of patients' actual roles in decisions with ratings of their care and whether this association varied by preferred decision roles. **Methods:** In the Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) cohort, a population- and health system-based study of lung and colorectal cancer patients, participants were surveyed about their preferred roles in treatment decisions and their actual roles in decisions about surgery, chemotherapy, and radiation. Among patients receiving treatments under consideration, we used logistic regression to assess associations between actual roles in decisions and patient-reported care quality, both overall and stratified by preferred roles, adjusting for clinical and demographic traits. **Results:** Among 8,191 decisions made by 5,170 patients treated with surgery, chemotherapy, and/or radiation, patients described 39.8% of decisions as patient-controlled, 47.1% as shared, and 13.1% as physician-controlled. Patients making these decisions more often reported preferring a shared role (58.5%) or a patient-controlled role (35.5%) than a physician-controlled decision role (6.0%). Overall, patients described excellent quality for 67.8% of treatments received. In adjusted analyses, patients reporting physician-controlled decisions were less likely to report excellent quality for each treatment than those reporting a shared role (OR 0.6, 95% CI 0.5-0.7). This association was similar regardless of preferred role (p for interaction=0.29). **Conclusions:** More active participation in treatment decisions for lung or colorectal cancer was associated with better reported care quality among patients receiving treatments under consideration. This effect did not vary by patients' preferred roles in treatment decisions. These findings underscore the importance of a shared approach to decision-making for all patients, even those who might prefer that physicians make final treatment decisions.

**6534 Poster Highlights Session (Board #23), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Medicare Part D low-income subsidy and disparities in breast cancer treatment.** *Presenting Author: Alana Biggers, Medical College of Wisconsin, Milwaukee, WI*

**Background:** Breast cancer outcomes are worse among black than white women, but the role of income and out-of-pocket costs (OOPCs) in these disparities is understudied. The Medicare D program provided medication insurance for older women and also included a low-income subsidy (LIS) which eliminated or reduced OOPCs among women with low assets and limited income (based on federal poverty level). We examined differences in adherence to HT by race/ethnicity among a Medicare D population, hypothesizing that LIS might reduce racial disparities in HT adherence. **Methods:** With data collected from a national sample of women enrolled in Medicare Parts A, B and D, we identified Medicare Part D enrollees ≥65 years diagnosed with breast cancer who underwent mastectomy or breast conserving surgery in 2006-07 and received either tamoxifen or an AI (anastrozole, letrozole, or exemestane) within one year of surgery. Non-adherence rates (medication possession rate of >0.80) were calculated by race and LIS status for each year after first fill up through December 2011. The association of race with HT adherence was examined in unadjusted Chi-square analyses and in regression models adjusted for age, comorbidity, chemotherapy use and zip code level- income and education. All models utilized GEE to account for within-patient clustering. **Results:** Among a sample of 23,299 women (50.6% age 65-74, 40.9% age 75-84), 27.2% received LIS. LIS (but not AI use) varied substantially by race, so that 20.6% of white women and 69.7% of black women received the subsidy. In the first year of therapy, differences in adherence by race were statistically significant, but small (79.3% for white, 78.1% for black and 80.9% for Hispanic). Adherence dropped during years 2-3 of the study, but reductions were much smaller among LIS recipients. Results were confirmed in adjusted models. **Conclusions:** Enrollment in the Medicare D LIS was high among black and Hispanic breast cancer patients, and disparities in adherence to breast cancer HT among these women were small and remained so over three years. Our study offers important information about the role of medication subsidies and SES in adherence, and suggests their potential to reduce the breast cancer outcomes gap by race.

**6535 Poster Highlights Session (Board #24), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Variation in hospital thromboprophylaxis rates for abdominal cancer surgery.** *Presenting Author: Robert Wallace Krell, University of Michigan, Ann Arbor, MI*

**Background:** Venous thromboembolism (VTE) remains a prominent cause of morbidity and mortality following cancer surgery. Though ASCO evidence-based guidelines recommend major cancer surgery thromboprophylaxis start before incision and continue at least 7-10 days postoperatively, the extent to which the guidelines are followed is unknown. We assessed variation in thromboprophylaxis practices for abdominal cancer surgery in a regional surgical collaborative. **Methods:** We studied abdominal resections for primary gastrointestinal, hepatopancreaticobiliary (HPB) and neuroendocrine malignancies in the Michigan Surgical Quality Collaborative from July 2012-Sep 2013 (N=1,444 patients in 52 hospitals). We obtained detailed perioperative and postoperative pharmacologic and mechanical thromboprophylaxis information for patients without documented exemptions (e.g. active bleeding, allergy). We then compared differences in procedure mix and operative complexity across hospitals based on their perioperative thromboprophylaxis rates. **Results:** Overall, 43.1% of eligible patients had perioperative pharmacologic thromboprophylaxis for abdominal cancer surgery, and 25.3% (318/1258) of the highest-risk patients had evidence of inadequate postoperative prophylaxis (under-prophylaxis either by dose or duration). Hospital perioperative thromboprophylaxis rates ranged from 0%-96.1%, and postoperative thromboprophylaxis rates ranged from 73.9%-100%. Compared to hospitals with the lowest perioperative thromboprophylaxis rates, hospitals with the highest perioperative prophylaxis rates performed more HPB procedures (24.1% vs. 5.3%) and fewer concomitant operative procedures (31.1% vs. 44.7%). Epidural use did not impact hospital pharmacologic thromboprophylaxis rates. **Conclusions:** Fewer than half of patients undergoing abdominal cancer surgery receive perioperative thromboprophylaxis, and there is wide variation in hospital thromboprophylaxis utilization despite strong evidence-based guidelines supporting its use. Identifying reasons for non-adherence to published guidelines and best practices will be important to improve outcomes in this vulnerable patient population.

**6536 Poster Highlights Session (Board #25), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Sustaining quality cancer care in the NCI Community Cancer Centers Program (NCCCP).** *Presenting Author: Kathleen M. Castro, National Cancer Institute of the National Institutes of Health, Rockville, MD*

**Background:** In 2007, the NCCCP pilot program launched with 16 sites and a goal to improve quality of care, reduce cancer disparities and increase participation in clinical trials. In 2008, NCCCP began to participate in the Commission on Cancer Rapid Quality Reporting System (RQRS). An evaluation of NCCCP in 2010 assessed changes in cancer care quality among the sites before vs. after program implementation compared to non-NCCCP hospitals during the same time period (Halpern et al. 2013). Our current analysis examines if improvements in quality were sustained. **Methods:** Conducted a retrospective analysis of patients diagnosed and receiving all or part of their initial cancer treatment at an NCCCP facility. Compared concordance rates for 6 NQF- approved quality of care measures (3 breast, 2 colon and 1 rectal) for patients diagnosed between 2006-2007 (pre-NCCCP), 2008-2010 (early NCCCP) and 2011-2013 (later NCCCP). **Results:** The sample included 17,288 breast, 6,655 colon and 569 rectal cancer patients. Patient-level concordance rates improved significantly for all 6 measures and were sustained for 5. Breast cancer measures showed the greatest improvement from pre-NCCCP and were subsequently sustained. Hormone therapy for hormone receptor positive breast cancer increased from 51% (pre) to 90% (early) to 92% (later). Radiation therapy for breast conserving surgery increased from 72% to 93% to 92%. Colon cancer measures also showed sustained improvements with adjuvant chemotherapy for stage III cancer increasing from 72% to 90% to 89%. However, adjuvant chemotherapy for stage III rectal cancer improved from baseline (83%) to early NCCCP (90%) but then returned to pre-NCCCP rates (83%) later in the program. Significant changes were also seen in disparate populations. **Conclusions:** Quality of care measures at NCCCP sites increased after program initiation, and this increase was largely sustained over time. Improvement in recording of treatment administration due to the RQRS was a factor in increasing concordance. Concurrent NCCCP activities, including a working group to improve RQRS reporting and presentations of NCCCP results to the participants, may have helped sites significantly improve and sustain quality cancer care.

**6537 Poster Highlights Session (Board #26), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Lymphadenectomy quality measure for colon cancer: Is it working?** *Presenting Author: Jennifer Leigh Paruch, Division of Research and Optimal Patient Care, American College of Surgeons, Chicago, IL*

**Background:** Endorsement of the 12 lymph node colon cancer measure has led to improvements in national performance. However, it is unknown whether hospital performance on this measure is associated with improved outcomes. The objectives of this study were to determine whether improvement on this measure impacts stage migration or survival. **Methods:** Patients in the National Cancer Data Base undergoing resection for stage I-III colon cancer (1995-2011) were identified. Three hospital improvement groups were created using change in median node count over time (< 5; 5-10; >10). Changes in the ratio of stage III patients over time were compared between groups. A hierarchical Cox model was used to assess the relationship between hospital improvement and 5 year overall survival for stage II patients. **Results:** A total of 455,155 patients from 1,047 hospitals were identified. Median hospital lymph node counts increased from 10 (IQR 8-10) to 17 (IQR 15-19) over the study period. Increase in stage III patients over time was related to hospital improvement group (1.2% for improvement <5; 3.2% for improvement 5 – 10; 4.4% for improvement > 10; p<.0001). Hospital improvement group was significantly associated with 5-year overall survival in stage II patients (improvement 5-10: HR 0.97 [0.84-0.99]; improvement >10: HR 0.95 [0.91-0.98]). **Conclusions:** Stage migration and improved stage II survival were related to degree of hospital improvement in median node count. Implementation of this quality measure at Commission on Cancer accredited facilities may have greatest impact on outcomes at centers with most improvement.

**6538 General Poster Session (Board #1), Mon, 1:15 PM-5:00 PM**

**Media reporting of practice-changing clinical trials in oncology: A North American perspective.** *Presenting Author: Peter Andrew, Department of Internal Medicine, The Ottawa Hospitals, Ottawa, ON, Canada*

**Background:** The median time interval from phase III trial completion to public availability of results is 29 months. Our primary objective was to characterize the accuracy of information regarding ASCO 2012 *Clinical Cancer Advances* (CCA, n=17) as reported by the media and Internet; important public sources during that time. **Methods:** The *first* articles referencing CCA conference material were collected from newspapers, cable news, cancer websites, and industry websites. Two investigators independently rated the completeness of information using a 15-point scoring system [media reporting score (MRS)]. Statistical analyses were by Kruskal-Wallis one-way ANOVA-by-ranks test with post hoc analysis (Statistica, Statsoft Inc., Tulsa, Oklahoma, USA). **Results:** From 163 media articles, 107 (66%) had sufficient data for analysis. Per MRS, information was most complete from industry > cancer websites > newspapers > cable news (Table; Kruskal-Wallis $H$ test = 8.52; $df$ = 3; $p<0.05$). The most commonly omitted items were: study limitations > exclusion criteria > conflict of interest > other. **Conclusions:** The media should be encouraged to use a standardized reporting template and provide access to original source information.

| | Newspapers (*New York Times*, *Wall Street Journal*, and *Globe & Mail*) | Cable news (CNN, Fox News, and CTV News) | Cancer websites (ascopost.com, cancer.org, and cancer.gov) | Industry websites |
|---|---|---|---|---|
| MRS; mean (range) | 53 (49-57) | 41 (39-46) | 62 (58-67) | 67 (58-73) |
| Outcomes; % (n) | | | | |
| Benefits not quantified | 16 (5) | 9 (2) | 7 (3) | 0 (0) |
| Quantified benefits | 84 (27) | 91 (22) | 93 (38) | 100 (0) |
| - Relative | 56 (18) | 75 (18) | 12 (5) | 0 (0) |
| - Absolute | 6 (2) | 13 (3) | 53 (22) | 100 (10) |
| - Relative and absolute | 22 (7) | 4 (1) | 27 (11) | 0 (0) |
| Adverse events; % (n) | | | | |
| Not reported | 53 (17) | 42 (10) | 29 (12) | 0 (0) |
| Reported | 47 (15) | 58 (14) | 71 (29) | 100 (10) |
| - With incidence | 13 (4) | 21 (5) | 63 (26) | 90 (9) |
| Conflict of interest; % (n) | | | | |
| Not reported | 41 (13) | 75 (18) | 22 (9) | 100 (0) |
| Reported | 59 (19) | 25 (6) | 78 (32) | 0 (0) |
| Link to original CCA article; % (n) | 20 (6) | 18 (4) | 64 (26) | 43 (4) |

**6539 General Poster Session (Board #2), Mon, 1:15 PM-5:00 PM**

**A prospective comparison of times to presentation and treatment of rural and urban head and neck cancer patients in Queensland, Australia.** *Presenting Author: Zulfiquer Ali Otty, James Cook University, Townsville, Australia*

**Background:** Rate of survival from head and neck (H and N) cancer is lower among rural patients compared with their urban counterparts. This study's aim was to examine whether there was any difference between Urban (U) and rural (R) areas in the time taken to receive various aspects of H and N cancer management. **Methods:** H and N cancer patients presenting to Townsville, Cairns and Mackay hospitals were prospectively recruited from January 2009 to January 2011. The demographic factors as well as median times between 1) symptoms and first consultation, 2) symptoms and referral to specialist, 3) symptoms and visit to specialist, 4 ) symptoms and first treatment, 5) diagnosis and first treatment, 6) consultation and referral to specialist, and 7) visit to specialist and treatment, were collected. Fisher's, Kruskal-Wallis and Mann-Whitney tests were used to compare the two groups. **Results:** Out of the total of 158 patients , 62 % were living in urban and 37.3 % were living in rural areas. According to univariate analysis, there was significant difference in median time between diagnosis and first treatment between U and R areas (p=0.015). Indigenous patients had significant delays from diagnosis to first treatment (p=0.013), and visit to a specialist and treatment (p=0.031), compared to non-indigenous patients. According to multivariate analysis, there was significant delay in time between symptoms and first treatment in low-income compared to high-income population (P =0.03) and in patients with lower level of education compared to those with higher level of education ( P=0.04). There was significant delay in time between diagnosis and treatment for patients living in R area compared to those living in U area (P=0.028). The time between first consultation and referral to a specialist and time between visit to specialist and treatment was significantly longer in patients living in R areas compared to U area ( P=0.025 and P=0.003). **Conclusions:** There are delays in various aspects of head and neck cancer management depending on remoteness of residence and socio-economic factors. Improvement in management pathways for rural patients may improve their survival rates from H and N cancer.

**6540 General Poster Session (Board #3), Mon, 1:15 PM-5:00 PM**

**Relationships among financial distress, emotional symptoms, and overall distress in insured cancer patients.** *Presenting Author: Yu-Ning Wong, Fox Chase Cancer Center, Philadelphia, PA*

**Background:** Cancer care can be a financial burden, even among those with insurance. Overall Distress (OvDis) in cancer patients (pts) may be caused by many factors including Emotional Symptoms (EmSx). We examined the degree to which Financial Distress (FinDis) affected both OvDis and EmSx. **Methods:** We surveyed pts from medical oncology clinics about demographics, clinical information and the InCharge Financial Distress/Financial Well-Being Scale (range 1-10, lower scores indicating greater FinDis). Overall distress (OvDis) was measured using the NCCN distress thermometer (DT) (range 0-10, higher scores worse). As part of the DT, pts also responded to a list of symptoms including EmSx(i.e. depression, anxiety). We used linear regression and ANOVA to investigate potential pathways linking FinDis, EmSx and OvDis. Accrual is ongoing. **Results:** Of 60 pts recruited, median age was 64 years (34-85), 53% were male, 32% were working, 28% had self reported annual income >$100,000, 100% were insured, 69% had prior chemotherapy. 60% had clinically relevant DT scores ≥ 4 (median 5, 0-10), 58% reported at least one EmSx. The most common EmSx were worry(44%) and nervousness (34%). Median FinDis score was 6.5 (1-10). Evaluating the impact of each separately, FinDis and EmSx explain 30% and 39.6% of the variability in among OvDis scores respectively. After accounting for EmSx, FinDis explained 10.1% of the variability in OvDis (full model $R^2$=0.497). Conversely, after accounting for FinDis, EmSx accounted for 19.75% of the variability in OvDis. Using linear regression, a 1 unit increase in FinDis was associated with a 0.79 unit worsening in DT (p<0.001). After adding EmSx, a 1 unit increase FinDis was associated with a 0.51 worsening in DT (p=0.002). The attenuation of the FinDis effect due to EmSx was significant (p=0.003). **Conclusions:** Even among this group of affluent pts seen at a tertiary referral center, OvDis, FinDis, and EmSx were common and inter-related. Even among pts who are insured, FinDis may play a profound role on both EmSx and OvDis. Focused interventions that help pts navigate insurance obstacles and address other financial concerns may help to reduce FinDis and EmSx and thus in turn reduce OvDis among cancer pts.

**6541 General Poster Session (Board #4), Mon, 1:15 PM-5:00 PM**

**Impact of care at NCI comprehensive cancer centers (NCICCC) on cancer outcome: Results from a population-based study.** *Presenting Author: Julie Anna Wolfson, City of Hope, Duarte, CA*

**Background:** Despite advances in therapy and supportive care, prognosis for certain cancers remains poor. Rigorous processes ensure quality of research, clinical care and education at NCICCC. However, impact of site of care on survival and access to NCICCC for vulnerable subpopulations (race/ethnicity, payor) remains unstudied. **Methods:** We constructed a population-based cohort of 53,618 patients diagnosed between 22y - 65y with adult-onset cancers and reported to LA County cancer registry between 1998 - 2008. Geographic Information Systems (ArcGIS) was used for geospatial analysis. **Results:** Across multiple diagnoses, patients at NCICCC showed superior 5y overall survival (OS) as compared to those at community sites (breast [n=31,770]: 89% vs. 86%, p<0.01; lung [n=10,855]: 28% vs. 17%, p<0.01; hepatobiliary [n=4,296]: 34% vs. 19%, p<0.01; gastric [n=2,678] 32% vs. 22%, p<0.01; pancreas [n=2,326]: 13% vs. 6%, p<0.01; oral [n=1,838]: 68% vs. 59%, p=0.01). Adjusting for clinical (age, stage, gender) and sociodemographic (race/ ethnicity, payor, socioeconomic status [SES]) characteristics, multivariable Cox regression revealed an increased risk of mortality in patients receiving care at non-NCICCC sites: Breast: hazard ratio (HR)=1.2, p<0.01; Lung: HR=1.5, p<0.01; Hepatobiliary: HR=1.4, p<0.01; Gastric: HR=1.4, p<0.01; Pancreas (n=2,326), HR=1.5, p<0.01; Oral: HR=1.3, p=0.05. Overall 7% of patients were seen at NCICCC (range 4-16%, p<0.01). Multivariable logistic regression adjusting for clinical characteristics revealed that low SES (OR range across diagnoses: 0.4-0.5, p<0.01), public (OR 0.4-0.9, p<0.03) or no (OR 0.1-0.7, p<0.04) insurance, African-American race (OR 0.4-0.6, p<0.03) or Hispanic ethnicity (OR 0.5-0.7, p<0.02), and residing > 9 miles from nearest NCICCC (OR 0.5-0.9, p<0.01) decreased likelihood of care at NCICCC. **Conclusions:** Population-based data reveal superior OS among adult-onset cancer patients receiving care at NCICCC. Patients without private insurance, from low SES, African-American and Hispanic backgrounds or living more than 9 miles from an NCICCC, are less likely to use NCICCC. Barriers to care at NCICCC are currently being explored.

**6542 General Poster Session (Board #5), Mon, 1:15 PM-5:00 PM**

**Effect of pre-existing mental health comorbidities (MHC) on stage and timeliness of care of solid tumors in Veterans Affairs Connecticut Healthcare System (VACHS).** *Presenting Author: Roxanne Jimmy Wadia, Yale-New Haven Hospital, New Haven, CT*

**Background:** Axis I MHC affects approximately 18% and 30% of the adult US and VA population, respectively. There are limited and conflicting data on the impact of MHC on stage and timeliness of cancer care. The purpose of this study was to compare stage and timeliness of care in colorectal (CR), urothelial (UR) and head/neck (HN) cancers among Veterans with and without MHC. **Methods:** After IRB approval, we reviewed charts of Veterans with CR, UR and HN cancers diagnosed at VACHS between 2008 and 2011. Pts were identified via the cancer registry. NCCN guidelines were used to define standard of care. MHC was defined as an Axis I diagnosis treated in the year prior to the cancer diagnosis. Three time intervals were calculated: initial cancer symptom to presentation to a provider (TSP); provider to tissue diagnosis (TPD); and diagnosis to initiation of treatment (TDT). Data was analyzed using Chi-square, Fisher's Exact and non-parametric Wilcoxon rank sum tests as appropriate, using SAS. **Results:** We reviewed 412 charts including 174 pts with UR, 155 with CR and 83 with HN cancers. Of our pts, 36.6% (151) had Axis I MHC, 18.7% (77) had alcohol abuse/dependence, and 5% (21) had illicit drug abuse/dependence. In regard to staging, 221 (45%), 171 (41.5%) and 96 (23.3%) had Stage 0-1, stage II-III, and stage IV cancer. Diagnosis and treatment delays of at least 2 weeks were found in 73 pts (17.7%) and 63 (15.3%), respectively. In addition, 61 pts (14.8%) chose not to accept the standard of care. We found no difference between pts with or without MHC in stage distribution, symptomatic disease at presentation, diagnostic or treatment delays, or deviation from standard of care. Furthermore, there were no significant difference in the three measures of timeliness of care (TSP, TPD and TDT) between pts with and without MHC. **Conclusions:** Stage at diagnosis of CR, UR and HN cancers in VACHS did not differ between pts with and without Axis I MHC. The presence of MHC did not result in delays in care. Our data provides reassurance that within a healthcare system that provides integrated, comprehensive medical and psychiatric care, pts with Axis I MHC do not experience significant delays in cancer care.

**6543 General Poster Session (Board #6), Mon, 1:15 PM-5:00 PM**

**Accrual of adolescents and young adults with cancer to eligible clinical trials: A report from the NCIC Clinical Trials Group (NCIC-CTG).** *Presenting Author: Lesleigh S. Abbott, NCIC Clinical Trials Group, Kingston, ON, Canada*

**Background:** Improvement in 5-year survival among adolescents and young adults with cancer (AYAWC) has not kept pace with gains made in other age groups. Further, in the United States, 40-70% of children younger than 15 years old are enrolled onto National Cancer Institute clinical trials while less than 2% of 20-29 year old participated (Burke et al. 2007; Bleyer et al. 2002; 2006). We hypothesized that AYAWC were also underrepresented on clinical trials performed through the NCIC CTG, a predominantly adult oncology group. **Methods:** For this analysis, we defined AYAWC as 15-29 years old. All relevant trials from 2003-2013 were reviewed. Canadian cancer incidence was obtained from the Canadian Cancer Statistics (CCS) registry, deriving the mean annual incidence from data collected over a three year period (Statistics Canada, 2005-2007). We assessed the ratio of the number of AYA enrolled in NCIC CTG trials over the average annual numbers of new cases of the cancers in the AYA population in Canada and the ratio of the total numbers of patients on the NCIC CTG trials over average new cases of the cancer. **Results:** A total of 24,044 patients were enrolled on NCIC CTG trials, including 159 AYAWC (0.66%), while AYAWC represented 1.6% of incident cases from 2005-2007. The table indicates a selection of key AYA cancers; however, the total represents all cancer types included in this study. **Conclusions:** Overall AYA patients are more than 2-fold under-represented in current adult clinical trials; however, certain cancer types such as colorectal, breast and non-Hodgkin lymphoma have better than expected accrual as compared to incidence data.

| | CCS incidence | | NCIC CTG accrual | | Accrued/incidence (%) | |
|---|---|---|---|---|---|---|
| **Disease** | **Total** | **AYAWC** | **Total** | **AYAWC** | **Total** | **AYAWC** |
| **Leukemia** | 1,206 | 97 | 372 | 6 | 31 | 6 |
| **Breast** | 20,757 | 93 | 10,509 | 60 | 51 | 64 |
| **Colorectal** | 20,043 | 44 | 3,244 | 12 | 16 | 27 |
| **Lung** | 22,562 | 27 | 4,460 | 2 | 20 | 7 |
| **Hodgkin** | 856 | 285 | 223 | 17 | 26 | 6 |
| **Non-Hodgkin** | 6,511 | 146 | 1,115 | 41 | 17 | 28 |
| **Total** | 104,314 | 1,480 | 24,044 | 159 | 23 | 11 |

**6544 General Poster Session (Board #7), Mon, 1:15 PM-5:00 PM**

**Exclusion of patients with prior cancers from clinical trials: Is this justified?** *Presenting Author: Noelia Tarazona, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*

**Background:** Strict eligibility criteria are necessary for clinical trials to maintain patient (pt) safety and scientific validity. However exclusion of pt populations leads to impaired generalizability of results. As survival in gastrointestinal (GI) cancer relates mainly to the GI malignancy, we hypothesised that previous unrelated cancers do not impact on pt survival and are not a rational reason to exclude pts from trials. **Methods:** Pts were identified for this retrospective observational study from the electronic patient record at the Royal Marsden Hospital, UK. Eligibility criteria included age ≥ 18 years, diagnosis of colorectal (CRC), gastric, pancreatic or hepatocellular cancer, and treated with chemotherapy from 1/1/2006 – 31/12/2006. Chart review was performed and pt age, gender, GI cancer stage, prior cancer stage, clinical trial availability/eligibility, and dates of cancer recurrence, death and last follow up were identified. Overall (OS) and GI cancer specific survival (SS) were estimated using the Kaplan Meier method and compared by the log-rank test for pts with/without prior cancer. **Results:** 701 pts were identified. Most GI cancers were CRC (74%) and stage III (41%) or IV (38%) at diagnosis. 58 pts (8%) had a prior cancer; commonly breast (26%), prostate (19%), colon (9%), or melanoma (7%) and most were stage I (52%) or II (27%). 299 (65%) pts had GI cancer recurrence, 8 (14%) pts had relapse of a prior cancer. Median follow up was 84 months (m): 505 (72%) pts have died, 172 (25%) are alive with no cancer and 24 (3%) pts are alive with cancer. 477 (95%) died of GI cancer, 2 (0.3%) of their prior cancer and 16 (3%) from other causes. 492 (70%) of all pts had an available trial but of pts with a prior cancer who had an available trial 30% were ineligible due to the previous cancer. OS and GI cancer SS were comparable for pts with/without a prior cancer at 45.9 versus 40.6 m, p=0.93 and 49.2 versus 41.2 m, p=0.74, respectively. **Conclusions:** Survival for pts with a GI cancer requiring chemotherapy relates to the GI cancer and rarely a prior cancer. As there is no statistically significant difference in OS and GI cancer specific survival between pts with and without prior cancer, these pts should not be excluded from clinical trial participation.

**6545 General Poster Session (Board #8), Mon, 1:15 PM-5:00 PM**

**Barriers to insurance coverage of next-generation tumor sequencing by U.S. payers.** *Presenting Author: Julia Rachel Trosman, Center for Business Models in Healthcare, Chicago, IL*

**Background:** Next-generation tumor sequencing (NGTS) panels, which include tens to hundreds of targets of varying clinical significance applicable across cancers, are crossing from research to clinical practice, but are not formally covered by U.S. payers. Lack of consistent coverage policy may impact access and adoption. Our study aimed to identify considerations used by payers for NGTS coverage decisions. **Methods:** We conducted semi-structured interviews with senior executives of 7 large national and 3 regional plans in the U.S., covering >125 million members. We used the framework approach of qualitative research for thematic analyses. **Results:** Most payers (80%) believe NGTS has a potential to transform cancer care, but all (100%) report barriers to coverage. (1) 70% of payers view NGTS as a 'bundle" of cancer markers, vs. comprehensive tumor characterization, and thus may evaluate evidence for one target and one cancer type at a time. Sufficient evidence for all targets included in an NGTS panel may be required for a positive coverage decision. (2) 80% of payers may predicate coverage policy for NGTS not only on validity of included targets, but also on outcomes from therapies informed by NGTS, with 30% requiring Phase 3 evidence for each new marker / drug indication. (3) 70% of payers note that NGTS converges clinical care and research by interrogating both established and novel targets, and thus does not fit the coverage framework separating "medically necessary" vs "experimental / investigational". Therefore, payers may not cover panels that include novel targets. However, 40% also note health reform requirements to cover trials for terminal conditions and may use NGTS as a means for complying with this requirement. (4) Payers cite challenges in assessing accuracy and value of bioinformatics required to implement NGTS. 70% do not believe that bioinformatics should be reimbursed. **Conclusions:** Next-generation tumor sequencing does not fit the current payer coverage and evidence framework and thus faces potential barriers to access. The entry of this rapidly evolving technology into clinical practice requires ongoing dialogue among payers, providers, and policy-makers to develop an innovative roadmap to coverage and reimbursement.

**6546 General Poster Session (Board #9), Mon, 1:15 PM-5:00 PM**

**A national survey of breast cancer screening in rural America.** *Presenting Author: Jeffrey M. Peppercorn, Duke Cancer Institute, Durham, NC*

**Background:** Breast cancer screening leads to improved survival yet disparities among rural women persist. The impact of inconsistent mammography guidelines on attitudes and utilization is unknown. **Methods:** We conducted a national self-administered survey of 2,000 randomly selected women between ages 40 and 65 insured by the National Rural Electric Cooperative Association (as utility workers or family members). A study-specific survey assessed mammography use, knowledge and attitudes about screening, awareness of guidelines, and correlation between knowledge, attitudes and screening. **Results:** 1,581 women responded (response rate 79%). 41% were age 40-49, 58% age 50-65. 74% were rural, 18% suburban, and 8% urban. 98% agreed that mammograms find cancer early and improve chance of cure. Only 19% believed that mammograms may lead to unneeded biopsies and 4% to unsafe radiation. 54% thought annual mammography was recommended for women 40-49, 22% biennial, 17% that expert views vary, 2% screening not recommended, and 5% unsure. Non-rural women were more likely to believe annual screening is recommended (64% vs. 51%, $p = 0.0002$). For women over 50, 66% believed annual screening was recommended, 14% biennial, 11% expert views vary, and 9% unsure. While only 9% reported confusion over guidelines, few reported practices consistent with U.S. Preventative Services Task Force (USPTF) recommendations. Among women < 50, 46% report annual screening, 32% biennial, and 23% rare/never. Among women > 50, 63% reported annual screening, 25% biennial, and 13% rare/never. Among younger women, belief that annual screening was recommended correlated with reported annual screening, (70% vs. 20%, $p < 0.0001$). Younger women who reported understanding current guidelines were also more likely to report annual screening (51% vs. 33%, $p = 0.0003$) and less likely to report rare/never screening (18% vs. 34%, $p = 0.0002$). Among women over 50, those reporting confusion over guidelines were twice as likely to report rare/never screening vs. those reporting understanding (18% vs. 9%, $p = 0.0004$) **Conclusions:** Perceptions of recommendations and confusion over guidelines correlate with screening behavior suggesting a need for expert consensus to inform appropriate utilization.

**6547 General Poster Session (Board #10), Mon, 1:15 PM-5:00 PM**

**A targeted intervention to improve awareness to molecular testing in NSCLC.** *Presenting Author: Alona Zer, Princess Margaret Cancer Center, Toronto, ON, Canada*

**Background:** Molecular testing is now standard of care to guide treatment selection in advanced NSCLC. Population-based implementation of testing remains a challenge in Ontario'spublic healthcare system, with ~37% of eligible samples undergoing testing and~12% insufficient for testing. We developed an intervention to improve understanding among Ontario specialists of the importance of molecular testing and appropriate diagnostic sampling in NSCLC. **Methods:** Based on IASLC guidelines for molecular testing in NSCLC, leaders in lung pathology, respirology, interventional radiology and thoracic surgery identified key messages for each specialty regarding molecular testing and diagnostic sampling in lung cancer. Specialty-specific educational programs (delivered by a multidisciplinary team) were developed and administered at provincial and national specialty meetings. Participants were assessed on their knowledge of targeted therapy, molecular testing and sample requirements **Results:** Ten educational programs were administered across the country targeting pathologists, thoracic surgeons, respirologists, interventional radiologists, medical and radiation oncologists. 210 pre- and 188 post-intervention surveys were completed.Baseline results demonstrated significant uncertainty: 30% were unsure regarding tissue handling techniques to ensure successful molecular testing, 20% chose an incorrect technique. Half were unfamiliar with how to initiate *EGFR* and *ALK*testing, and 17% were uncertain of whom to test. After the intervention, specialist knowledge increased regardingtissue handling techniques (OR=3.01, p<0.0001), appropriate fixation (OR=2.48,p<0.0001), and the level of uncertainty decreased from 30% to 3% (p<0.0001). Participants understood the importance of initiating testing as soon as possible rather than deferring to the medical oncologist (p<0.0001), and to send samples even if unsure they met technicalrequirements (OR=4.63,p<0.0001). **Conclusions:** Significant knowledge gaps existabout molecular testing in NSCLC among specialists that diagnose the disease. Specialist education significantly improves knowledge and awareness about molecular testing and its importance in NSCLC.

**6548 General Poster Session (Board #11), Mon, 1:15 PM-5:00 PM**

***BRCA1/BRCA2* (*BRCA*) testing in young women with breast cancer: Patterns, motivations, and implications for treatment decisions.** *Presenting Author: Shoshana M. Rosenberg, Harvard School of Public Health, Boston, MA*

**Background:** While BRCA testing is recommended for women diagnosed with breast cancer before age 50, little is known about decisions surrounding testing in young patients. **Methods:** As part of an ongoing cohort study, we surveyed 765 women diagnosed with breast cancer at age ≤ 40 about their experience with BRCA testing at approximately 1 year after diagnosis. We used Chi-square tests to evaluate differences in how genetic information was used to make treatment decisions among women who 1) tested positive 2) tested negative 3) were not tested. Among untested women, we assessed whether 1) genetic risk was discussed with a provider 2) reasons why they were not tested. **Results:** 655/765 (86%) of women reported undergoing BRCA testing by 1 year from diagnosis. 31% (232/746) said that knowledge/concern about genetic risk influenced treatment decisions. Among these women (Table), 87% of mutation carriers, 50% of non-carriers, and 45% of untested women chose bilateral mastectomy; fewer women reported that adjuvant treatment decisions were influenced by genetic risk concern. Among untested women, 32% (35/110) had not discussed the possibility that they might have a mutation with their doctor. The top 5 reasons cited for not testing were: patient perceived risk low (25%), doctor perceived risk low (24%), not a priority (18%), insurance/work (14%), financial (11%). 39% were thinking of testing in the future. **Conclusions:** >10% of women with breast cancer ≤ 40 were not tested for a BRCA mutation within a year of diagnosis. Among these women, 1/3 did not discuss genetic risk with their doctor. Given that knowledge/concern about genetic risk influences surgical decisions and can affect systemic therapy trial eligibility, all young breast cancer patients should have access to adequate genetic counseling and testing if desired.

**Genetic concerns influenced use/choice of treatment in the following ways.**

| (N=232) | BRCA+ N=71 N (%) | BRCA- N=139 N (%) | Not tested N=22 N (%) | p |
|---|---|---|---|---|
| Mastectomy instead of lumpectomy | 3 (4) | 14 (10) | 7 (32) | 0.001 |
| Bilateral mastectomy | 62 (87) | 70 (50) | 10 (45) | <0.0001 |
| Salpingo-Oophorectomies | 37 (52) | 6 (4) | 2 (9) | <0.0001 |
| Endocrine therapy | 12 (17) | 28 (20) | 4 (18) | 0.78 |
| Chemotherapy | 14 (20) | 17 (12) | 3 (14) | 0.35 |

**6549 General Poster Session (Board #12), Mon, 1:15 PM-5:00 PM**

**Burnout among Canadian oncologists and oncology residents.** *Presenting Author: Thao Phuong Nguyen, Tom Baker Cancer Centre, Calgary, AB, Canada*

**Background:** The objective of this study was to evaluate characteristics associated with burnout in Canadian oncologists and oncology resident physicians (ORP). **Methods:** Canadian medical oncologists (MO), radiation oncologists (RO) and ORP were asked to complete a self-administered survey which included: a validated single-item measure of burnout, questions regarding personal and professional characteristics, impact of work-related stress on family life and an exploration of the oncologists' support network. A similar survey was sent to spouses to determine the spouse's perception of oncologist burnout **Results:** A total of 307 oncologists and ORP completed the survey (median age 47, including 45% MO, 43% RO, 12% ORP). The response rate was 31%. The prevalence of high burnout in each group was: 20% MO, 14% RO, and 20% ORP. Overall, 61% MO and 37% RO reported a high work-overload, 25% MO and 22% RO had high work-family conflict, and 11% MO and 14% RO had family-work conflict. Regarding career satisfaction, 15% MO and 16% RO regreted their decision to become a physician, 23% MO and 29% RO considered leaving their current province, 17% MO and 20% RO considered leaving oncology as a career altogether. The concordance rate for burnout between physicians and spouses was 77.6% (kappa = 0.32). On multivariable analysis, factors associated with burnout included female gender, less exercise, less alcohol consumption and lower level of co-worker support. Factors included in the multi-variable analysis that were not associated with burnout include: age, number of cancer sites covered, spousal support, as well as time allocated to patient care and doing work tasks at home. **Conclusions:** Across Canada, one in five oncologists reported having high burnout. This is a lower rate than previously reported. Predictors of burnout in Canadian oncologists are different compared to a recently reported study of medical oncologists in the United States.

| Multivariable analysis predictors | OR | P-value |
|---|---|---|
| Female | 2.409 | 0.0277 |
| Exercise (several times/ week min.) | 0.324 | 0.0045 |
| Alcohol (4 drinks/week versus less) | 0.333 | 0.019 |
| Coworker support (more versus less) | 0.946 | 0.0305 |

**6550 General Poster Session (Board #13), Mon, 1:15 PM-5:00 PM**

**Do special access programs facilitate off-label prescribing? The experience of enzalutamide in prostate cancer.** *Presenting Author: Nimira S. Alimohamed, Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada*

**Background:** There is limited data on prescribing patterns during special access programs. Enzalutamide, a novel oral anti-androgen, improves overall survival in patients with metastatic castration resistant prostate cancer (mCRPC). In the post-docetaxel setting, enzalutamide was Health Canada approved in May 2013 and publically funded in Ontario in December 2013. In the pre-docetaxel setting, data demonstrating benefit of enzalutamide (PREVAIL study) was only recently released and it is yet to be approved in this setting. Enzalutamide was provided free of charge by the manufacturer as part of a patient assistance program from June-December 2013. To understand factors influencing decision to offer enzalutamide in this program, we surveyed treating oncologists. **Methods:** Following ethics approval, oncologists at our institution prescribing enzalutamide completed an anonymous paper or electronic survey asking questions about the patient's disease characteristics, prior treatments, and reasons for prescribing enzalutamide. **Results:** Of 193 patients enrolled, surveys were completed on all 155 patients prescribed enzalutamide by oncologists. The majority of patients had metastatic CRPC (92%), while a minority had non-metastatic CRPC (8%); 95% had progressive disease at initiation while 5% did not. Pre-docetaxel prescribing occurred in 65% of cases; with 54% of those being after PREVAIL data was released. The primary reasons for prescribing enzalutamide were data supporting its use (50%) and its availability at no charge (35%). Enzalutamide was felt to be the best choice or as good as other options by 82%; 11% stated enzalutamide would be the next line of treatment but only at the time of further disease progression; 7% stated enzalutamide would not be their next line of treatment and only prescribed it because of the program. **Conclusions:** During this patient access program, off-label use of enzalutamide was seen, perhaps because it is a well-tolerated hormonal agent, which may delay the need for chemotherapy. This study demonstrates that funding and accessibility issues impact prescribing practices.

**6551 General Poster Session (Board #14), Mon, 1:15 PM-5:00 PM**

**Choosing a cancer surgeon: Analyzing factors in patient decision making using a best-worst scaling methodology.** *Presenting Author: Aslam Ejaz, The Johns Hopkins University School of Medicine, Baltimore, MD*

**Background:** Surgeon experience has been shown to influence outcomes for many types of cancer. The attributes and factors that patients utilize when selecting a hospital or surgeon for cancer treatment remain poorly defined. **Methods:** All patients with a cancer diagnosis seeking treatment at a surgical clinic at Johns Hopkins Hospital were asked to participate. A survey utilizing a best-worst scaling methodology was constructed to elicit the importance of various factors when selecting a cancer surgeon. Attributes were chosen based on an extensive review of the literature and a pre-test analysis. Attributes were grouped into four categories: surgeon reputation, surgeon qualifications, hospital-related and non-clinical factors. **Results:** 194 patients with a cancer diagnosis participated in the study (80.8% response rate). Median age was 62 years (IQR: 51.5, 70). Patients had a variety of primary tumor diagnoses with the most common being hepatobiliary (N=35, 18.1%) and breast (N=31, 16.1%). Among the attributes, patients placed the highest value on physician qualifications and hospital-related factors. Specifically, surgeon case-specific experience (coefficient: 2.52, SE 0.06) and the receipt of specialized training experience (coefficient: 2.28, SE 0.06) ranked highest (both $P<0.001$). Among hospital-related factors, hospital case-specific volume (coefficient: 1.31, SE 0.06; $P<0.001$) was most important. The lowest rated factors were parking availability (coefficient: -2.80, SE 0.064) and home-to-clinic distance (coefficient: -2.09, SE 0.06) (both $P<0.001$). The majority of patients reported their ideal surgeon to have at least 6 years of experience (N=153, 86.0%) and to have performed their specific procedure at least 50 times (N=144, 76.6%). After stratifying patients by education level and state of residence, the ranking of factors remained unchanged. **Conclusions:** Patients consider several factors when choosing a cancer surgeon. Surgeon qualifications and hospital-related factors appear to be most influential in their decision. Easier and more widespread dissemination of surgeon and hospital cancer data such as case volume may be useful for patients in the future.

**6552 General Poster Session (Board #15), Mon, 1:15 PM-5:00 PM**

**Why is it so difficult to enroll patients in clinical trials?** *Presenting Author: Norma Kanarek, The Johns Hopkins University School of Medicine, Baltimore, MD*

**Background:** Nationwide, approximately 3% of patients participate in therapeutic clinical trials. It is presumed that patient education and navigation will increase enrollment. For these interventions to work, a clear understanding of the reasons patients do not enroll is needed. Employing our enrollment framework (Kanarek et al, 2012), we set out to define, at one comprehensive cancer center, the reasons new cancer patients fail to enroll onto clinical trials. **Methods:** Medical Oncology records from a consecutive series of new breast, non-small cell lung (NSCLC), pancreas and prostate cancer patients were abstracted. Abstraction was based on seven framework sequential steps: 1) trial availability, 2) trial eligibility, 3) physician triage 4) physician-patient discussion, 5) patient's interest, 6) consent, and 7) enrollment. Each step depends on the prior step (e.g. if there were no trial available then eligibility for a trial could not be considered). Reasons noted for failing any step were summarized. **Results:** Between 2012 and 2013, records from 688 patients were reviewed. Clinical trial enrollment varied: 5% NSCLC, 12% pancreas and prostate, and 17% breast. The 4 most common reasons for non-enrollment were: no trial available or patient did not meet eligibility (36-55%); standard treatment was recommended or preferred (6-23%); distance from the cancer center (1-22%); and lost to clinical follow-up or patient chose to receive care elsewhere (5-14%). Combined, these 4 reasons eliminate 64% of breast, 83% of pancreas, 84% of prostate and 89% of NSCLC patients from trial participation. About half of the remaining patients enrolled onto clinical trials. **Conclusions:** Our study suggests that these 4 common reasons for clinical trial non-participation may need to be addressed to increase clinical trial percentages.

Patient distribution n(%).

| | n | No available trial w/eligibility | Distance | Sth tx recomm./ preferred | Lost to follow up/ care elsewhere | Total not available (4 reasons) | Remaining available | Enrolled on to clinical trials |
|---|---|---|---|---|---|---|---|---|
| Breast | 293 | 106 (36) | 13 (4) | 39 (13) | 29 (10) | 187 (64) | 106 (36) | 50 (17) |
| Lung | 154 | 78 (51) | 2 (1) | 36 (23) | 21 (14) | 137 (89) | 17 (11) | 8 (5) |
| Pancreas | 147 | 81 (55) | 24 (16) | 9 (6) | 8 (5) | 122 (83) | 25 (17) | 17 (12) |
| Prostate | 94 | 43 (46) | 21 (22) | 9 (10) | 6 (6) | 79 (84) | 15 (16) | 11 (12) |

**6553 General Poster Session (Board #16), Mon, 1:15 PM-5:00 PM**

**The cost of thromboembolic events in French hospitalized patients with breast or prostate cancer.** *Presenting Author: Isabelle Borget, Institut Gustave Roussy, Villejuif, France*

**Background:** Cancer is associated with a high risk of venous thromboembolism. We aimed to determine the number of stays and the cost of hospital management of thromboembolic events (TEEs) occurring in patients with breast cancer (BC) or prostate cancer (PC). **Methods:** The French national hospital database (PMSI) was analysed in order to identify patients whose BC or PC was diagnosed in 2010 and who were hospitalized for a TEE at least once during the following two years. The numbers of stays induced by a TEE, and the corresponding number of patients hospitalized, were determined using the disease-specific ICD-10 codes. Associated hospital costs were estimated from the perspective of the third-party payer, using the French official tariffs. **Results:** We identified 62,365 patients with BC and 45,551 patients with PC; in each group, 1,271 (2.0%) and 997 (2.2%), respectively, were hospitalized for a TEE or had a TEE during their hospital stay. During the 2 years of follow-up of these 2,268 patients, 346 (15.3%) were hospitalized for a TEE recurrence. In total, 1,604 stays for BC patients and 1,210 stays for PC patients were analyzed. In BC patients, the mean cost per stay amounted to €3,302 and €2,916 for first event and recurrence, respectively, and in PC patients, €3,611 and €3,363 for first event and recurrence, respectively. In patients who had at least one recurrence, mean hospitalization cost per patient was €5,545 and €5,692 in BC and PC, respectively. Over a 2-year period, the total cost of hospital stays induced by TEEs reached €1.98 million and €1.43 million for BC and PC, respectively. **Conclusions:** The burden of TEE in cancer patients is high; costs would be reduced by decreasing the occurrence of thromboembolic complications in this at-risk population. Better prevention and follow-up measures may reduce recurrence and TEE costs.

**Cost of hospital stays for patients with BC or PC and TEE.**

| | First event | Recurrence | Total |
|---|---|---|---|
| **Breast cancer** | | | |
| **Mean cost/stay** | €3,302 | €2,916 | €3,261 |
| **Total cost** | €1,789,615 | €186,620 | €1,976,235 |
| **Prostate cancer** | | | |
| **Mean cost/stay** | €3,611 | €3,363 | €3,584 |
| **Total cost** | €1,278,397 | €147,959 | €1,426,357 |

**6554 General Poster Session (Board #17), Mon, 1:15 PM-5:00 PM**

**Physician communication on cost of cancer care under the Affordable Care Act.** *Presenting Author: Laura LaNiel Tenner, Melvin and Bren Simon Cancer Center, Indianapolis, IN*

**Background:** The steeply rising cost of cancer care in the United States adversely impacts the economy as well as patient emotional well-being and financial stability. The aim of this study was to assess U.S,oncologists' attitudes and perceptions about the cost of cancer care in the wake of ACA implementation. **Methods:** From June through August 2013, a survey instrument was emailed to practicing oncologists in 50 states. Survey items included assessments of self-reported practices concerning communication of cost of therapy as well as influences of the ACA. Other survey items assessed oncologists' perceptions of cost effectiveness data. **Results:** The electronic survey response rate was 16% with respondents from 35 states. Respondents were more likely to strongly or somewhat agree that it was important to discuss out-of-pocket costs [OPC] (89%) and healthcare system costs [HSC] (66%) with patients, $p<0.0001$. 70% reported that OPC of therapy influence their treatment decisions. 60% agreed that OPC and HSC of cancer treatments were likely or extremely likely to have a larger effect on their decisions regarding which cancer treatments to recommend to patients in the future under the ACA. While 4% agreed the government should play a role in determining the value of a cancer therapy, 53% of respondents thought that government price controls for cancer drugs were needed. A large majority agreed that physician education on the use of cost-effectiveness data (91%) and communicating cost of therapies with patients (85%) was needed. **Conclusions:** U.S. oncologists reported that they desire more cost and comparative effectiveness research as well as more education on how to communicate with patients about costs of therapy. Respondents perceived that both OPC and HSC will play a larger role in their cancer treatment decisions over the next five years, and that they will need to increase their communication with patients about both OPC costs as well as HSC. Respondents appeared divided on the topic of government intervention on pharmaceutical price controls and unified in their resolve to maintain control of decisions on the value of therapy.

**6556 General Poster Session (Board #19), Mon, 1:15 PM-5:00 PM**

**A cost-effectiveness analysis evaluating allogeneic hematopoietic cell transplantation (AHCT) versus consolidation chemotherapy for the treatment of acute myeloid leukemia (AML) in first complete remission.** *Presenting Author: Abby Statler, Cleveland Clinic Taussig Cancer Institute, Case Western Reserve University, Shaker Heights, OH*

**Background:** The objective of this study was to determine which treatment strategy for AML in first complete remission (CR) is more cost-effective: consolidation chemo or AHCT. **Methods:** Simple decision analyses were performed for the cost and the effectiveness of each strategy; the cost-effectiveness was subsequently compared using incremental cost-effectiveness analysis. The population modeled included AML pts $<$ 60 years old in first CR. The majority of the outcome data pulled from the literature included pts with unfavorable cytogenetics (poor/intermediate risk AML). The analyses assumed a 5-year time horizon and assessed medical costs and health benefits, which were measured in quality adjusted life years (QALYs). Costs and QALYs were discounted 3% per year. Sensitivity analyses were performed on the probabilities, costs, and utilities. **Results:** Chemo was the more effective (2.67 vs. 1.79 QALYs; 3.04 vs. 2.15 5 year overall survival) and less expensive ($163,391 vs. $182,018) strategy. Chemo was cost-saving compared to AHCT, i.e. it was both more effective and less expensive. The Sensitivity analyses did not change the results. Exploratory sensitivity analyses did however demonstrate if the probability of dying from AHCT was the same as chemo and the probability of relapsing after AHCT was $\leq$ .17, AHCT would dominate the chemo strategy. **Conclusions:** The chemo strategy was more effective because its QALY and OS outcomes were superior to AHCT. The contribution of the Quality-of Life (QoL) outcomes depreciated the effectiveness (i.e. QALYs) of each strategy almost equally (chemo: 0.37 vs. AHCT: 0.36). This finding demonstrates although the overall QALYs were greater in the chemo strategy, the contribution of the QoL outcomes were virtually the same for both strategies. As the clinical effectiveness of AHCT improves over time, the QoL outcomes will become more influential. In the future, if the improvement in AHCT efficacy is coupled with a meaningful increase in the AHCT QoL outcomes, AHCT could become the more cost-effective treatment strategy.

**6557 General Poster Session (Board #20), Mon, 1:15 PM-5:00 PM**

**Developing a predictive model for cancer clinical trial accrual.** *Presenting Author: Wendy R. Tate, The University of Arizona Cancer Center, Tucson, AZ*

**Background:** With increasing cost to conduct clinical trials, it is imperative to select trials rationally for local activation. We sought to create a predictive model with an outcome of anticipated accrual that can be used when considering a prospective clinical trial. **Methods:** This retrospective cohort study used 5.8 years of registry data to predict clinical trial accrual at our center. A negative binomial regression model was employed using variables known pre-study. These were abstracted from the OnCore clinical trial management system (Forte Systems, Madison, WI) and clinicaltrials-.gov. Statistical significance was set a priori to 0.05. Normality and collinearity of independent variables and model fit were assessed. Variables modified an effect if the beta coefficient of the other independent variable changed by $>$10%. Accrual was predicted for the studies used to build the model. **Results:** The model included 207 trials with complete information. Mean accrual was 7.3 per trial ($\pm$18.4) and 55 (26.6%) trials did not succeed in accruing subjects locally. In univariate analysis, use of an investigational drug, local disease management team (DMT), number of national sites, use of local IRB, number of total months open nationally, months of accrual already completed, and overall proposed national enrollment were significantly associated with accrual. In multivariate analysis, DMT, proposed national enrollment, number of sites, use of local IRB, number of total months open, and the number of months already opened were significantly and independently associated with accrual. The full model was statistically significant (P$<$0.001), demonstrating these variables' contribution to protocol accrual. Accrual was predicted at 94% of the actual value and maintained predictive value at multiple cutoff values. **Conclusions:** We identified key factors, both nationally and locally, associated with the accrual of subjects to a therapeutic clinical trial at our site. This model can aid in deciding whether a study is likely to accrue a desirable number of subjects. We plan to prospectively validate the model. If valid, this model would provide a quick and valuable metric in assessing trial success as well as planning resource allocation and estimating costs.

**6558 General Poster Session (Board #21), Mon, 1:15 PM-5:00 PM**

**How much is the pharmaceutical industry's cost of capital for clinical research of novel drugs?** *Presenting Author: Henry Jacob Conter, University of Western Ontario, London, ON, Canada*

**Background:** Attracting private research investment to fund clinical trials in rare tumor types can be difficult. This is compounded by the inability of investors to directly invest in higher-risk trials, lack of interest in by large pharmaceutical companies, and a lack of understanding of what return on investment would be acceptable. **Methods:** A project finance model was created. The owner of the desired compound would license it to a special investment vehicle (SIV). The SIV would purchase the license from the holder by raising cash through a repurchase agreement with a financial institution in exchange for zero-coupon (Z-) bonds issued by the SIV. The financial institution could short sell the bonds to investors. Bond holders could hold the debt or purchase credit default swaps (CDS) to hedge risk. The Merton Model was employed to value the debt and calculate the yield per dollar of future revenue. Published clinical trial phase transition probabilities were used to estimate success. The hazard for failure was calculated from the time from phase I initiation (extracted from clinicaltrials.gov) to FDA approval, assuming an 80% failure rate, for all novel drugs approved since 2000. **Results:** Phase transition probabilities were 76.8%, 59.4%, and 57.1% for phase I-II, phase II-III, and phase III-FDA approval, respectively. After completion of pre-clinical work, the value of the compound would be $0.24. The value of the license could either be $0 or $0.31, $0.31 or $0.49, $0.49 or $0.74 at the end of phase I, II, or III trials, when adjusted for inflation. If the face value of debt was equal to the initial value of the compound, the z-bond would yield 20.7%, 8.2% and 13.6% annually with continuous compounding for phase I, II, and III, trials. A minimum equity of 29.3%, 19.7%, and 37% would need to be raised in addition to the debt financing to purchase the license for phase I, II, and III trials, respectively. For the 28 drugs approved, the mean approval time was 6.5 years (range 3.2-10.9). A perfectly hedged CDS would cost $0.84. **Conclusions:** Project financing techniques allow for a quantitative determination of the cost of capital for different stages of drug development. This financial structure could be employed to finance trials for rare tumors.

**6559 General Poster Session (Board #22), Mon, 1:15 PM-5:00 PM**

**Does cancer treatment-related financial distress worsen over time?** *Presenting Author: Lena Van Nimwegen, Duke University School of Medicine, Durham, NC*

**Background:** Patients with cancer are at risk for experiencing financial distress. Prior studies have indicated that objective financial burden follows trends associated with treatment course. However, little is known about whether patients' subjective financial distress follows similar trends during the course of their treatment. The ability to predict risk of financial distress in relation to time on treatment may facilitate timing of interventions to alleviate financial distress. **Methods:** This was a cross-sectional study of insured adults with solid tumors on anticancer therapy for $\geq$1 month. Consecutive patients were surveyed, in person, at a referral center and 3 rural oncology clinics. Participants were asked about financial distress (via a validated measure) and out-of-pocket costs. Medical records were reviewed for disease and treatment data. We used the Spearman Rank Correlation Coefficient test and multivariable logistic regression to assess the correlation between months on treatment and financial distress. **Results:** 300 participants (86% response rate) had a median age of 60 years (range 27-91). 79% had incurable cancer. 56% had private insurance. Median income was $60,000/yr. Median OOP costs were $592/mo. The median FD score (7.4 out of 10, SD 2.5) corresponded to moderate FD with 16% reporting high/overwhelming FD. The median time on treatment was 4.6 months (range 1-156 months). Treatment duration was not correlated with financial distress (p=0.89). In adjusted analyses, having curable disease (p=0.02) was associated with higher odds of experiencing high/overwhelming financial distress. **Conclusions:** Severity of cancer treatment-related financial distress did not correlate with time on treatment. However, patient and disease characteristics may predict risk of financial distress. Consistent with prior studies, patients receiving curative treatment might be at higher risk of experiencing financial distress possibly due to higher costs incurred in the initial period following diagnosis. Sociodemographic characteristics might be useful for targeting early interventions in patients who are at risk for treatment-related financial distress.

**6560 General Poster Session (Board #23), Mon, 1:15 PM-5:00 PM**

**Estimation of drug cost avoidance (DCA) and pathology cost avoidance (PCA) through participation in NCIC clinical trials group (NCIC-CTG) phase III clinical trials in Canada.** *Presenting Author: Patricia A. Tang, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada*

**Background:** Cost avoidance (CA) occurs when, due to the provision of a drug therapy (DCA) or a pathology test (PCA) via trial participation, payment for standard treatment or testing is not required. The aim of this study was to estimate the total DCA and PCA for Canadian patients (pts) enrolled in NCIC-CTG conducted phase 3 trials. **Methods:** Phase 3 trials that had completed accrual and resulted in DCA or PCA were identified. PCA was calculated based on the number of pts screened and test cost. DCA was estimated based on pts randomized, protocol dosing regimen, drug cost, median dose intensity and median duration of therapy. If this information was incomplete, assumptions were made based on published literature. Costs for Canadian pts accrued are presented in Canadian dollars. No adjustment was made for inflation. **Results:** From 1999-2011, 4 trials resulted in PCA (1,479 pts) and 17 trials resulted in DCA (3195 pts). Total PCA was estimated at $4,194,849, which included testing for KRAS ($141,058), microsatellite instability ($18,600), and 21-gene recurrence score ($4,035,191). Total DCA was estimated at $27,935,957, of which targeted therapy comprised 42.6% of DCA (5 trials). The combined PCA and DCA was $32,130,806. **Conclusions:** Over the time period studied, these NCIC-CTG trials resulted in total CA (PCA and DCA) of approximately $7514/pt. Although not all trials lead to CA, these savings should be taken account when considering the financial impact of conducting clinical research.

| Trial (drug with CA) | Mean DCA per pt ($) | Total DCA for trial ($) |
|---|---|---|
| **CO.13 (irinotecan)** | 10,565 | 1,595,249 |
| **CO.20 (cetuximab)** | 22,588 | 7,544,519 |
| **CRC.2 (oxaliplatin)** | 13,665 | 3,689,425 |
| **CRC.5 (bevacizumab)** | 17,430 | 1,115,520 |
| **PA.2 (5FUFA)** | 93 | 3,993 |
| **MA.27 (exemestane, anastrazole)** | 9,034 | 9,519,856 |
| **MA.31 (trastuzumab)** | 31,784 | 1,239,595 |
| **MAC.1 (CMF/AC)** | 535 | 6,959 |
| **MAC.4 (tamoxifen)** | 639 | 21,000 |
| **MAC.5 (tamoxifen)** | 639 | 39,319 |
| **MAC.7 (anastrazole)** | 2,005 | 88,209 |
| **REC.1 (interferon)** | 4,290 | 68,643 |
| **OV.16 (paclitaxel)** | 3,011 | 710,586 |
| **OV.17 (paclitaxel)** | 4,996 | 169,858 |
| **HN.6 (cisplatin)** | 90 | 14,391 |
| **LY.12 (rituximab, cytarabine)** | 6,660 | 2,104,412 |
| **BRC.3 (etoposide)** | 1,106 | 4,423 |

**6561 General Poster Session (Board #24), Mon, 1:15 PM-5:00 PM**

**Physician experience and attitudes toward addressing the cost of cancer care.** *Presenting Author: Ivy Altomare, Duke University Medical Center, Durham, NC*

**Background:** ASCO recommends that patient-physician treatment discussions include addressing costs of cancer care; when and how these conversations should optimally take place is unclear. We sought to determine contemporary attitudes of US cancer physicians toward discussing treatment costs as a part of medical decision-making. **Methods:** A 15-question, self-administered, anonymous, electronic survey was distributed to US ASCO physician members after conducting 10 pilot interviews to improve usability and face validity. Differences in answers among groups were compared using simple logistic regression with 2-sided p-values. **Results:** 333 of 2290 physicians responded (RR=15%; 35% medical oncologists, 35% radiation oncologists, and 31% surgeons; 45% academic, 55% community practice). Overall, 67% agreed that doctors should discuss costs of care with patients; 33% disagreed. 60% reported addressing costs frequently/always and 40% rarely/never in their own practice. Medical oncologists were more likely than radiation or surgical oncologists to discuss costs with patients (OR 3.14 and 3.75, p$\leq$.00001). Compared to community physicians, academic physicians were less likely to discuss costs (OR 0.41, p=.00012), and felt less prepared for such discussions (OR 0.492, p=.005), but were more likely to consider costs to the patient (OR 2.68, p=.02) and to society (OR 1.822, p=.02) when planning treatment. Physicians who reported frequent discussions were significantly more likely to prioritize treatments in terms of cost, have a sense of their patients' financial well-being, feel their patients were well-informed about costs and believe doctors should explain both out of pocket and societal costs of care to their patients. Surgeons were most likely to refer patients to financial counselors (p=.01). The most common reported barriers were lack of resources to guide cost discussions (58%) and lack of time (44%). **Conclusions:** Though a majority of oncology physicians believe it is important to discuss costs of care, practice is inconsistent and there is no consensus on when and how to discuss costs. There is a need to define the goals and content of cost discussions and to address perceived barriers that limit this aspect of quality cancer care.

**6562 General Poster Session (Board #25), Mon, 1:15 PM-5:00 PM**

**Cancer cost evaluation in chemotherapy (chemo)-naive patients (pts) treated under a payer-sponsored pathway program.** *Presenting Author: Bruce A. Feinberg, Cardinal Health Specialty Solutions, Dublin, OH*

**Background:** US cancer costs are projected to increase to over $173 billion in 2020. Clinical pathways can help curb rising costs by reducing unnecessary and costly treatment variation while improving pt outcomes. Initial treatment may have the greatest pathway impact as it influences pt outcomes and subsequent care. We evaluated cost savings of a payer-sponsored pathway program for pts with cancer receiving first chemo intervention. **Methods:** A large payer for the Mid-Atlantic region of the US collaborated with its community oncology provider network to create a 3-year pathway program, managed by Cardinal Health, for chemo-naïve pts. Using claims data, 3 years of chemo and supportive care drug use were evaluated to establish a baseline cost trend for pts with breast cancer (BC), colorectal cancer (CRC), and lung cancer. Using this baseline as historical control, pts who started first-line treatment in pathway year 1 were included in the analysis. All drug costs were standardized to average sales price effective in the last quarter of the program year. Although voluntary, participating physicians received financial incentives for additional work required to manage the program. **Results:** The pathway cohort consisted of 453 pts; historic control cohorts for years 1-3 consisted of 362, 325, and 387 pts, respectively. Arms were well balanced; 24% were diagnosed with CRC in the study arm vs 26% in the control arm; 45% vs 44% for BC, and 31% vs 30% for lung cancer, respectively. Savings relative to projected cost/pt/year for pathway cohorts were $21,106 for CRC and $2,964 for lung cancer. For BC, cost increased $9,271. Overall mean cost/pt, adjusted for trastuzumab use (29% study vs 21% control), decreased 5% ($1,698 pt/yr) for an aggregate savings of $750,436. **Conclusions:** Voluntary pathway participation can lower drug cost of common malignancies even in first-line treatment. The approach of limiting pathway inclusion to chemo-naive pts will provide the greatest clarity of pathway impact throughout the duration of illness. This is our third report of reduced cancer care cost despite enhanced physician reimbursement. We believe the body of evidence dispels concerns about reproducibility of pathways benefits.

**6563 General Poster Session (Board #26), Mon, 1:15 PM-5:00 PM**

**Patients and physicians can discuss the actual costs of cancer treatment with high interest and little conflict.** *Presenting Author: Ronan Joseph Kelly, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

**Background:** As one solution to reducing costs and medical bankruptcies, experts such as the Institute of Medicine and ASCO have suggested patients and physicians should discuss the cost of care before doing the treatment. Whether these discussions are possible in an oncology setting, and their effects on the doctor-patient relationship are not known. We could find no published study of actual patients reviewing their costs in real time with their oncologist. **Methods:** We used the National Comprehensive Cancer Network (NCCN) Guidelines and the eviti Advisor platform to show patients with metastatic breast, lung, or colorectal cancer the costs associated with their treatment options during an oncology consultation. We measured provider attitudes and assessed patient satisfaction when the consultations included the costs of expected care. **Results:** We approached 107 patients: 96 (90%) enrolled in the study, 3 (3%) asked if they could be interviewed at a later date, and only 8 (7%) did not want to participate. Only 5/18 oncologists (28%) felt comfortable discussing costs, and only 1/18 (6%) regularly asked patients about financial difficulties. The majority of patients (80%) wanted cost information, and 84% reported that these conversations would be even more important if their co-pays were to increase. In total, 72% of patients responded that no health care professional has ever discussed costs with them. The majority of patients (80%) had no negative feelings to hearing cost information, and did not think it added conflict to the patient-physician relationship. **Conclusions:** In an era of rising co-pays, the great majority of cancer patients want cost of treatment discussions, especially if they have increased personal financial responsibility. These conversations do not lead to negative feelings in the great majority of patients. Additional training to prepare clinicians for how to discuss costs with their patients is needed.

**6564 General Poster Session (Board #27), Mon, 1:15 PM-5:00 PM**

**Staging in early breast cancer: Help or hindrance?** *Presenting Author: Naera Waters, Medical Oncology Department, Auckland City Hospital, Auckland, New Zealand*

**Background:** In 2012, ASCO identified staging CT, radionuclide or PET scans for asymptomatic, low risk breast cancer pts as one of the 5 big money wasters in oncology, due to a lack of demonstrated benefit and the potential harm of a false positive diagnosis. We assessed the frequency of staging CT and bone scans in asymptomatic pts with early breast cancer, whether metastases were conclusively detected, and the impact of inconclusive results. **Methods:** 664 consecutive pts with breast cancer referred to the Auckland Regional Cancer and Blood Service between 1 Nov 2010 and 25 Oct 2013 were identified from a prospectively collated referral database. 273 pts were excluded for locally recurrent or metastatic disease, symptoms requiring investigation, or neoadjuvant therapy. Age, LN status, tumour type and grade, receptor and HER2 status and results of staging and follow up scans were recorded in 391 women. **Results:** 81/330 (25%) pts with <4 nodes involved (N0/1) had staging CT, bone scan or both. Metastatic breast cancer (MBC) was found in 2/81(2%) and staging was negative in 51%. 38(47%) pts had radiological abnormalities of uncertain importance. Follow up scans showed 2/38 of these abnormalities were MBC, and 2 lung cancer (1 early stage, 1 metastatic), (total metastatic 3/38=8%). 59/61(97%) pts with >4 nodes (N2+) had staging. MBC was identified in 2 pts (3%), 1 of whom also had early stage lung cancer. 33 (56%) pts had indeterminate radiological findings, of which 5 (15%) were later confirmed to be MBC. Staging was negative in 41%. Up to 5 follow up scans per pt and 1-24 mo were required to clarify indeterminate findings **Conclusions:** Staging investigations modified adjuvant treatment plans in only 4/140 (3%) pts who were found to have MBC. 11% of women with indeterminate lesions on staging were later shown to have either metastatic breast (n=7) or metastatic lung cancer (n=1) underscoring the importance of continuing adjuvant therapy where uncertainty exists. Indeterminate results were frequent, imply the possibility of incurable cancer, and required up to 24 mo and 5 extra scans before pts could be reassured. This causes great uncertainty and distress for pts and consumes limited healthcare resources. The harms and benefits of staging in early breast cancer should be carefully weighed.

**6565 General Poster Session (Board #28), Mon, 1:15 PM-5:00 PM**

**Cost-effectiveness of alternative adjuvant bisphosphonate regimens in postmenopausal women with early breast cancer.** *Presenting Author: Katherine Elizabeth Reeder-Hayes, Lineberger Comprehensive Cancer Center, Chapel Hill, NC*

**Background:** The benefit of bisphosphonate drugs in adjuvant breast cancer care has been a topic of clinical debate. A recently presented meta-analysis of clinical trials by Coleman et al (2013) suggested recurrence and survival gains from adding bisphosphonates to the adjuvant treatment of post-menopausal women, but the most efficacious bisphosphonate dose and schedule has not been defined. Our study assessed the cost-effectiveness of bisphosphonate regimens available in the United States based on available clinical trials and meta-analysis data. **Methods:** We used a decision tree model to assess costs and benefits of the following regimens: no treatment, alendronate (A) 70 mg/week, low dose ibandronate (I) 150 mg/month, high dose I 50 mg/day, low dose zoledronic acid (Z) 4 mg/6 months, or high dose Z (six doses in the first 6 months, eight doses in the next 24 months and five doses in the final 30 months). All regimens except high dose Z were continued for three years. The model followed a simulated cohort of 100,000 post-menopausal women with non-metastatic breast cancer over ten years. Using a payer perspective, we considered direct medical costs and quality of life effects of initial treatment, distant recurrence, and complications of bisphosphonate therapy. The primary outcome was cost per quality-adjusted life year (QALY). We performed one-way and probabilistic sensitivity analyses to assess the robustness of results to variations in parameter estimates. **Results:** In the base-case model, A and low dose I were cost-saving compared to no therapy, while low dose Z was cost-effective with an incremental cost-effectiveness ratio (ICER) of $10,317/QALY gained. More intensive regimens including high dose I and high dose Z were not cost-effective at a willingness-to-pay threshold of $50,000/QALY gained. **Conclusions:** The cost-effectiveness of adjuvant bisphosphonate therapy in this patient population varies considerably depending on the choice of regimen. Until further evidence is available regarding the comparative benefit of differing regimens used in clinical trials, clinicians seeking to integrate bisphosphonates into adjuvant breast cancer care should consider lower dose regimens.

**6566 General Poster Session (Board #29), Mon, 1:15 PM-5:00 PM**

**Impact of prior cancer on eligibility for lung cancer clinical trials.** *Presenting Author: David E. Gerber, The University of Texas Southwestern Medical Center, Dallas, TX*

**Background:** Fewer than 3% of adult oncology patients in the U.S. enroll onto clinical studies. Stringent eligibility criteria are a key factor limiting accrual. Among these, the assumption that a prior cancer diagnosis could interfere with study conduct or outcomes results in frequent exclusion of subjects with a prior cancer. We determined the prevalence and characteristics of prior cancer-related exclusion criteria in lung cancer clinical trials, and estimated their impact on study accrual. **Methods:** We reviewed lung cancer clinical trials sponsored or endorsed by the Eastern Oncology Cooperative Group, 1986-2013, for exclusion criteria related to a prior cancer diagnosis. We assessed the association between trial characteristics and prior cancer exclusion using chi-square analysis. We estimated prevalence of prior primary cancer diagnoses among lung cancer patients using Surveillance Epidemiology and End Results (SEER)-Medicare linked data. We applied these figures to trial accrual goals to estimate the percent and absolute number of patients excluded. **Results:** Fifty-one clinical trials were included. Trial accrual ranged 10-1500 patients (mean 290; total 14,785). Forty trials (78%) excluded patients with a prior cancer diagnosis as follows: any prior (16%), diagnosed within 5 years (39%), diagnosed within 2 or 3 years (7%), or active cancer (16%). Eighty-nine percent of trials with survival as a primary endpoint and 70% of trials with non-survival primary endpoints excluded patients with prior cancer ($P$=0.12). In SEER-Medicare data (N=210,509), rate of prior cancer diagnosis ranged 14-24% according to lung cancer stage and histology; 56% of prior cancers were diagnosed ≤5 years before the lung cancer diagnosis. Across trials, the estimated number and proportion of patients excluded due to prior cancer ranged from 0 to 207 (0-18%). **Conclusions:** A substantial proportion of patients are reflexively excluded from lung cancer clinical trials due to prior cancer. This inclusion criterion is applied widely across studies, including more than two-thirds of trials with non-survival endpoints. More research is needed to understand the basis and ramifications of this standard exclusion policy.

**6567 General Poster Session (Board #30), Mon, 1:15 PM-5:00 PM**

**Asian and non-Asian disparities in outcomes of head and neck cancer (HNC).** *Presenting Author: Jason D. Kim, British Columbia Cancer Agency, Vancouver, BC, Canada*

**Background:** Racial differences in cancer outcomes are frequently observed for specific tumor types, including nasopharyngeal cancers, but prior research has mainly focused on disparities between Black and White races. Our aim was to evaluate the impact of Asian and non-Asian races on overall survival (OS) in a large population-based cohort of HNC. **Methods:** All patients diagnosed with non-nasopharyngeal HNC from 2001 to 2010 and referred to any 1 of 5 regional comprehensive cancer centers in British Columbia, Canada were reviewed. Using specialized software (Onomap, Inc.) that recognized common and distinctive surnames based on race, patients were classified as Asians vs. non-Asians. Using Kaplan-Meier methods and Cox regression, we examined the relationship between race and OS while controlling for confounders that consisted of additional socio-demographics and other tumor and treatment-related characteristics. **Results:** We identified a total of 3,036 patients: median age was 64 years (range 20-100), 74% were men, 32% were ECOG 0/1, and 7% and 93% were Asian and non-Asian, respectively. Comparing baseline characteristics between racial groups, Asians tended to exhibit worse prognostic features in that they had poorer functional status (ECOG 2+, 29% vs. 23%, p=0.07) and were more frequently affected by larger tumors (>4 cm, 33% vs 21%, p=0.02) and by oral cavity cancers (38% vs. 25%, p<0.001) than non-Asians. With respect to treatment, Asians were less likely to receive multimodality therapy than non-Asians (90% vs. 95%, p=0.02). Upon adjusting for prognostic factors, multivariate models showed that non-Asians actually had significantly higher odds of death when compared to Asians (HR 2.46, 95%CI 1.25-4.87, p=0.009). Advanced age, worse ECOG, greater tumor size, and lack of treatment also correlated with inferior OS. **Conclusions:** In addition to the racial differences reported in the literature for nasopharyngeal carcinoma, we observed variations in non-nasopharyngeal HNC outcomes between Asians and non-Asians. Despite worse prognostic features and less treatment, Asians exhibited better survival than non-Asians, suggesting a potential difference in tumor biology, pharmacogenetics, or predisposition to HPV exposure.

**6568 General Poster Session (Board #31), Mon, 1:15 PM-5:00 PM**

**Socioeconomic status and lifestyle behaviors in cancer survivors.** *Presenting Author: Hiten Naik, Ontario Cancer Institute, Princess Margaret Cancer Centre, Toronto, ON, Canada*

**Background:** Socioeconomic disparities in cancer survival exist even in universal healthcare systems. These disparities may be explained in part by lifestyle behaviors such as smoking and physical activity (PA). We evaluated the associations between socioeconomic variables and changes in smoking and PA after diagnosis in Ontario cancer survivors. **Methods:** 1,252 adult cancer survivors across diverse disease sites were surveyed about their smoking and exercise habits. Using multivariate logistic regression models, we evaluated the association of income, occupation, and education with each behavior, after adjusting for clinicodemographic and pathological covariates. **Results:** Cancer survivors were surveyed at a median of 26 months after diagnosis. 16% had breast cancers, 12% gastrointestinal, 26% gynecological/genitourinary, 14% head and neck, 6% lung and 19% hematologic. 15% reported being smokers at diagnosis; 45% reported being physically inactive; after diagnosis, 56% had quit smoking and 18% increased their PA. Survivors with a lower education level were more likely to be current smokers (p<0.0001) and less likely to quit if they were smoking at diagnosis (p=0.02). Similarly, patients with less education were more likely to be physically inactive currently (p<0.0001), and less likely to improve if they were inactive when they were diagnosed (p=0.004). In contrast, household income and occupation were not associated with current engagement or changes in these behaviours. Population-based marginalization indices confirmed that factors related to education level were significantly associated with smoking cessation (p<0.05). **Conclusions:** Cancer survivors with lower educational levels were more likely to have at baseline, and maintain, after diagnosis, unhealthy lifestyle behaviors. Targeting at-risk survivors by education level should be evaluated as a strategy in cancer survivorship programs.

**6569 General Poster Session (Board #32), Mon, 1:15 PM-5:00 PM**

**Impact of patient navigation on women with cervical abnormalities.** *Presenting Author: Electra D. Paskett, The Ohio State University Comprehensive Cancer Center - Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH*

**Background:** Almost 40% of women with cervical abnormalities fail to return for timely and proper follow-up care with higher rates among minority/underserved populations. As part of the Patient Navigation Research Program (PNRP), we examined the effect of patient navigation (PN), vs usual care on timely follow-up for women with cervical abnormalities. **Methods:** Cervical patients from 4 PNRP sites were divided into low- and high-risk sets and analyzed separately. Low-risk patients (n=2,088) were those who enrolled with an initial pap finding of ASCUS with a positive high-risk HPV serotype, atypical glandular cells or LGSIL. High-risk patients were those who enrolled with an initial finding of HGSIL (n=229). A dichotomous outcome of resolution within 180 days was used for the low-risk set, and resolution by 60 days for the high-risk, consistent with guidelines. A logistic mixed-effects regression model was used to evaluate the intervention effect using a random effect for arm within institution. A backwards selection process was used for multivariable model building considering the impact of each predictor on the intervention effect. **Results:** The final multivariable model for resolution within 180 days for the low-risk cases included arm, age, race and an interaction between race and arm. Patients aged 30+ years showed an increased odds of resolution as compared to those under 30, regardless of arm (Table). The PN arm showed an improvement in the odds of resolution across all racial groups, but significant positive effects were observed in non-English speaking Hispanics (p=0.0002). **Conclusions:** Patients with low-risk lesions showed a benefit from PN with a significantly increased odds of resolution within 180 days for non-English speaking Hispanics. At-risk populations can particularly benefit from PN programs. Clinical trial information: NCT01569672 NCT00613275.

**Multivariable model estimated ORs (95% CI) for resolved within 180 days for low-risk patients.**

| Predictor | Comparison | OR for resolved within 180 days (95% CI) | p-value |
|---|---|---|---|
| Age | 30-39 vs. <30 | 1.74 ( 1.32, 2.30) | <.0001 |
| | 40+ vs. <30 | 1.65 ( 1.20, 2.25) | 0.002 |
| Race by arm | Black: PN vs. control | 1.41 ( 0.69, 2.88) | NS |
| | White: PN vs. control | 1.58 ( 0.78, 3.17) | NS |
| | Hisp-Eng: PN vs. control | 2.02 ( 0.95, 4.32) | 0.07 |
| | Hisp-NonEng: PN vs. control | 5.88 ( 2.81, 12.29) | 0.0002 |

**6570 General Poster Session (Board #33), Mon, 1:15 PM-5:00 PM**

**Urban and rural differences in outcomes of head and neck cancer (HNC).** *Presenting Author: Tian Yang Darren Liu, British Columbia Cancer Agency, Vancouver, BC, Canada*

**Background:** Management of HNC is becoming more specialized where effective treatments frequently require multidisciplinary and multimodality care. Concerns exist that access to such complex care may be suboptimal for marginalized subsets of the population. Our aim was to examine for potential urban and rural disparities in HNC outcomes within a population-based single payer healthcare system. **Methods:** All patients diagnosed with HNC from 2001 to 2010 and referred to any 1 of 5 regional comprehensive cancer centers in British Columbia, Canada were reviewed. Based on census data, patients were classified into 4 categories: 1) rural 2) small urban 3) moderate urban and 4) large urban areas. Kaplan Meier methods and Cox regression were used to correlate site of residence with overall survival (OS), controlling for prognostic factors that included socio-demographics and other tumor and treatment-related characteristics. **Results:** A total of 3,036 patients were included: median age was 64 years, 74% were men, and 32% were ECOG 0/1. The majority resided in large urban areas (55%) followed by rural (22%), moderate urban (13%), and small urban (10%). There were no clinically significant differences in baseline characteristics across the 4 groups. In multivariate-adjusted models, advanced age >/= 65 years (HR 1.58, 95%CI 1.21-2.06, p<0.001), ECOG 2+ (HR 4.20, 95%CI 2.41-4.93, p<0.001), and lack of multimodality treatment (HR 2.88, 95%CI 1.72-4.81, p<0.001) correlated with inferior OS, but site of residence did not (Table). In subgroup analyses that stratified by type of treatment (radiation, chemotherapy, and/or surgery) and anatomic location of HNC (oral cavity, oropharynx, larynx, hypopharynx, nasopharynx), OS remained similar irrespective of urban or rural residence. **Conclusions:** Urban-rural differences in outcomes were not observed. The centralization of HNC management in this large population-based cohort represents an appropriate model of care for cancers in which multimodality treatments are increasingly complex and where disparities in access may be prevalent.

| Residence | HR for death | 95%CI | P-value |
|---|---|---|---|
| **Rural** | 1.0 | -- | -- |
| **Small urban** | 1.27 | 0.77-2.10 | 0.35 |
| **Moderate urban** | 0.84 | 0.52-1.37 | 0.49 |
| **Large urban** | 1.19 | 0.80-1.56 | 0.51 |

**6571 General Poster Session (Board #34), Mon, 1:15 PM-5:00 PM**

**Bridges to care: Results from a novel cancer outreach initiative.** *Presenting Author: Christopher S. Lathan, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Disparities in incidence and mortality for ethnic minorities have been described for a multitude of cancers, yet few interventions have been established in underserved areas. This study, started in 2012, describes preliminary results from a collaboration between a Federally Qualified Health Center (FQHC), in Roxbury, Massachusetts, and Dana-Farber Cancer Institute. The intervention is based on a co-location model with medical oncologists evaluating patients on site at the FQHC. Services include screening, diagnosis, survivorship, and if needed expedited evaluation and treatment at Dana-Farber. **Methods:** Pre-intervention clinical data on incident cancer cases was collected from the FQHC over a 2 year period and compared to intervention data, which included demographics, total number of patients with a cancer diagnosis, percentage of patients on clinical trial, and our outcome of interest: median time from presentation to resolution.(MTR) Non-parametric analyses of the effect of demographics on the primary outcome was performed. 160 patients were evaluated at the outreach facility over a two year period, with 84 patients having a cancer diagnosis. 94 patients were consented into a prospective research cohort, the basis of this analysis. **Results:** 40 patients with cancer were diagnosed at the FQHC from 2009-2011 before the intervention. The MTR for all cancers was 32.5 days. From 2012-2013, 160 patients were evaluated via the outreach initiative. The majority of the patients were African American (81%), with a median age 55. Of the 94 research cohort patients, 60% were women, 53% had a cancer diagnosis. (N=50), and 50% of the patients on active treatment were on a clinical trial. The MTR for patients seen via the intervention, was 11.5. Race, language, and insurance all had no significant effect on MTR. **Conclusions:** Compared to historical data, preliminary analysis of the clinical outreach initiative showed an increase in cancer diagnoses, favorable reduction in time to resolution, and high clinical trial enrollment. A future prospective case control analysis is planned, but initial observational data is encouraging.

**6572 General Poster Session (Board #35), Mon, 1:15 PM-5:00 PM**

**Patterns of hospice use for metastatic cancer in the American Indian/Alaska Native and non-Hispanic white populations.** *Presenting Author: Stacey Shiovitz, University of Washington, Seattle, WA*

**Background**: Hospice care should be available to all individuals with terminal cancer, regardless of race or ethnicity. Little is known about end-of-life care for American Indian/Alaska Native (AI/AN) persons with cancer. Accordingly, the aim of this study was to compare the use of hospice care between AI/AN individuals with non-Hispanic Whites (NHW) with metastatic cancer. **Methods**: Using the linked Surveillance, Epidemiology and End Results (SEER)-Medicare database, we identified AI/AN and NHW who were diagnosed with distant-stage breast, prostate, lung, colorectal, stomach, or ovarian cancer from 2001 to 2008 and had Medicare claims records through 12/31/09. Among individuals who died during the study period and were enrolled in Medicare until death, we evaluated the proportion with hospice initiation. Among hospice initiators, we also assessed late utilization of hospice, defined as enrollment <7 days prior to death. Logistic regression models were used to compare the AI/AN and NHW patients. **Results**: Compared to NHW (n=70,990), AI/AN (n=370) with metastatic cancer were younger (74.6 v. 76.2 yr, p<0.001), but had similar gender distribution (male: 52 v. 48%, p=0.2) and Klabunde co-morbidity scores at diagnosis (0.37 v. 0.36, p=0.75). Rural residence was similar, but AI/AN had lower reported income (p<0.001) and proportion who were married (p<0.001). Among patients who died, enrollment in hospice was lower for AI/AN (46%) compared to NHW (58%), with AI/AN race associated with a significantly lower odds of hospice enrollment (OR 0.72, 95% CI 0.57-0.91, p=0.01). However, late enrollment on hospice was not significantly different between AI/AN and NHW (28 v. 34%; OR 0.87, 95% CI 0.60-1.26, p=0.45). Male gender, higher Klabunde score, and certain SEER catchment areas were also associated with lower hospice enrollment (all p<0.001). **Conclusions**: AI/AN metastatic cancer patients were less likely than NHW patients to use hospice services. However, the proportion with late utilization of these services was similar. It is unclear if decreased utilization of hospice in AI/AN terminal cancer patients is due to decreased access to hospice or differences in beliefs about end-of-life care.

**6573 General Poster Session (Board #36), Mon, 1:15 PM-5:00 PM**

**The association between American Indian/Alaska Native race and time to treatment initiation for nonmetastatic breast, colorectal, and lung cancer patients in Medicare.** *Presenting Author: Scott V. Adams, Hutchinson Institute for Cancer Outcomes Research, Fred Hutchinson Cancer Research Center, Seattle, WA*

**Background:** Early initiation of treatment following a cancer diagnosis is associated with better patient outcomes. Therefore, we compared time to treatment initiation in American Indian/Alaska Native (AIAN) vs. non-Hispanic White (NHW) cancer patients, with the goal of identifying a modifiable factor to improve survival among AIAN cancer patients. **Methods:** We used Surveillance, Epidemiology, and End Results (SEER) registry data linked to Medicare claims to identify new cases of colorectal, lung, or female breast cancer who were: 1) diagnosed from 2001-2007 with local or regional stage disease, 2) residing in a SEER catchment area, 3) enrolled in Medicare A and B at diagnosis, 4) ≥65 years old, and 5) AIAN or NHW. Cancer diagnosis date was obtained from SEER; the date of first surgical, chemotherapeutic, or radiation treatment was ascertained from Medicare claims. We used Cox regression models to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) comparing the rate of treatment initiation during the 6 months following diagnosis between AIAN and NHW patients, stratified by cancer site and stage. Model covariates were age, sex, diagnosis year, marital status, rural residence, and pre-diagnosis Klabunde comorbidity score. **Results:** 146,877 NHW and 522 AIAN patients were diagnosed with local or regional breast, colorectal, or lung cancer over the study period. Compared to NHWs, AIANs were younger (mean age 75.0 vs. 76.2y), more likely to live in rural areas (37% vs. 22%), and had higher co-morbidity scores (mean Klabunde 0.43 vs. 0.36). The rate of treatment initiation during the 6 months following diagnosis was lower in AIAN compared to NHW patients diagnosed with breast (HR=0.85, CI: 0.72-0.99), colorectal (HR=0.74, CI: 0.63-0.87), or lung (HR=0.82, CI: 0.67-1.00) cancer. **Conclusions:** Our results suggest that despite equal Medicare insurance coverage, AIANs may experience delays in treatment initiation compared to otherwise similar NHWs. Decreasing the time to treatment initiation may improve survival rates for AIAN cancer patients, who currently have among the lowest five-year survival rates of any racial group.

**6574 General Poster Session (Board #37), Mon, 1:15 PM-5:00 PM**

**Impact of race on outcome of stage II colon cancer subjects not receiving adjuvant therapy.** *Presenting Author: Amy L. Cleveland, University of Arkansas for Medical Sciences, Little Rock, AR*

**Background:** The etiology of racial disparity in colorectal cancer outcome has been controversial. Higher mortality rates (per 100,000/yr.) of 31.4 in African Americans [AA] compared to 21.4 in Caucasians [C] could be due to biology or treatment-related variables. Access to care within the Veterans Affairs [VA] health system is similar for all veterans. The outcome of subjects with stage II colon cancer treated with surgery alone in the VA system was investigated in order to evaluate the possibility of difference in tumor biology rather than patient and treatment related variables. **Methods:** A retrospective study of recurrence and overall survival [OS] comparing AA vs. C was conducted using data from the VA health system's 10-institution database (VISN-16) from 10/1/1996 to 3/31/2010 adjusted for age, gender, T-stage, and number of lymph nodes (LN) resected at the time of surgery. None of the subjects received adjuvant therapy. Patient characteristics were analyzed via chi-square tests. OS was analyzed using Kaplan-Meier methods. **Results:** There were 226 deaths among 513 subjects during 2,645.4 total years of follow-up. Median OS was 9.9 years in AA versus 7.9 years in C (log-rank p=0.22). Age, gender, T stage, and number of lymph nodes were balanced between races (see table). **Conclusions:** There was no difference in OS of AA compared to C with stage II colon cancer subjects treated with surgery alone. The two groups had no statistical difference in stage, median age, gender, lymph node resection or T stage. These results indicate that the difference in the outcome of AA and C with colon cancer may not be due to tumor biology.

| Variable | | African American | Caucasian | p Value |
|---|---|---|---|---|
| N=513 | | 135 (26%) | 378 (74%) | |
| Median age (range) in years | | 71 (40-91) | 71 (44-87) | 0.98 |
| ≥12 lymph nodes excised | | 69 (49%) | 175 (46%) | 0.57 |
| T stage | T1 | 1 (0.7%) | 5 (1.3%) | 0.83 |
| | T2 | 3 (2.2%) | 7 (1.8%) | |
| | T3 | 60 (44%) | 182 (48%) | |
| | T4 | 69 (51%) | 180 (48%) | |
| Gender | | 97.0% male | 97.9% male | 0.82 |
| Recurrence | | 18/120 (15%) | 37/346 (11%) | 0.21 |
| Median overall survival (years) | | 9.94 | 7.91 | 0.22 |

**6575 General Poster Session (Board #38), Mon, 1:15 PM-5:00 PM**

**Low area-level socioeconomic status and breast cancer biologic features in a diverse population-based sample.** *Presenting Author: Jennifer J. Griggs, University of Michigan, Ann Arbor, MI*

**Background:** The purpose of this study was to investigate the association between area-level socioeconomic status (SES) and breast cancer biology controlling for demographic factors and comorbid conditions in a diverse population-based sample. **Methods:** We enrolled women with Stages I – III breast cancer reported to the Los Angeles County and Detroit Tri-County Surveillance, Epidemiology and End Results (SEER) registries between 1998 and 2004. Black women and Latinas were over-sampled. Census block-level SES was assigned using a validated composite of six variables from the 2000 Census and then divided into quartiles. Clinical and pathology data from medical records supplemented SEER registry data. Bivariate and multivariate analyses investigated relationships between SES and tumor grade, hormone receptor status, triple-negative status, and lymphovascular invasion (LVI) controlling for race/ethnicity, obesity status, diabetes, hypertension, and menopausal status. **Results:** The sample included 1,931 women (988 non-Hispanic whites, 611 blacks, and 332 Hispanics). In bivariate analyses, lower SES was associated with higher grade ($p < 0.001$), higher rates of LVI ($p = 0.007$), and hormone receptor-negative disease ($p < 0.001$). In multivariate analyses, area-level SES was significantly associated with Grade 3 disease (OR 1.86, 95% CI 1.11 – 3.09 for the lowest SES quartile), hormone receptor-negative disease (OR 1.96, 95% CI 1.11 – 3.46 for the lowest quartile, p value for trend 0.02). SES was also significantly associated with triple-negative disease (OR 4.93, 95% CI 1.37 – 17.82 for the lowest quartile, p value for trend 0.01). Black race was not associated with tumor biologic features with the exception of hormone receptor -negative disease (OR 2.11, 95% CI 1.41 – 3.18). **Conclusions:** In this population-based study, low area-level SES was independently associated with unfavorable tumor biology. Environmental factors, the allostatic load caused by chronic stress, and lifestyle behaviors may contribute to the poorer breast cancer-specific outcomes associated with lower SES.

**6576 General Poster Session (Board #39), Mon, 1:15 PM-5:00 PM**

**Disparities in breast cancer surgery: The lingering effect of race.** *Presenting Author: Vanessa Sheppard, Georgetown University, Washington, DC*

**Background:** Stage migration may be associated with delays in surgical breast cancer treatment >90 days. Although it is not recommended to have a 3-month span from diagnosis to definitive surgical management, there are no precise guidelines that establish a model time interval. This study investigates racial disparities in time to receiving first surgical treatment (i.e. surgical delay) in breast cancer patients. **Methods:** A cohort study of 290 insured Black (56%) and White (44%) women with primary breast cancer participated in telephone interviews that gathered data on psychosocial (e.g., self-efficacy) and healthcare factors (e.g., communication, barriers). Clinical data were abstracted from medical records. Time to surgical delay was defined as the time in days between diagnosis and definitive surgical treatment. We also considered 60-day and delay outcomes. We used unadjusted hazard ratios to examine univariate relationships between delay outcomes and covariates. Cox proportional hazard models were used for multivariate analyses. **Results:** Median time to surgery was 41 days and was higher in Blacks (m=47 days) compared to Whites (m=33 days) (p= .001). Considering the 90-day outcome, Black women had greater delay to surgery than White women after covariates adjustment (HR= 1.7; 95% CI: 1.2 to 2.3). Women reporting internet use (vs. not) and those with breast conserving surgery (vs. mastectomy) had greater delay to surgery (p<. 01) after adjustment. **Conclusions:** Prolonged delays to definitive breast cancer surgery persist among Black women. Most notably, racial differences persisted for the 90-day interval that has been associated with poorer outcomes. Interventions to address delay in Black patients are needed.

**6577 General Poster Session (Board #40), Mon, 1:15 PM-5:00 PM**

**Impact of location to repeat mobile mammography utilization trends: 10-year analysis of a comprehensive urban cancer center.** *Presenting Author: Elizabeth Carloss Riley, University of Louisville, School of Medicine, Louisville, KY*

**Background:** Mobile Mammography Units (MMU) are a model of community outreach through targeted locations. The purpose of this study was to analyze the association between MMU utilization and screening location in the largest county in Kentucky. **Methods:** From January 2001- December 2010, 48,324 screening mammograms were performed with 21,587 unique subjects. Locations were divided into three categories: Corporate, Partnership Clinics (public health clinics) and Partnership Community (local events.) Utilization was defined as once, twice or more than 3 times in a 10 year period. The *p*-values were computed using the Pearson Chi-square test. The comparison with a *p*-value $< 0.05$ was considered statistically significant. **Results:** Partnership Clinic accounted for the majority of encounters (40.6%) and was most likely to repeat twice (19.1%) or 3 or more times (30.2%) in a 10 year period. Partnership Community accounted for the least at 24% and was least likely to utilize the van repeatedly (p=<.001.) The majority of screens occurred only once in a 10 year period regardless of location. **Conclusions:** To our knowledge this is the largest database of MMU reported in the literature. We previously reported on race and insurance status as predictors of repeat utilization. The current dataset suggests women referred from the Partnership Clinic (Public Health Clinics) are most likely to repeat utilize the van which would be consistent with the intended purpose of the MMU as these patients are most likely to be uninsured or underinsured. Partnership Community are the least likely to repeat utilize however further analysis is needed to determine whether consistency of offered location from year to year could impact these trends as the Community group locations may be less consistent annually. Analysis of the trends of utilization of MMU based on location has implications for funding and outreach.

| | Total N= 21857 | 1 screen N=11816 | 2 screens N=3983 | >/= 3 screens N=6058 | P value <.001 |
|---|---|---|---|---|---|
| Corporate (%) | 7741 (35.4) | 4223 (54.6) | 1385 (17.9) | 2133 (27.6) | |
| Partnership clinic (%) | 8874 (40.6) | 4499 (50.7) | 1694 (19.1) | 2681 (30.2) | |
| Partnership community (%) | 5242 (24.0) | 3094 (59.0) | 904 (17.2) | 1244 (23.7) | |

**6578 General Poster Session (Board #41), Mon, 1:15 PM-5:00 PM**

**Misconceptions in colorectal cancer among a community-based population and CRC screening adherence.** *Presenting Author: Thomas Guerrero, Internal Medicine Residency Program, Memorial Hospital of RI, W Alpert Medical School, Brown University, Pawtucket, RI*

**Background:** Colorectal cancer (CRC) screening rates among Latinos are lower than those of non-Latinos. Prior research suggests that a higher proportion of Latinos have erroneous understandings of cancer and many have misperceptions about cancer that may negatively impact their preventive behavior. The goal of this study was to estimate the prevalence of previously identified CRC misconceptions among a sample of primary care patients. **Methods:** Cross-sectional survey of primary care primary care patients with an oversampling of Spanish-speaking patients. The survey included items specifically developed to assess participants' knowledge regarding previously identified misconceptions of CRC risk factors: (1) constipation increases risk of developing CRC, (2) constipation increases the risk of developing polyps, (3) polyps consist of excess cholesterol, and (4) rectal sex increases the risk of developing CRC. Individual misconceptions and a composite misconception score were calculated based on these items and compared across race, ethnicity, and language of survey respondent (English vs. Spanish). **Results:** Of 1,600 surveys mailed, the response rate was 41.1% with 346 responding in English and 311 responding in Spanish. Mean age for the sample was 59 years, 60% of respondents were female, and 40% had less than high school education. For each individual misconception item, Spanish-speaking Latinos had rates of endorsing the misconception that were nearly twice those of non-Latinos: 76% vs. 38% for constipation increases risk of developing CRC; 63% vs. 32% for constipation increases the risk of developing polyps: 20% vs. 9% for polyps consist of excess cholesterol; and 38% vs. 21% for rectal sex increases the risk of developing CRC ($p<0.001$ for all comparisons). Ninety percent of Latino respondents vs. 64% of non-Latino respondents endorsed 2 or more misconceptions. **Conclusions:** In this sample of primary care patients, Latinos are more likely to hold misconceptions about CRC risk. While it is uncertain whether these beliefs negatively impact actual screening rates, it provides an opportunity for education.

**6579 General Poster Session (Board #42), Mon, 1:15 PM-5:00 PM**

**Disparities in age-related incidence of colon and rectal cancer in the United States, 1975-2010.** *Presenting Author: Christina Edwards Bailey, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** The overall incidence of colorectal cancer (CRC) has been decreasing since 1998, but there has been an apparent rise in the incidence of CRC in young adults. The primary aim of this study was to evaluate age-related disparities in secular trends in CRC incidence in the United States. **Methods:** A retrospective cohort study was performed using the Surveillance, Epidemiology, and End Results (SEER) registry. All patients diagnosed with colon or rectal cancer from 1975 to 2010 was queried. SEER*Stat (version 8.04, National Cancer Institute) was used to obtain the annual cancer incidence rates, annual percent change (APC), and corresponding p-values for the secular trends. **Results:** Overall age-adjusted CRC incidence decreased by 0.92% between 1975 and 2010. There has been a steady decline in the incidence of CRC in patients age 50 years or older, but the opposite trend has been observed in patients 20 to 34 years of age. The APC for patients with localized, regional, and distant colon cancer at diagnosis in the 20 to 34 year age group was 1.10 (95% CI 0.28 to 1.93; P=0.01), 0.91 (95% CI 0.23 to 1.61; P=0.01) and 1.81 (95% CI 0.88 to 2.75; P<0.001). The APC for patients with localized, regional and distant rectal cancer in the 20 to 34 year age group was 4.03 (95% CI 3.02 to 5.05; P<0.001), 3.05 (95% CI 1.95 to 4.17; P<0.001) and 2.66 (95% CI 1.33 to 3.99; P<0.001). Based on current trends, in 2030 the incidence rate for colon and rectal cancer will increase by 90% and 124.2% respectively for patients 20 to 34 years of age while decreasing by 37.8% and 34.3% for patients 50 to 75 years of age. **Conclusions:** There has been a significant increase in the incidence of CRC diagnosed in patients aged 20 to 34, with a decline in older patients. Further studies are needed to determine the cause for these trends and identify potential preventive and early detection strategies.

**Percent change of APC-based predicted incidence rate of colon and rectal cancer by age compared to incidence rate in 2010.**

| | Colon | | Rectal | |
|---|---|---|---|---|
| **Age group** | **2020** | **2030** | **2020** | **2030** |
| **20-34** | 37.8% | 90.0% | 49.7% | 124.2% |
| **35-49** | 13.0% | 27.7% | 20.8% | 46.0% |
| **50-75** | -21.2% | -37.8% | -19.0% | -34.3% |
| **>75** | -25.5% | -44.5% | -30.3% | -51.5% |

**6580 General Poster Session (Board #43), Mon, 1:15 PM-5:00 PM**

**Use of the 21-gene recurrence score assay (RS) and chemotherapy (CT) across health care (HC) systems.** *Presenting Author: Anosheh Afghahi, Stanford University School of Medicine, Stanford, CA*

**Background:** The Onco*type* DX (Genomic Health, Redwood City, CA; GHI) RS estimates 10-yr risk of distant recurrence and CT benefit in patients (pts) with ER+, early-stage breast cancer (EBC). After 10 yrs of RS use, variability across HC settings is poorly understood. **Methods:** Patient-level clinical data from electronic medical records (EMR) of Stanford University (HC-U) and Palo Alto Medical Foundation, a community practice (HC-C) in the same catchment area, were linked with demographic data from the California Cancer Registry. RS results were obtained from GHI. Multivariable analysis, adjusted for patient age, year of diagnosis, race/ethnicity, institution, stage, nodal status, grade and histology, was used to identify factors associated with use of RS and CT. **Results:** 3,584 EBC pts met RS indications (Stage I-II, ER+, HER2-negative). RS use was only 10.4% (373 pts, 95% confidence interval [CI] 9.5-11.5%), increasing over time (2010-2011 vs. 2005-2007: odds ratio [OR] 3.03, CI 2.23-4.10). On multivariable analysis, based on subjects with complete data, factors inversely associated with RS use were high grade (vs. low: OR 0.66, CI 0.44-0.99), involved nodes (vs. none: 0.17, 0.11-0.27) and age <40 (vs. 50-64: 0.37, 0.20-0.70) or ≥65 (0.24, 0.18-0.34). Low RS results were usually associated with less (vs. no RS: 0.39, 0.25-0.59), and high results with more (7.96, 2.49-25.5) CT use. However, the 638 (17.8%) pts seen in both HC systems more often had RS (vs. HC-U only: 3.72, 2.77-5.01), and received more CT (1.51, 1.17-1.95). **Conclusions:** In 2 HC systems, CT use usually followed RS guidance. Although lower than expected, RS use rose over time, perhaps a sign of clinicians' growing familiarity with RS. By contrast, the 17.8% of pts treated in both HC systems used more CT across all RS risk groups, suggesting less guidance by RS and over-utilization of care. These results may inform efforts to reduce unwarranted variability and optimize value.

**6581 General Poster Session (Board #44), Mon, 1:15 PM-5:00 PM**

**Current quality gaps in rectal cancer pathology reports.** *Presenting Author: Zaid M. Abdelsattar, University of Michigan, Ann Arbor, MI*

**Background:** High-quality pathology reporting is important for optimal management of rectal cancer (RC). To this end, several quality measures have been clinically validated or endorsed by the National Quality Forum (NQF). In this multi-institutional study, we assess the adherence to these measures and explore pathologists' perspectives. **Methods:** Seven quality measures (4 NQF endorsed) were assessed for adherence at 10 community and academic hospitals from 2007 to 2012 via trained data abstractor chart review. Measures included documentation of T stage, N stage and histologic grade; ≥12 lymph nodes; measurement of distal and radial margin; and grading of total mesorectal excision (TME) quality. Open-ended phone surveys were conducted with pathologists from six hospitals to identify differences in practice and barriers to improved practice. **Results:** A total of 333 patients underwent radical RC surgery. Adherence to all measures varied by hospital (Table). For example, only 75% of cases (range by hospital 64-100%) had ≥12 lymph nodes examined and the median number was 15 (range by hospital 13-34). Surveys revealed that pathologists would not find it burdensome to increase requirements for nodes or margin measurements; however, there were greater barriers to TME grading. Although all pathologists aim to retrieve ≥12 nodes, their methods vary and 33% routinely use defatting solutions. TME quality reporting is uncommon. 83% of pathologists were familiar with this measure; however, half of those were not comfortable reporting it to the surgeon. When asked about facilitators of best practices, pathologists emphasized: 1) comprehensive checklists, 2) pathology assistants, and 3) better communication with surgeons. **Conclusions:** Hospitals vary on the quality of RC pathology reporting, indicating significant room for improvement. Based on pathologist surveys, quality improvement interventions might include peer mentoring of node retrieval methods and strategies for better communication with cancer surgeons.

**Adherence to pathology quality measures.**

| Quality measure | Overall adherence, % | Range by hospital, % |
|---|---|---|
| **T stage** | 94 | 74 – 100 |
| **N stage** | 93 | 74 – 100 |
| **Grade** | 78 | 29 – 100 |
| **≥12 nodes** | 75 | 64 – 100 |
| **Radial margin** | 57 | 11 – 95 |
| **Distal margin** | 89 | 62 – 100 |
| **TME quality** | 12 | 0 – 69 |

**6582 General Poster Session (Board #45), Mon, 1:15 PM-5:00 PM**

**Survival of U.S. Medicare patients with advanced non-small cell lung cancer by line of therapy.** *Presenting Author: John R. Penrod, Bristol-Myers Squibb, Princeton, NJ*

**Background:** Prior real-world (RW) studies of advanced non-small cell lung cancer (adv NSCLC) have described overall survival (OS) from diagnosis (Dx) for all patients (pts) as well as separately by whether chemotherapy was received. More recently, innovations in systemic anti-cancer treatment (SATx) have expanded to include oral targeted agents. Current RW data on OS of advanced pts in the US are limited, particularly by line of therapy (LOT). In this study, we use data from a recent cohort of SEER-Medicare pts to examine OS from adv NSCLC Dx for all pts and separately by SATx status. For treated pts, we also describe OS from initiation of each LOT. **Methods:** Fee-for-service pts aged ≥66 enrolled in Medicare Parts A/B/D with an incident Dx of adv NSCLC (Stage IIIB/IV) during 2007–9 were identified in the SEER-Medicare linked database. OS follow-up was available through 12/31/2011. We examined demographic and clinical characteristics, including histology, and the receipt of SATx (chemotherapy, tyrosine kinase inhibitors, or monoclonal antibodies). We performed descriptive and Kaplan Meier (KM) analysis of OS from adv NSCLC Dx for all pts and separately by receipt of SATx. KM OS analysis by LOT was performed from date of treatment initiation. **Results:** Of 7,080 eligible pts, 26% had squamous, 51% had nonsquamous, and 24% had not otherwise specified histology; 28% of pts were Stage IIIB and 72% were Stage IV. Overall, 44% of pts received SATx. For all pts, median OS from Dx was 4.9 months, and 1- and 2-year OS rates were 23% and 7%, respectively (Table). Median OS from adv NSCLC Dx was 2.8 months for pts not receiving SATx and 9 months for pts receiving SATx ($P<.0001$). From initiation of each LOT, OS declined with each successive line, with median OS of 6.6, 5.9, and 5.3 months for 1L, 2L, and 3L, respectively. **Conclusions:** Despite advances in SATx for adv NSCLC, more than half of RW pts do not receive such treatment and outcomes for both treated and untreated pts remain poor, with fewer than 10% of pts alive at 2 years following Dx or initiation of SATx.

**OS of adv NSCLC pts.**

| | N (%) | Median OS (months) | 1-yr OS, % | 2-yr OS, % |
|---|---|---|---|---|
| **All pts** | 7,080 (100) | 4.9 | 23 | 7 |
| **SATx (from adv Dx)** | | | | |
| **Yes** | 3,131 (44) | 9.0 | 37 | 11 |
| **No** | 3,949 (56) | 2.8 | 11 | 3 |
| **LOT** | | | | |
| **1L** | 3,113 (44) | 6.6 | 28 | 8 |
| **2L** | 1,320 (19) | 5.9 | 25 | 7 |
| **3L** | 535 (8) | 5.3 | 21 | 5 |

**6583 General Poster Session (Board #46), Mon, 1:15 PM-5:00 PM**

**Influence of age on incident diabetes (DM) and cardiovascular disease (CVD) among prostate cancer survivors receiving androgen deprivation therapy (ADT).** *Presenting Author: Alicia Katherine Morgans, Vanderbilt University Medical Center, Nashville, TN*

**Background:** ADT has been associated with increased risk of developing DM and CVD, though this is controversial, particularly for CVD. We prospectively assessed the relationship between ADT and incident DM and CVD in the Prostate Cancer Outcomes Study (PCOS), a population-based cohort of prostate cancer survivors followed longitudinally for 15 years from diagnosis. **Methods:** We identified men in the PCOS with non-metastatic prostate cancer diagnosed from 1994-1995 and followed through 2009-2010. We used multivariable logistic regression models to compare groups receiving short-term ADT (<2 years), prolonged ADT (≥2 years) and no ADT to assess the relationship between ADT exposure and subsequent diagnoses of DM and CVD (determined by patient report and cause of death data). We evaluated the effects of age at diagnosis, race, stage, and comorbidity on the development of DM and CVD. **Results:** Among 3,526 men with comorbidity and treatment data, 2985 men without baseline DM and 3,112 men without baseline CVD constituted the DM and CVD cohorts, respectively. Regardless of duration of ADT exposure, there was not an increased risk of DM or CVD in men younger than 70 at diagnosis. Compared to no ADT exposure, prolonged ADT was associated with an increased risk of DM and CVD that increased steadily over age 76 at diagnosis for DM (OR 2.11 at age 74, 95% CI 1.02 – 4.36; OR 2.65 at age 80, 95% CI 1.09 – 6.47) and age 74 at diagnosis for CVD (OR 1.89 at age 74, 95% CI 1.02 - 3.49; OR 3.19 at age 80, 95% 1.25 – 8.17). Increasing comorbidity burden modified risk of DM and CVD (for ≥ 3 comorbidities versus no comorbidities; for DM, OR 4.25, 95% CI 2.3 - 7.9; and for CVD, OR 8.1, 95% CI 4.3 -15.5 P<0.001). **Conclusions:** The relationship between ADT and development of CVD and DM may be dependent upon age at diagnosis in addition to length of ADT administration, with longer ADT exposure predominantly increasing risk among older men only. Men with greater comorbid burden had increased risk of developing DM and CVD. Younger men with few comorbidities may not have an increased risk of developing DM or CVD despite treatment with ADT.

**6584 General Poster Session (Board #47), Mon, 1:15 PM-5:00 PM**

**Reporting quality of abstracts in cancer clinical trials.** *Presenting Author: Shanthi Sivendran, Hematology/Oncology Medical Specialists, Lancaster General Health, Lancaster, PA*

**Background:** Detailed and transparent abstracts are critical for assessing clinical trials. For some practitioners, access to full text manuscripts may be limited due to financial, language, and information technology considerations. In 2007, the Consolidated Standards of Reporting Trials (CONSORT) group generated an extension statement with recommendations regarding the minimum elements that should be included in an abstract. The degree to which these recommendations are adhered to in oncology publications has not been previously evaluated. **Methods:** A review of citations from PubMed, Medline, and Embase published between Jan 1, 2009 and December 31, 2011, identified randomized, controlled, phase III trials in metastatic solid malignancies. Abstracts were assessed for the 18 elements recommended in the CONSORT extension statement for abstracts; a completeness score (range, 0 to 18) was calculated by adding the number of elements reported. **Results:** 175 eligible publications with data for 96,125 patients were included in this analysis. The median completeness score was nine (range, three to 17). 67% of the abstracts also had a full text available for review through open access. The median completeness score of abstracts with available full text on open access (nine; range, four to 14) was similar to those full texts that were not available (10; range, three to 17). Of the 18 abstract elements, the items that were least frequently reported included - description of the trial design (18%), the method by which participants were allocated to interventions (14%), use of blinding (22%), whether the trial is ongoing (23%), registration and name of trial (25%) and the funding source (19%). Although 46% of publications included the number of participants randomized to each group only 26% of publications included the number of patients analyzed. **Conclusions:** Cancer clinical trial abstracts typically report only half of the reporting elements recommended by the CONSORT group. Further, there is significant heterogeneity in the quality of reporting. Inclusion of the CONSORT elements may allow for better interpretation and application of clinical information.

**6585 General Poster Session (Board #48), Mon, 1:15 PM-5:00 PM**

**Factors associated with loss of employment among metastatic patients.** *Presenting Author: Amye Tevaarwerk, University of Wisconsin Carbone Cancer Center, Madison, WI*

**Background:** Up to a third of those diagnosed with cancer do not return to work. Metastatic patients seem particularly vulnerable, but few data exist. We examined employment outcomes for working age metastatic patients on EZ202 (a symptom-based study conducted through ECOG) to understand metastatic employment patterns, and potentially modifiable factors associated with employment loss. **Methods:** E2Z02 prospectively enrolled cancer patients irrespective of therapy or stage. Employment was assessed by questionnaire: "Has your employment status changed due to illness?" [Answer = Yes/No] and "What is your current employment status?" [Answer = full-time; part-time; not in the workforce]. We excluded patients >65 years and without metastatic cancer. Factors associated with employment group (no longer working vs. stably employed) were evaluated using logistic regression. Variables examined included cancer type (breast, prostate, colon, lung), therapy status (none, hormone, all other treatment), gender, age (≤ 45, >45-55, >55-65), race/ethnicity (non-Hispanic white, all other), metastatic sites (none, bone/soft tissue, visceral, other, >2 sites), ECOG performance status (0-1, 2-4) and symptom interference on the MD Anderson Symptom Inventory (none-mild, moderate-severe). Factors with p-value <0.10 on the univariable analysis were further fitted into the multivariable model. **Results:** 3,106 analyzable patients accrued between 3/06 and 5/08; 668 metastatic patients had employment data. 236 of 668 (35%) worked full or part-time; 154 of 236 (65%) reported working without any change. Among patients no longer working, 302 of 432 (70%) reported change as being due to illness. PS, race/ethnicity, therapy status, and symptom interference were significantly associated with no longer working in multivariable analysis (respectively, p=0.0007, 0.03, 0.03, 0.0008). **Conclusions:** Working age metastatic patients often remain employed. Worse ECOG performance status and higher symptom interference were more likely among patients no longer working while hormone therapy and non-Hispanic white race were more likely among those stably working. These factors should be considered when counseling metastatic patients about continued employment. Clinical trial information: NCT00303914.

**6586 General Poster Session (Board #49), Mon, 1:15 PM-5:00 PM**

**Impact of National Cancer Institute (NCI)-mandated scientific review on protocol development and content.** *Presenting Author: Ning Ning, The University of Texas Southwestern Medical Center, Dallas, TX*

**Background:** The National Cancer Institute (NCI) requirement that all clinical trials involving cancer patients at NCI-designated cancer centers undergo a scientific review in addition to Institutional Review Board (IRB) review is unique among medical specialties. We evaluated the impact of this process. **Methods:** We collected data on oncology clinical trials undergoing full board review by the UT Southwestern Protocol Review and Monitoring Committee (PRMC) 2009-2013. We analyzed associations between trial characteristics, PRMC decisions, protocol changes requested, and protocol changes implemented using Chi-square testing, Fisher's exact testing, and logistic regression. **Results:** The analysis included 226 trials. Initial PRMC decisions were: approve (40%), approve pending response (52%), defer (7%), and disapprove (1%). Final PRMC decision was approve for 96% of trials. The PRMC requested a total of 270 changes (range 0-17 per protocol). Number of requested changes per protocol was associated with trial type (mean 0.7 for industry-sponsored versus 3.0 for investigator-initiated; $P<0.001$) and study year (mean 0.7 in 2009 versus 2.4 in 2013; $P=0.03$). Requested protocol changes included design (53%), intervention (24%), evidence-background-rationale (14%), and population (11%). Compared to those for industry-sponsored trials, PRMC requested changes for investigator-initiated trials were more likely to be implemented (91% versus 83%; $P=0.08$). A pronounced difference was noted for requested changes related to trial design: among 154 industry-sponsored trials, 28 changes to study design were requested (average 0.2 per trial), of which 29% were implemented; among 52 investigator-initiated trials, 39 changes to study design were requested (average 0.8 per trial), of which 90% were implemented. **Conclusions:** The NCI-mandated scientific review of cancer clinical trials appears to have a substantial impact on investigator-initiated protocols, but the effect on industry-sponsored protocols is less clear. Given heightened interest in the quality and timeliness of oncology clinical trials, further research into this process is warranted.

**6587 General Poster Session (Board #50), Mon, 1:15 PM-5:00 PM**

**Looking beyond the first cycle in phase I cancer clinical trials.** *Presenting Author: Shing Mirn Lee, Columbia University, New York, NY*

**Background:** Phase I cancer trials use toxicity data from the first cycle to define dose limiting toxicity and guide dose escalation. Since doses are assigned only after outcomes for previous patients are observed, a short assessment period allows for more realistic time-frames to complete studies when using conventional methods to determine the maximum tolerated dose. However, in phase II and III clinical trials, toxicities are generally summarized for the entire treatment period into a maximal toxicity grade. **Methods:** Toxicity data from two phase II lung cancer trials conducted by the Southwest Oncology Group were obtained. Toxicities were graded for each cycle of treatment up to six cycles. The percentage and severity of toxicities in cycle 1 are compared to the maximal toxicity across all cycles. Moreover, summarizing toxicities by patient, the percentage of patients with dose limiting toxicities using data cycle 1 versus all cycles are compared. **Results:** For the first study, 779 toxicities were reported for 57 patients and summarized into 610 maximal toxicities. Out of the 610 maximal toxicities, 28% were not reported in cycle 1. Among the 442 maximal toxicities that were present in cycle 1, 9% worsened in a later cycle. Using data from cycle 1 yielded 7 dose limiting toxicities (12%); across all cycles, the dose limiting toxicity rate was 47% (27/57). The second study had a higher number of toxicities and of greater severity. There were 3510 toxicities coming from 115 patients. These yielded 1655 maximal toxicities. 46% were not reported in cycle 1. Among the 901 toxicities that were present in cycle 1, 18% worsened in a later cycle. Using data from cycle 1 yielded 60 dose limiting toxicities (52%); across all cycles, the dose limiting toxicity rate was 90% (103/115). **Conclusions:** Given the substantial amount of under reporting observed, further research is warranted to compare toxicity data from cycle 1 alone versus all cycles in a prospective manner. If discrepancy exists, the time-to-event continual reassessment method, a model-based design for estimating the maximum tolerated dose, can be used since it allows for inclusion of late-onset toxicities during dose escalation and uninterrupted patient recruitment due to toxicity assessment.

**6588 General Poster Session (Board #51), Mon, 1:15 PM-5:00 PM**

**The risks of debilitating falls (DFs) in patients (pts) with cancer: The Manitoba experience.** *Presenting Author: Joel Roger Gingerich, CancerCare Manitoba, Winnipeg, MB, Canada*

**Background:** Falls and fall-related injuries are significant pt safety challenges. We sought to identify if cancer pts were at greater risk of DFs. **Methods:** Using a retrospective population-based study design, we linked the Manitoba Cancer Registry with health care use records from Manitoba, Canada. Our study cohort consists of all adult community-dwelling pts with a first cancer diagnosis between April 1, 2003 and March 31, 2008, matched by age and gender to three cancer-free controls. DFs were defined as falls requiring hospitalization (ICD billing codes) between the time of cancer diagnosis and Dec 31, 2009. Regression models using death as a competing risk were used to compare DFs separately for those <65, 65-79 and 80+. Each model was adjusted for individual year of age, sex, medication use, neighborhood income, previous falls and co-morbidities. Results were expressed using sub-hazard ratios (SHR). **Results:** 27,164 cancer pts were matched to 83,928 controls; 50% of the overall cohort was female, with a median age of 68 years. For each group, the median length of follow-up ranged from 1.6 and 3.7 years and decreased with age. DFs occurred in 866 cancer pts (3.2%) vs. 2883 (3.4%) controls. Without adjustment, short-term (<1 year) DF risk was greater in cancer versus control pts (Table 1). For all pts except those 80+ this increased risk was explained by study covariates. Adjusted long-term (>1 year) DF rates were statistically lower in cancer pts 65+ years old vs. controls. The SHRs for death in cancer pts compared to controls during <1 and >1 years were: <65, 104.4 and 20.6 (p<.001); 65-79, 41.2 and 7.7 (p<.001); 80+, 26.6 and 3.7 (p<.001). **Conclusions:** In this population-based study, cancer pts were at increased risk of DFs compared to matched controls during the 1st year after diagnosis. The risk disappeared after adjusting for confounding factors except in those > 80. After 1 year of follow-up, cancer pts no longer had a higher risk of falls in part due to their higher risk of death.

**Subhazard ratios for cancer versus cancer-free cohorts.**

| | < 1 year of follow-up | | >1 year of follow-up | |
|---|---|---|---|---|
| **Age** | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** |
| **<65** | 2.005 [t] | 0.943 | 1.137 | 0.892 |
| **65–79** | 1.547 [t] | 0.996 | 0.869 | 0.652 [t] |
| **80+** | 1.774 [t] | 1.440 * | 0.520 [t] | 0.466 [t] |

[t] < 0.001;* < 0.05.

**6589 General Poster Session (Board #52), Mon, 1:15 PM-5:00 PM**

**Medical oncology patient readmissions: Are they preventable?** *Presenting Author: Andrew S. Epstein, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** As part of the Affordable Care Act, Centers for Medicare and Medicaid Services has initiated programs for certain non-cancer index admissions aimed to improve patient care and reduce costs, via preventing readmissions (defined as an admission within 30 days of a discharge). Readmissions for cancer patients have not been extensively evaluated, and might or might not be reasonably preventable. We therefore examined readmissions of patients on an inpatient service of a comprehensive cancer center. **Methods:** An institutional electronic database was queried to identify patients with a readmission and for demographics and other data related to the readmissions of patients to the Gastrointestinal (GI) Oncology service of Memorial Sloan Kettering Cancer Center (MSKCC). Of these, 50 patients were randomly selected for manual review to assess reasons for index admission and readmission, nature of index admission discharge plan, and whether readmission was preventable (defined pre-study as likely preventable by either prolongation of the index admission or a foreseeable, and accomplishable change in an agreed upon index admission discharge plan). **Results:** Between September 1, 2008 and March 1, 2013, 3,995 patients with GI cancers had an index admission to the MSKCC GI Oncology Service, of whom 876 (22%) had at least one readmission. Index admission discharge plans for these 876 index admissions were as follows: home without supportive services (64%), home with supportive services (32%), rehab facility (2%), home hospice (1%), or long term care facility (1%). From the 50 manually-reviewed cases, the most common diagnosis categories for either index admission or readmission were infection, pain, or GI issues. For each readmission, the diagnosis was different from the index admission diagnosis in 64% of the cases. Disagreement between the care team and patient/family about index admission discharge plan was documented in 10% of cases. One case (2%) was preventable. **Conclusions:** Readmissions in this population are common and reflect high disease burden. Our data suggest that readmissions in the population studied do not overall represent lapses in care or discharge management during the index admission and are not reasonably preventable.

**6590 General Poster Session (Board #53), Mon, 1:15 PM-5:00 PM**

**Evaluating the utility of baseline cardiac function assessment in early-stage breast cancer treatment.** *Presenting Author: Sandy R. Truong, Harvard Medical School, Boston, MA*

**Background:** Cardiotoxicity is a rare complication of anthracycline or trastuzumab-based therapy for patients with early-stage breast cancer. Screening echocardiogram (ECHO) and radionuclide ventriculogram (RVG) are often performed prior to administration of these agents to evaluate cardiac function. Only limited evidence for the clinical utility of these screening tests is available. We sought to determine the role of baseline cardiac imaging in treatment planning in asymptomatic patients without prior cardiac problems. **Methods:** Early-stage breast cancer patients diagnosed from 2006 to 2011 (n=1067) with a baseline ECHO/RVG were identified in a single institution prospective registry. Chart review was performed to obtain pre- and post-ECHO/RVG treatment plans, baseline ECHO/RVG results, and cardiac risk factors. A total of 600 patients had available medical records, as well as no prior chemotherapy, radiation therapy, or cardiac history or complaints. ECHO/RVG abnormalities were defined as ejection fraction (EF) <55%, valvular disease, left ventricular hypertrophy, and diastolic dysfunction. **Results:** Among 600 eligible patients, average age was 48 (range 23-80); 79% of treatment plans included anthracycline, 34% included trastuzumab, 16% both. Abnormal ECHO/RVG results were observed in 13 of the 600 patients (2.2%, 1.2%-3.7%), including 9 with baseline EF <55%. There were no detected changes in treatment plans (e.g., switching to a less cardiotoxic agent) in any of these patients, although 2 were recommended to undergo more frequent cardiac function monitoring in follow-up. There were no statistically significant differences in age, race, menopausal status, smoking history, alcohol use, BMI, or medical comorbidities (hypertension, diabetes, or hyperlipidemia) between patients with abnormal and normal ECHO/RVG results. **Conclusions:** Baseline screening ECHO/RVG rarely yields an abnormality that prompts change in anthracycline and/or trastuzumab-based treatment plan. Further investigation should include determination of the utility of baseline screening ECHO/RVG among patients who develop cardiac problems during or following breast cancer treatment.

**6591 General Poster Session (Board #54), Mon, 1:15 PM-5:00 PM**

**What is the extent of the AYA gap for young adults with cancer?** *Presenting Author: Julie Anna Wolfson, City of Hope, Duarte, CA*

**Background:** Poorer outcome is documented among AYA (15-39y at diagnosis [dx]) with cancer as compared to younger (<15y) or older (40-65y) patients with similar dx, coining the term AYA Gap. While this phenomenon has been examined in cancers spanning the age spectrum, those typical in young adults (YA: 22-39y) remain unstudied. **Methods:** We constructed a population-based cohort of 67,292 patients dxed between 22y - 65y with adult-onset cancers and reported to LA County's cancer (ca) registry from 1998 - 2008 (YA 22-39y: n=5,801; adults 40-65y: n=61,491). Multivariate Cox regression stratified by disease and adjusted for clinical characteristics (stage, gender, race/ ethnicity) compared outcome between age groups. Analysis of variance compared change in 3y overall survival (OS) over time between age groups; interaction between age/dx year was examined for statistical significance (p<0.05). **Results:** Outcome by age group is shown in Table: YA with breast ca had poor outcome compared to adults. YA with lung, hepatobiliary, gastric, colorectal ca had superior outcome. There was no difference in mortality in oral or cervical ca. For patients with lung, hepatobiliary and gastric ca, change in 3y OS over time differed significantly (p=0.05) between YA (saw no improvement) and adults (there was improvement); 3y OS over time did not differ significantly (P>.05) between YA and adults with breast or colorectal ca (both saw survival improvements) as well as oral or cervical ca (neither saw change over time). **Conclusions:** YA with breast ca demonstrate inferior outcome compared with adults. Furthermore, there appears to be no improvement over time for YA with lung, hepatobiliary and gastric ca, while adult patients with similar dx demonstrate improvement in outcome. Thus YA with breast, lung, hepatobiliary and gastric ca constitute a vulnerable population vis a vis their adult counterparts, and need to be studied.

**Likelihood of mortality [22-39y vs. 40-65y: Adjusted for stage, gender, race/ethnicity].**

| Primary diagnosis | HR | CI | P value |
|---|---|---|---|
| **Breast (n=31,767)** | 1.2 | 1.1-1.3 | <.0001 |
| **Hepatobiliary (n=4,194)** | .7 | .6-.9 | .0004 |
| **Lung (n=10,848)** | .8 | .7-1.0 | .02 |
| **Colorectal (n=12,301)** | .8 | .7-1.0 | .005 |
| **Gastric (n=2,667)** | .8 | .7-.9 | .003 |
| **Cervix (n=3,691)** | .9 | .8-1.0 | .1 |
| **Oral (n=1,824)** | 1.0 | .7-1.3 | .9 |

**6592 General Poster Session (Board #55), Mon, 1:15 PM-5:00 PM**

**Utilizing nomogram-predicted outcomes as the control group in randomized clinical trials.** *Presenting Author: Arielle C. Lutterman, Emory University School of Medicine, Atlanta, GA*

**Background:** Phase III randomized clinical trials require a large study population to demonstrate improved outcomes. Validated nomograms exist that predict survival outcomes for cancer patients. Nomogram-predicted outcomes for a study population could be used as a virtual control group, obviating the need for a live control group. To test this hypothesis, we used data from CLB 9344, a randomized study demonstrating a benefit of adjuvant paclitaxel in breast cancer. **Methods:** The nomogram developed by Michaelson (http://cancer.lifemath.net) was used to create a virtual control group matching the 1570 paclitaxel treated participants from 9,344. This virtual control group was compared to observed data to determine whether paclitaxel improved survival over that predicted for AC alone. Cumulative deaths were compared with the cumulative hazard (expected deaths) using a one-sample log-rank test. Sample size estimates were calculated for deaths and total study population needed for 80% power, with a type I error of 0.05. **Results:** See Table. A statistically significant mortality benefit favoring the experimental group emerged by year 7. By year 15, cumulative hazard is significantly higher than the observed number of deaths, indicating paclitaxel improves survival over standard of care. **Conclusions:** These results validate the use of existing nomograms as a virtual control group in clinical trials, allowing for smaller, faster, statistically valid Phase III studies. The lack of a live control group together with tighter prediction of expected outcomes for the participants suggest sample sizes could be reduced by 50-80%.

**Nomogram-predicted survival with AC and observed survival with AC + T.**

| Year | P value | #Deaths/1,570 | Cumulative hazard | Nomogram-predicted survival rate (AC) | 9,344 observed KM survival rate (AC + T) |
|---|---|---|---|---|---|
| **1** | 0.09 | 21 | 30.27 | 0.98 | 0.99 |
| **2** | 0.90 | 94 | 95.28 | 0.94 | 0.94 |
| **3** | 0.31 | 187 | 173.73 | 0.89 | 0.88 |
| **4** | 0.71 | 256 | 250.03 | 0.84 | 0.84 |
| **5** | 0.67 | 312 | 319.52 | 0.80 | 0.80 |
| **6** | 0.14 | 357 | 385.77 | 0.75 | 0.77 |
| **7** | 0.02 | 398 | 447.99 | 0.72 | 0.74 |
| **8** | 0.001 | 429 | 506.39 | 0.68 | 0.72 |
| **9** | <0.001 | 461 | 563.03 | 0.64 | 0.70 |
| **10** | <0.001 | 491 | 614.04 | 0.61 | 0.68 |
| **11** | <0.001 | 515 | 666.13 | 0.58 | 0.66 |
| **12** | <0.001 | 548 | 715.83 | 0.54 | 0.63 |
| **13** | <0.001 | 579 | 762.72 | 0.51 | 0.61 |
| **14** | <0.001 | 610 | 807.66 | 0.49 | 0.58 |
| **15** | <0.001 | 623 | 849.14 | 0.46 | 0.57 |

**6593 General Poster Session (Board #56), Mon, 1:15 PM-5:00 PM**

**Experimental fertility preservation (FP) interventions in prepubertal (PP) boys with cancer: A report on preferences of teenage cancer survivors, parents, and providers.** *Presenting Author: Abha A. Gupta, Hospital for Sick Children, University of Toronto, Toronto, ON, Canada*

**Background:** Risk of infertility from cancer therapy is a source of great distress for young cancer survivors. FP can be a challenge in PP boys who are unable to produce bankable sperm through ejaculation. We sought to determine factors influencing patient, parental and provider preferences for testicular biopsy (TBx) even though the utility of PP tissue for FP remains experimental. **Methods:** Oncology providers, parents, and teenage cancer survivors were recruited from 3 pediatric centers in Canada. During participant surveys, a hypothetical decision was made between TBx and no TBx. Top factors influencing decisions were identified and willingness to accept complications, costs, risk of infertility, and chance of technology developing were used to measure strength of preference for TBx. Multiple regression was used to associate predictors with TBx desirability scores (under risk of infertility condition). **Results:** The proportion of respondents who preferred TBx (vs no TBx) were: 110/153 (72%) parents, 22/30 (73%) providers, and 52/77 (67%) cancer survivors. The top ranked factor influencing decisions for all groups was risk of infertility. For those that chose biopsy, a switch to no TBx occurred at very low chance technology developed (median 9%), highest cost point (median $500/year), and low risk of infertility (median 9.5%). Providers would accept much lower level of complications from TBx (median 21%), compared to parents (41%) and survivors (100%). Child age, type of cancer, ethnicity, or hospital were not significant factors associated with preference for TBx, but parents who reported a higher income were more likely to prefer TBx (p=.05). Some providers would not present TBx in cases of lower risk of infertility and poor prognosis. In contrast, parents (96%) and survivors (89%) wanted information on TBx before treatment began to ensure they had choice; no matter the factors of the case. **Conclusions:** Parents, survivors, and providers strongly favor TBx. Parental income was the only predictor of preferences under the risk of infertility condition. Addressing the costs associated with FP should remain an important focus of advocates for FP.

**6594 General Poster Session (Board #57), Mon, 1:15 PM-5:00 PM**

**Comparison of RCC surveillance guidelines: Competing tradeoffs.** *Presenting Author: Tracey Lynn Krupski, University of Virginia, Charlottesville, VA*

**Background:** Renal cell carcinoma (RCC) is now detected at earlier stages than in the past due to increased use of abdominal imaging for unrelated medical conditions. Three organizations offer differing guidelines for surveillance imaging strategies following partial nephrectomy (PN). We hypothesized that published surveillance patterns would have previously unrecognized sizable differences in intensity, cost, and radiation exposure and real world experience would not adhere to guidelines. **Methods:** Cost ($2,012) and radiation exposure in millisieverts (mSv) were compared between the following surveillance guidelines:American Urological Association (AUA), Canadian Urology Association (CUA), and the European Association of Urology (EAU). These were stratified into low-risk and high-risk based on tumor characteristics and compared to patients undergoing PN for RCC at the from 2009-2010. The intensity, cost, and estimated radiation exposure were calculated for each subject. We used the Welch's t-test to test for significant differences in cost and radiation exposure between the low-risk and high-risk groups. **Results:** The median cost of low risk surveillance from least expensive to most expensive is as follows: CUA ($481), EAU ($928) and AUA ($1,320). For high risk surveillance, least expensive was CUA ($543), EAU ($1,447) and AUA ($2,621). Radiation exposure was least for the CUA guidelines (low and high risk was 16.2 and 16.4 mSv ) and highest for the AUA guidelines at ( low and high risk was 48mSv and 92). The EUA guideline exposures were 23 mSv and 46mSv for low and high risk respectively. For comparison with a real world subset, 43/63 patients undergoing PN had complete records. We identified wide variability in intensity, frequency, and modality of surveillance imaging. These were not correlated to risk category or guidelines. **Conclusions:** Published surveillance strategies for RCC following PN differ greatly in terms of cost and radiation dose. Practicing clinicians do not seem to stratify patients by tumor-risk category as recommended by the published guidelines. It is important for clinicians to adopt standardized surveillance strategies that limit unnecessary cost and radiation exposure.

**6595 General Poster Session (Board #58), Mon, 1:15 PM-5:00 PM**

**Biomarker testing and time-to-treatment decision in patients with advanced non-small cell lung cancer.** *Presenting Author: Charles Henry Lim, University of Toronto, Toronto, ON, Canada*

**Background:** Testing for tumour biomarkers including *EGFR* mutation and *ALK* rearrangement has become standard in the management of advanced non-small cell lung cancer (NSCLC). At our institution, *EGFR* testing became routine in March 2010 and *ALK* testing in April 2012. We assessed the prevalence and timing of biomarker testing for advanced NSCLC patients and whether testing affected the timeliness of treatment decisions. **Methods:** We conducted a retrospective chart review of patients with advanced NSCLC referred to the Princess Margaret Cancer Center from April 1, 2010 to March 31, 2013. A random sample of one fourth of patients referred was chosen using a random numbers generator. **Results:** Of 278 patients reviewed, 136 (49%) had biomarker testing performed. Of these, 29% had documented *EGFR* mutations and 2% *ALK* rearrangement. Patients tested for biomarkers were more likely to be female (50% vs. 34%, $p=0.006$), Asian (22% vs. 9%, $p=0.008$) and non-smokers (41% vs. 8%, $p<0.0001$). Of 137 patients with newly diagnosed non-squamous NSCLC, 96 (69%) had biomarker testing performed and 16 (12%) had results available at the time of initial oncology consultation. There was a non-significant trend towards shorter mean time from consultation to treatment decision (29 vs. 42 days, $p=0.42$) and mean time to treatment start (38 vs. 50 days, $p=0.46$) for patients with results available at initial consultation compared to those without. Reflex testing resulted in 84% of samples undergoing testing compared to 59% if clinician-initiated, and a non-significantly shorter mean time for results (53 vs. 84 days, $p=0.34$). 10% of patients did not have adequate tissue for biomarker analysis at the time of first consultation; 56% of these went on to have repeat biopsy for molecular testing. Of those with an *EGFR* mutation, 16% started chemotherapy prior to results becoming available to the clinician. **Conclusions:** Awaiting biomarker test results can increase wait times to treatment decisions for patients with advanced NSCLC. This may be improved by incorporating reflex biomarker testing into diagnostic algorithms for NSCLC at the level of the pathologist, and further education of specialists involved in obtaining diagnostic cancer specimens.

**6596 General Poster Session (Board #59), Mon, 1:15 PM-5:00 PM**

**Staging imaging for metastatic disease in patients with early-stage breast cancer: What do physicians think of the ASCO top-5 recommendation?** *Presenting Author: Demetrios Simos, Division of Medical Oncology, The Ottawa Hospital Cancer Center, University of Ottawa & The Ottawa Hospital Research Institute, Ottawa, ON, Canada*

**Background:** In 2012, ASCO's inaugural "Top 5" list recommended against the routine use of imaging to look for metastases in asymptomatic women with early breast stage cancer. Despite this recommendation being in close agreement with published guidelines, staging imaging is frequently over-utilized. The objective of this study was to determine physicians views on the ASCO "Top 5" and guidelines pertaining to staging imaging for metastatic disease. **Methods:** A questionnaire was developed and circulated electronically using a modified Dillman technique to Canadian medical, radiation, and surgical oncologists. **Results:** The questionnaire was completed by 173 physicians (26% response rate). 82% indicated awareness of at least one published guideline on this issue. 60% indicated that they had read the ASCO recommendation and of those, 81% agreed with it. 24% indicated that the ASCO recommendation has influenced them to order less staging imaging. The percentage of respondents who would seldom order imaging for stage 1, 2 and 3 disease was 88%, 37% and 2% respectively. >95% of physicians identified a suspicious history, physical exam, and inflammatory breast cancer as important factors to be taken into consideration when deciding whether or not imaging should be done. The majority did not feel patient demand, fear of litigation or ease of access to imaging were important indications for imaging. **Conclusions:** Despite awareness of and general agreement with the staging imaging recommendations of the ASCO "Top 5" for early breast cancer, most physicians who treat breast cancer patients have not reduced their use of perioperative imaging. Disease stage, clinical evaluation, and tumour biology were identified as the most important factors influencing their decision of whether to do or not do staging imaging. Alternative strategies, beyond simply publishing recommendations, are therefore required if there is to be a sustained change in physician behaviour.

**6597 General Poster Session (Board #60), Mon, 1:15 PM-5:00 PM**

**A rank-based randomized phase II design when the phase III design is based on overall survival (OS).** *Presenting Author: William Leonard Mietlowski, Novartis Oncology, East Hanover, NJ*

**Background:** Gan (2013) reported that approximately 27% of 120 randomized phase III trials with a primary endpoint of OS had statistically significant outcomes. Ratain (2005) suggests that the low phase III success rate in Oncology may stem from a low positive predictive value (PPV) in phase II trials. There were four 2012 publications that independently reported that the components of tumor assessment were independent predictors of OS. Consequently, we proposed a rank-based (RB) (Lachin 1992) randomized phase II design that differentially weights the risk of death by the type and time of disease progression and the percentage change in tumor burden and compared this design with one based on progression-free survival (PFS). **Methods:** We chose CONFIRM-2, a randomized phase III trial in second-line colorectal cancer comparing chemotherapy±PTK787 as a negative OS trial ($n=855$, hazard ratio (HR)=1.00). In the absence of a database for a positive phase III trial based on OS, we constructed two positive-OS phase III trials by oversampling long-term survivors from the CONFIRM-2 database (P1: OS HR=0.75, PFS HR=0.85 and P2: OS HR=0.74, PFS HR=0.72). We simulated 2500 phase II trials ($n=150$, 80% power based on a one-sided test at the 10% significance level, after 110 events, when PFS is mature) from each of the three phase III trials. We compared the specificity, sensitivity, PPV and negative predictive value (NPV) of the RB method with PFS. **Results:** See Table. **Conclusions:** We show that the rank based method may have a substantial increase in specificity and PPV for OS compared to PFS. This may reflect the ability of the components of the tumor measurement process to predict OS since a lack of effect on OS would imply a lack of effect on the components (i.e. very good specificity and PPV). The comparison of sensitivity and NPV appears to depend on the PFS HR. Further studies with other tumor types and treatment modalities are warranted. Clinical trial information: NCT00056446.

| | | Operating characteristic | | | |
|---|---|---|---|---|---|
| **Positive OS trial** | **Design** | **Specificity** | **Sensitivity** | **PPV *** | **NPV*** |
| **P1** | RB | 0.89 | 0.56 | 0.65 | 0.84 |
| | PFS | 0.72 | 0.50 | 0.40 | 0.79 |
| **P2** | RB | 0.89 | 0.77 | 0.72 | 0.91 |
| | PFS | 0.72 | 0.91 | 0.55 | 0.96 |

* Assuming a prevalence of a positive phase III trial for OS of 27%.

**6598 General Poster Session (Board #61), Mon, 1:15 PM-5:00 PM**

**Impact of weekend admission on hospital length of stay and organ failure in pediatric leukemia patients at free-standing U.S. children's hospitals.** *Presenting Author: Elizabeth K. Goodman, The Children's Hospital of Philadelphia, Philadelphia, PA*

**Background:** In adult leukemia patients, weekend admission is associated with increased inpatient mortality. We used a U.S. cohort of pediatric leukemia patients to evaluate the impact of weekend admission on clinical outcomes in index leukemia admission. **Methods:** The Pediatric Health Information System (PHIS) database was used to assemble a retrospective cohort of children with newly diagnosed ALL or AML identified from 43 freestanding children's hospitals between January 1, 1999 to December 31, 2011. Index admissions were dichotomized as 'weekend' (Saturday or Sunday) and 'weekday'. Admission mortality, length of stay, time to chemotherapy, and organ system failure were compared between weekday and weekend admissions. Bivariate analyses were performed using Chi-square and Student's *t* tests. Adjusted analyses were performed using logistic regression. **Results:** 10,720 ALL patients and 1,323 AML patients were identified; 2,009 patients (16.7%) were admitted on weekends. Weekend admissions had a significantly higher proportion of young, non-white, and publically-insured patients. Patients receiving ICU-level resources within the first 2 days of admission represented a higher percentage of total weekend admissions although the absolute numbers of these severely ill patients was constant. Patients admitted on the weekend did not have an increased index admission mortality (OR 0.96, 95% CI 0.57-1.61 %); however, they had significantly increased length of stay (1.38 day increase, $p<.001$), time to chemotherapy (0.36 day increase, $p<.001$), and risk of respiratory failure (OR 1.47, 95% CI 1.16-1.71) after adjusting for demographics, severity of illness, and hospital level factors. **Conclusions:** While newly diagnosed children with leukemia admitted on weekends do not have higher index admission mortality, they have an increased length of stay, time to chemotherapy, and rate of respiratory failure. A higher proportion of patients are severely ill at presentation. Optimizing weekend resources may reduce hospital length of stay across all weekend admissions and ensure the availability of comprehensive care for those weekend admissions with higher acuity.

**6599 General Poster Session (Board #62), Mon, 1:15 PM-5:00 PM**

**Conditional survival in melanoma and thyroid cancer patients.** *Presenting Author: Megan Rist Haymart, University of Michigan, Ann Arbor, MI*

**Background:** Melanoma and thyroid cancer are two increasingly common malignancies. Although likelihood of survival from both cancers can vary by disease severity, it isn't known how patients' life expectancy changes the further they are from time of diagnosis. **Methods:** Using Surveillance, Epidemiology, End Results (SEER) data we selected patients diagnosed with melanoma (N=95,041) or well-differentiated thyroid cancer (N=43,392) between 1998 - 2005. Patients were followed for up to 12 years. Cox regression provided estimates of disease-specific survival by SEER stage and age, which we then transformed to estimate conditional five year survival. **Results:** Patients with localized melanoma and thyroid cancer have an excellent five year survival at time of diagnosis and for subsequent years. For both regional melanoma and thyroid cancer there is an age gradient with improved conditional survival in melanoma patients over time. For distant melanoma, the initial five year survival is poor but improves rapidly whereas the improvement is gradual with distant thyroid cancer. There is an age effect for disease-specific survival for both cancers, but it persists across all stages for thyroid cancer: for local disease [hazard ratio for age 70-79 versus <30 is 26.6 (95% confidence interval is 8.08-164)], for regional disease [59.4 (30.1-140)], and for distant disease [54.5 (20.7-221)]. For melanoma, the age effect is smaller and only present for local disease [3.79 (3.01-4.84)] and regional disease [2.36 (1.93-2.91)]. **Conclusions:** The likelihood of continued survival in a patient with melanoma or thyroid cancer differs based on age and how long the patient has already survived. Understanding the five year conditional survival of these cancers can help patients and physicians with their treatment plans.

**6600 General Poster Session (Board #63), Mon, 1:15 PM-5:00 PM**

**Clinical utility of tumor measurement (TM)-based metrics in phase II (P2) to predict phase III (P3) overall survival (OS) outcomes using the RECIST 1.1 database.** *Presenting Author: Sumithra J. Mandrekar, Mayo Clinic, Rochester, MN*

**Background:** While many alternative TM-based metrics to RECIST tumor response (TR) have been proposed, none have replaced TR in practice. The abilities of TR and previously proposed TM-based metrics to predict OS was assessed using simulation studies. **Methods:** 2,000 randomized P2 trials of 90 to 160 patients were resampled from 2 (lung) negative (-ve) (each with 2 active treatment arms) and 2 (colorectal) positive (+ve) P3 trials for OS. Cox models (landmarked at 12 weeks (w)), adjusted for baseline tumor size (mm) were fit to each P2 trial – Model 1: slope1 (baseline to 6w, mm/w), slope2 (6w to 12w, mm/w) and linear spline terms for +ve slope1 and slope2; Model 2: %change1(%change/w), %change2 (%change/w) and linear spline terms for +ve %change1 and %change2; Model 3: best TR within 12w. The +ve (-ve) predictive value (PPV/NPV), defined as the probability (Pr) of a +ve (-ve) phase II trial (using model predicted risk score differences, 1-sided p=0.20) yielding a +ve (-ve) P3 trial outcome (OS benefit associated with treatment), was calculated across the 2000 P2 trials for a given P3 trial for a range of false +ve (-ve) rates (FPR (FNR)) and Pr(+ve/-ve P3 trial). **Results:** Compared to TR, the slope and %change P2 models had lower OS prediction error for all P3 trials and better PPV/NPV for all but one P3 trial; however the absolute differences in PPV/NPV/prediction errors were negligible. **Conclusions:** TR has similar PPV/NPV as the continuous TM-based metrics, and should not necessarily be replaced. Acknowledgement: CA167326.

| | | | | PPV | |
|---|---|---|---|---|---|
| **+ve P3 trials** | **FPR** | **Pr(+ve P3 trial)** | **Model 1** | **Model 2** | **Model 3** |
| **1: treatment (t) vs control (c)** | 0.1 | 0.1 | **0.24** | 0.20 | 0.21 |
| | 0.8 | 0.4 | **0.65** | 0.61 | 0.61 |
| | | 0.1 | **0.04** | 0.03 | 0.03 |
| | | 0.4 | **0.19** | 0.16 | 0.16 |
| **2: t vs. c** | 0.1 | 0.1 | 0.12 | 0.15 | **0.27** |
| | 0.8 | 0.4 | 0.44 | 0.52 | **0.69** |
| | | 0.1 | 0.02 | 0.02 | **0.04** |
| | | 0.4 | 0.09 | 0.12 | **0.22** |
| | | | | **NPV** | |
| **-ve P3 trials** | FNR | Pr(-ve P3 trial) | Model 1 | Model 2 | Model 3 |
| **3: t1 vs. c** | 0.1 | 0.9 | **0.99** | 0.99 | 0.98 |
| | 0.8 | 0.6 | **0.93** | 0.89 | 0.85 |
| | | 0.9 | **0.91** | 0.86 | 0.81 |
| | | 0.6 | **0.63** | 0.50 | 0.41 |
| **3: t2 vs. c** | 0.1 | 0.9 | 0.99 | **0.99** | 0.98 |
| | 0.8 | 0.6 | 0.93 | **0.93** | 0.91 |
| | | 0.9 | 0.90 | **0.91** | 0.88 |
| | | 0.6 | 0.61 | **0.62** | 0.56 |
| **4: t1 vs c** | 0.1 | 0.9 | 0.97 | **0.99** | 0.98 |
| | 0.8 | 0.6 | 0.86 | **0.92** | 0.91 |
| | | 0.9 | 0.82 | **0.89** | 0.88 |
| | | 0.6 | 0.43 | **0.58** | 0.55 |
| **4: t2 vs c** | 0.1 | 0.9 | **0.99** | 0.97 | 0.98 |
| | 0.8 | 0.6 | **0.92** | 0.86 | 0.87 |
| | | 0.9 | **0.89** | 0.82 | 0.83 |
| | | 0.6 | **0.58** | 0.43 | 0.45 |

**6601 General Poster Session (Board #64), Mon, 1:15 PM-5:00 PM**

**A virtual consult service to optimize clinical trial participation in patients with metastatic breast cancer.** *Presenting Author: Karen Anne Cadoo, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** With an increasing complexity and number of endocrine, molecularly-targeted and immunotherapeutic clinical trial and standard-of-care therapies available for patients with metastatic breast cancer (MBC), rapidly identifying appropriate options is a challenge for physicians. We designed and piloted an email-based virtual consult system to facilitate matching of patients to appropriate studies. **Methods:** We assembled eligibility criteria and slot availability for 10 therapeutic Phase Ib/II clinical trials in the Breast Cancer Medicine Service at a tertiary referral center. Service physicians emailed patient details to a centralized address, one of three consulting fellows reviewed the patient's chart and responded within 24 hours with a ranked list of relevant studies. **Results:** 56 unique consults were received in 4 months. Median age was 56 (21-83), median ECOG performance status 0 (0-3). Reflecting the trials available, the majority (96%) of patients had estrogen receptor positive, human epidermal growth factor receptor 2 (HER2) negative disease. Mutational analysis of PIK3CA, AKT and HER2 was available for 35 tumors (62.5%); 21 had an actionable mutation, all of these tumors harbored *PIK3CA* mutations, one had a concurrent *AKT* mutation. 44/56 patients (79%) were eligible for at least one trial, of which 24 (55%) are enrolled onto or waitlisted for a specific study. Of the 20 eligible patients who did not pursue a trial, reasons included: the attending recommended alternate therapy with cause (9, 45%) patient declined (4, 20%), trial slot was unavailable (2, 10%), or unknown (5, 25%). 12 patients (21%) were ineligible due to site of progressive disease, second active malignancy, number of prior therapies or declining performance status. **Conclusions:** This virtual consult system is a potential strategy to assist physicians in identifying clinical trial options for patients. This process can be performed by supervised non-professional personnel with defined criteria, which will be the next phase of the pilot, incorporating prespecified metrics to ascertain the benefit.

**6602 General Poster Session (Board #65), Mon, 1:15 PM-5:00 PM**

**Improving cancer clinical trial accrual in Ontario, Canada: The clinical trials infrastructure fund (CTIF) experience.** *Presenting Author: Lesleigh S. Abbott, NCIC Clinical Trials Group, Kingston, ON, Canada*

**Background:** Participation in clinical trials is essential to evaluating safety and efficacy of emerging cancer therapies. To improve trial activities in the province of Ontario, Canada, the CTIF was established in 2002 and operationalized from 2004-2008 by the Ontario Cancer Research Network (OCRN), Ontario Institute for Cancer Research's (OICR) predecessor and funded by the Ontario government. The goals were to double trial recruitment from the baseline of 2001 and have self-sustaining trial units over 4 years. **Methods:** Beginning in 2004, the CTIF awards were issued in 3 phases – phase 1: 14 adult cancer centers, phase 2: 9 community hospitals, phase 3: 5 pediatric cancer centers. Per case funding (PCF) provided was $3300/patient; $4000/patient to community hospitals. The total program cost was $12.9 Million/3 years. Participating sites reported recruitment to academic and industry trials and shared 11% of additional industry trial funding over 5 years back to OCRN/OICR. The number of patients accrued was divided by the number of patients treated at sites to calculate the percentage of cancer patients accrued to clinical trials. **Results:** Trial recruitment and personnel increased during the years of the CTIF peaking in 2007. Trial increase was most marked for larger adult cancer centers. Successful sites maintained an average of 40% industry trials within their clinical trials portfolio and had a clinical trials manager with business experience. **Conclusions:** Providing additional PCF improved clinical trials accrual in Ontario, particularly in larger cancer centers that could rapidly expand their trial activities and personnel, but the effect was not sustained. Defining the best business model(s) and trial portfolio for trial units requires further elucidation.

| Year | Cancer centers | | | Patient accrual | | |
|---|---|---|---|---|---|---|
| % Change accrual from baseline | %Overall accrued to trials | Patient accrual | % Change accrual from baseline | %Overall accrued to trials | Community hospitals | |
| Baseline | 2797 | | N/A | 173 | | N/A |
| 2004 | 4126 | 48 | 9 | | | |
| 2005 | 4948 | 77 | 11 | - | | |
| 2006 | 5167 | 85 | 12 | 161 | -7 | N/A |
| 2007 | 5572 | 100 | 13 | 187 | 8 | 4 |
| 2008 | 4428 | 58 | 9 | 76 | -56 | 2 |
| 2009 | 4321 | 54 | 8 | 190 | 10 | 4 |
| 2010 | 3757 | 34 | 7 | 83 | -52 | 2 |

**6603 General Poster Session (Board #66), Mon, 1:15 PM-5:00 PM**

**The clinical oncology treatment plan and summary implementation guide: An interoperable HL7 document standard to improve the quality of cancer care.** *Presenting Author: Jeremy Warner, Vanderbilt University Medical Center, Nashville, TN*

**Background:** Cancer care is interdisciplinary and longitudinal, and increasingly depends on seamless electronic transmission of clinical data. Accurate health information exchange, using structured and unambiguous data elements, is critical for coordination of care across all phases of the cancer journey. However, sharing data across multiple clinical practices remains difficult due to lack of standardization and general incompatibility between electronic health records. There is a growing need for well-designed, oncology-specific interoperability standards. Thus, ASCO is developing standards to improve the quality of cancer care. **Methods:** ASCO volunteers formed a Standards Work Group (SWG), and ASCO engaged an independent consulting firm for technical work. The SWG adapted ASCO's Breast Cancer Adjuvant Treatment Plan and Summary, originally developed as a paper-based form, for translation to an interoperable standard. The standard was developed using Health Level Seven International (HL7) Clinical Document Architecture (CDA), an ANSI-recognized standard in broad use. This required extensive input from medical and surgical oncologists, ASCO staff, and the consultants in order to define and disambiguate clinical concepts. Several concepts not represented in the Systematized Nomenclature of Medicine, Clinical Terms were added by the National Library of Medicine. **Results:** The HL7 Implementation Guide for CDA, Release 2: Clinical Oncology Treatment Plan and Summary, DSTU Release 1 (COTPS) was successfully balloted in May 2013 and published in late 2013. Several organizations have already expressed interest in the standard; the Athena Breast Health Network of five University of California sites has begun trial implementation. **Conclusions:** The COTPS is the first oncology-specific standard approved through the HL7 balloting process. Experience gained through trial implementation will continue to inform future work by the SWG. Oncology standards will improve quality by allowing efficient transmission of reliable, meaningful, and up-to-date clinical data between providers, patients, quality improvement initiatives, and registries.

**6604 General Poster Session (Board #67), Mon, 1:15 PM-5:00 PM**

**Febrile neutropenia and mortality in patients with breast cancer, lung cancer, and non-Hodgkin lymphoma.** *Presenting Author: Aniket A Kawatkar, Kaiser Permanente Southern California, Pasadena, CA*

**Background:** Chemotherapy-induced febrile neutropenia (FN) contributes considerably to morbidity and mortality. This retrospective cohort analysis evaluated FN incidence and mortality in patients with breast cancer, lung cancer, and non-Hodgkin lymphoma (NHL) identified in the Kaiser Permanente Southern California (KPSC) Cancer Registry. **Methods:** Adults age ≥18 years with newly diagnosed breast cancer, lung cancer, or NHL who initiated myelosuppressive chemotherapy between January 1, 2000 and December 31, 2009 were included. Patients who had undergone bone marrow/stem cell or solid organ transplantation, had white blood cell diseases within 6 months of starting chemotherapy, or received prior chemotherapy in the 12 months immediately preceding their cancer diagnosis were excluded. Each cycle within the first course of chemotherapy was identified, as were FN events (per ICD-9 codes for neutropenia and/or fever) and deaths (any cause). Patients were followed until the end of study (60 days after last treatment) for no more than 9 cycles. Data were included for all KPSC medical centers within the Southern California region. Outcomes stratified by cancer type and time period are shown below. **Results:** Overall, 12,086 patients across the 3 tumor types were identified (mean age [SD], 59.7 [11.8] years; females, 77.9%; Caucasians, 69.9%; Hispanic, 18.2%). Patient-level rates of FN and mortality are shown in the Table. **Conclusions:** This study found variation in the rate of chemotherapy-induced FN and mortality by cancer type and time period among patients with lung cancer, breast cancer, or NHL identified in the KPSC Cancer Registry. Differences across time periods may reflect changes in cancer treatment and FN management.

| | Breast | Lung | NHL |
|---|---|---|---|
| FN, n/N (%) | | | |
| Overall | 814/7268 (11.2) | 682/3730 (18.3) | 321/1088 (29.5) |
| 2000–2005* | 387/4615 (8.4) | 366/2160 (16.9) | 205/689 (29.8) |
| 2006–2009* | 429/2848 (15.1) | 317/1654 (19.2) | 118/433 (27.3) |
| Deaths (any cause) among patients with FN events, n/N (%) | | | |
| Overall | 14/814 (1.7) | 99/682 (14.5) | 21/321(6.5) |
| 2000–2005* | 8/387 (2.1) | 46/366 (12.6) | 17/205 (8.3) |
| 2006–2009* | 6/429 (1.4) | 53/317 (16.7) | 4/118 (3.4) |

* Some patients with multiple FN events may have been counted in both time periods.

**6605 General Poster Session (Board #68), Mon, 1:15 PM-5:00 PM**

**Trends in the quality of preventive care before and after prostate cancer diagnosis.** *Presenting Author: Lauren P. Wallner, Kaiser Permanente Southern California, Pasadena, CA*

**Background:** Most men diagnosed with prostate cancer will die from other causes, making preventive care for comorbid diseases of aging critical. However, concerns exist that the diagnosis often focuses subsequent care on prostate-related issues rather than overall health. Therefore, we examined the use of preventive services before and after diagnosis among men with prostate cancer and compared it to non-cancer controls. **Methods:** 15,631 men enrolled in Kaiser Permanente Southern California who were newly diagnosed with prostate cancer from 2002 through 2008 were matched 1:1 to non-cancer controls on age, race and timing of PSA test. They were passively followed through electronic medical records to determine the use of preventive services, including screening for colorectal cancer (CRC) (colonoscopy and/or fecal occult blood tests), tests for diabetes (glucose and hemoglobin A1c (HbA1c)) and heart disease (lipid panel test) and vaccinations (influenza and pneumococcal) in the 5 years before and diagnosis (or index date for controls). Rates of use were calculated for cases and controls separately and compared using Poisson regression. **Results:** CRC screening rates were 3-fold greater after diagnosis compared to before and were equivalent across group (Relative Rate (RR): 2.97, 95%CI: 2.89-3.05). The rates of lipid testing were similar before and after diagnosis, but increased an additional 10% in cases relative to controls after diagnosis (RR: 1.10, 95%CI: 1.14-1.25). HbA1c rates were lower among cases when compared to controls both before and after diagnosis (RR: 0.73, 95%CI: 0.72-0.74). Rates of glucose testing increased 25% more in the cases after diagnosis relative to the controls (RR: 1.25, 1.23-1.27), with the highest rate in the first 6 months after diagnosis. Influenza vaccination rates increased 24% after diagnosis in both groups (RR: 1.24, 95%CI: 1.22-1.26). **Conclusions:** Our results suggest that in this system, once diagnosed with prostate cancer, no less attention is paid to general preventive care. The increased use of preventive services may be the result of an integrated care model, further supporting the importance of the provider and system in the delivery of high quality survivorship care.

**6606 General Poster Session (Board #69), Mon, 1:15 PM-5:00 PM**

**Treatment decision making in advanced cancer: Communication about patient values and preferences.** *Presenting Author: Hanneke W.M. Van Laarhoven, Department of Medical Oncology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands*

**Background:** Medical decision making profoundly influences the quality of life of advanced cancer patients and, hence, strongly depends on patients' values and preferences. This observational study examines the type of values and preferences patients express in treatment decision consultations and how medical oncologists invite and react to such expressions. **Methods:** Advanced cancer patients for whom undergoing systemic treatment is medically not self-evident were identified. Patients (n = 43) were included when they met with a medical oncologist (n = 13) for the first time or to evaluate current treatment. Either one or two consultations were taped (total n = 64). Verbatim transcripts were analysed using MAXqda10 software. Independent coders identified and categorised patient expressions of values or preferences. Oncologists' utterances preceding or following such expressions were coded. **Results:** Preliminary analysis (n = 20; 31%) shows that patient expressions of values and preferences were more frequent in first consultations (M =7) than in evaluation consultations (M = 2). Expressions often concerned (54%) either a general goal, a wish to receive treatment or an evaluation of a treatment option. One third of expressions (37%) were qualified as patient-initiated. Two thirds (63%) were qualified as oncologist-invited, triggered by e.g., a direct question, a referral to the importance of patients' preferences or a treatment advice. Half of oncologists' responses qualified as space reducing (51%), i.e., not responding or by providing information. Responses qualified as space providing (39%) were probe questioning, checking, reflecting or providing an alternative perspective. A minority of oncologist responses qualified as solving (10%), including offering advice or consideration time. Sequences (30%) instead of isolated patient expressions (70%) often occurred when oncologists gave space providing responses. **Conclusions:** Shared decision making in advanced cancer can be improved by teaching oncologists to invite and provide space to patient expressions of values and preferences. Particularly when evaluating current treatment, patients' values and preferences should be put on the agenda.

**6608 General Poster Session (Board #71), Mon, 1:15 PM-5:00 PM**

**Trends and safety of image-guided percutaneous pleural biopsies in cancer patients.** *Presenting Author: Melissa Kate Accordino, Columbia University College of Physicians and Surgeons, New York, NY*

**Background:** Image-guided percutaneous pleural needle biopsy (IGPPB) is an important tool in the diagnosis and management of cancer patients. Complications of IGPPB include pneumothorax and chest tube placement. Small, single institution studies report rates of pneumothorax between 8-60% and subsequent chest tube in 6-53%. We performed a population-based analysis to evaluate patterns of use, complication rates, and cost associated with IGPPB. **Methods:** The Premier Perspective database was used to identify cancer patients with at least 1 claim for IGPPB from 2006-2012. Perspective is a fee-supported database created to measure resource utilization and quality from >600 US hospitals. Patients with a pneumothorax were defined by claims within 1 month of IGPPB; rates of hospitalization, chest tube placement and hospital length of stay (LOS) after pneumothorax were analyzed. Multivariable analysis was performed to further examine patient, insurance and hospital characteristics associated with biopsy setting (outpatient vs. inpatient). Pleural biopsy volume and procedure-associated costs over time were evaluated. **Results:** We identified 59,796 cancer patients who received ≥1 IGPPB, 32,474 (54.3%) in outpatients and 27,322 (45.7%) in inpatients. Characteristics associated with outpatient IGPPB included: younger age, white race, less comorbidity, tumor type, commercial insurance and larger hospitals ($p<0.01$). Of patients who received outpatient IGPPB, 3,835 (11.8%) developed a pneumothorax, 749 (19.5%, 2.3% of total) were hospitalized and 140 (3.7%, 0.4% of total) required chest tube. Among patients who received IGPPB as an inpatient, 5,638 (20.6%) developed a pneumothorax and, of those, 2,321 (41.2%, 20.4% total) required chest tube. LOS was similar for patients hospitalized after outpatient IGPPB (median 6, mean 7.9) compared to inpatient IGPPB (median 6, mean 8.7). Over time, IGPPB volume increased by 33%, patient costs rose by 53% and outpatient costs rose by 16%. **Conclusions:** We have shown that in a large population-based sample the use of IGPPB has increased substantially. While pneumothorax was frequent in outpatients, the rate of hospitalization and chest tube placement was small.

**6609 General Poster Session (Board #72), Mon, 1:15 PM-5:00 PM**

**The association of treatment breaks with survival in metastatic cancer.** *Presenting Author: Kuan Rui (Sean) Tan, The University of British Columbia, Vancouver, BC, Canada*

**Background:** As outcomes for specific metastatic cancers continue to improve, the concept of treatment to disease progression must be tempered by the potential for cumulative toxicities of ongoing therapy. Early research suggests that treatment holidays or "breaks" may provide improved quality of life without significantly compromising outcomes, but data are inconsistent. Using a population-based cohort of metastatic colorectal cancer (mCRC) patients to test this hypothesis, our aim was to determine the impact of treatment breaks on overall survival (OS). **Methods:** Patients diagnosed with mCRC from 2008 to 2010 and who initiated palliative systemic therapy at any 1 of 5 regional cancer centers in British Columbia were reviewed. Treatment breaks were defined as any intervals of >/= 4 weeks without receipt of any systemic therapy. The number and average length of breaks were characterized for first (1L) and second (2L) line therapy. Using Cox regression that controlled for confounders that included number of lines of therapy and total duration of therapy, we examined for the effect of treatment breaks on OS. **Results:** In total, 946 patients were identified: median age 64 (IQR 55-72) years, 521 (55%) were men, and 624 (66%) had colon cancer. The median number of treatments received in 1L and 2L therapy were 9 (IQR 4-13) and 7 (IQR 4-12) cycles, respectively. Treatment breaks were prevalent with 223 (24%), 76 (8%) and 55 (6%) patients in the cohort experiencing 1, 2 and >/=3 breaks, respectively. The median length of breaks varied depending on the line of therapy: 49 (IQR 36-99) days for 1L and 56 (IQR 38-100) days for 2L. There were no differences in baseline patient and tumor characteristics between subjects who underwent breaks and those who did not (all p>0.05). On multivariate analyses that adjusted for prognostic factors, patients who received more and longer treatment gaps did not experience worse OS (Table) **Conclusions:** This study suggests that treatment breaks from systemic therapy in carefully selected patients with mCRC do not compromise outcomes.

| Total number of breaks | HR for death | p-value | Median duration of breaks (days) | HR for death | p-value |
|---|---|---|---|---|---|
| None | 1.0 | <0.001 | 0 | 1.0 | <0.001 |
| 1 | 0.72 | | 1 to 30 | 0.79 | |
| 2 | 0.62 | | 31 to 60 | 0.58 | |
| 3+ | 0.46 | | 61 to 90 | 0.30 | |

**6610 General Poster Session (Board #73), Mon, 1:15 PM-5:00 PM**

**Influence of extent of lymphadenectomy on survival for localized non-small cell lung cancer.** *Presenting Author: Daniel Jacob Becker, Mount Sinai St. Luke's Hospital, Mount Sinai Roosevelt Hospital, Icahn School of Medicine at Mount Sinai, New York, NY*

**Background:** Several studies suggest that more extensive lymph node dissection during surgery for localized non-small cell lung cancer (NSCLC) is associated with better prognosis. Given recent changes in therapy we sought to update previous analyses and include patients with higher stage, pathologically node negative (N0) disease. We further sought to identify clinical and demographic predictors of more extensive lymphadenectomy. **Methods:** We reviewed the SEER records of patients with N0 NSCLC, stage I-III diagnosed 2000-2010, who underwent lobectomy or pneumonectomy, with removal of > 1 lymph node (LN). We used the Cox proportional hazards model to examine the relationship between the number of LN examined and lung cancer specific survival (LCSS). We used linear and logistic regression to examine the relationship between clinical/demographic variables and number of LN removed. **Results:** We identified 34,233 patients with N0 NSCLC, treated with lobectomy/pneumonectomy between 2000 and 2010. The patients were 55.5% malewith medianage of 68;78.9% stage I, 7.9% stage II and 13% stage III. The median number of LN sampled was 7 (IQR 4-12). More LN resected at surgery were associated with improved OS and LCSS. Compared to patients with 1-3 LN resected, the hazard ratios for LCSS were 0.90 (CI 0.85-0.95) for 4-6 LN resected, 0.86 (CI 0.80-0.91) for 7-9 LN, 0.84 (CI 0.79-0.91) for 10-12 LN, 0.85 (CI 0.78-0.92) for 13-15 LN and 0.80 (CI 0.75-0.86) for > 16 LN resected. After controlling for age, gender, race, ethnicity, grade, stage, year of diagnosis and registry, little additional benefit was seen for resection of >7-9 LN. Older patients (age 70-80, OR 0.91), black race (OR 0.79), female (OR 0.90) and Hispanics (OR 0.81), were less likely to have > 7 LN resected. Patients diagnosed in 2005 and after (OR 1.15 - 1.62) were more likely to have > 7 LN resected. We also noted significant heterogeneity of LN resected by registry. **Conclusions:** In a current cohort of patients who had curative intent surgery for N0 NSCLC, the number of lymph nodes resected is strongly associated with LCSS. We propose that resection of 7 lymph nodes is feasible and may be considered a minimally acceptable number of nodes to be removed at curative resection of localized NSCLC.

**6611 General Poster Session (Board #74), Mon, 1:15 PM-5:00 PM**

**The impact of PET-CT on staging, management, and prognostication of small-cell lung cancer.** *Presenting Author: Alona Zer, Princess Margaret Cancer Center, Toronto, ON, Canada*

**Background:** Although frequently used, there is no randomized data assessing the role of PET CT in the staging process of SCLC patients, or its impact on patients' management. We aimed to review the utility of PET-CT in patients diagnosed with SCLC in a single tertiary medical center. **Methods:** All patients diagnosed with SCLC for 5 consecutive years were included, either staged by PET-CT or not. We retrieved clinical data, staging procedures, PET parameters (SUVmax and TLG) progression free survival (PFS) and Overall Survival (OS). In the group of patients who underwent PET CT during initial evaluation, re-assessment staging was performed by two independent radiologists: one according to PET-CT findings, and the other according to chest, abdomen and pelvic contrast-enhanced CT scan findings (with bone scan results if available) and blinded to the PET results. **Results:** 108 patients were identified. 2 patients were excluded from the analysis for lack pathology or staging procedure data and 10 patients were excluded since their PET imaging was not accessible. Out of 96 patients, 54 had a PET-CT done as part of their staging procedure. PET-staged patients had significantly less staging procedures (including FDG-PET scan, CT scans, MRIs, Bone Scans, BMBs) done than non-PET-staged patients (24% underwent 3-4 staging procedures versus 62%, p=0.04). PET altered management in 19 patients (35%), with 13 patients with suspected metastatic disease, who benefited from down-staging by PET. Treatment was delayed in PET-staged patients by 4 days; 30 vs 26 days from diagnostic procedure to treatment (p=0.04). High TLG level predicted poorer survival (HR=3.38, p=0.007). **Conclusions:** PET-CT adds to SCLC patients' management by reducing the amount of staging procedures and possibly down staging patients who otherwise would have been treated for palliative intent. In the setup of a public health system, waiting for the PET to be done and reported could result in treatment delay. TLG appears to be a new promising prognostic biomarker in small cell lung tumors. Prospective randomized trials are warranted to properly evaluate sensitivity, specificity and influence on management.

**6612 General Poster Session (Board #75), Mon, 1:15 PM-5:00 PM**

**Measurement of urinary incontinence after prostate surgery from data-mining electronic health records (EHR).** *Presenting Author: Tina Hernandez-Boussard, Stanford School of Medicine, Stanford, CA*

**Background:** National initiatives to develop quality metrics emphasize the need to include patient-centered outcomes, yet rely on manual chart abstraction or administrative data. Chart abstraction is expensive and labor intensive, while administrative data are incomplete. We sought to use EHR to examine post-operative urinary incontinence (PO-UI) as a patient-centered outcome, as this is prevalent in prostate cancer patients (reported ranges are 10% to 40%) yet rarely recorded in administrative data. **Methods:** We included patients who underwent prostatectomy at the Stanford Cancer Institute (SCI), 1995 - 2013. We processed clinician-generated encounter notes from EHRs using a validated text-mining workflow to measure PO-UI (PloS one. 2013;8(5):e63499). Our analysis included coded data (ICD-9-CM and CPT codes) as well as term-mentions extracted from unstructured clinicians' notes. **Results:** We identified 5,353 patients who underwent prostatectomy; 43.8% open, 7.2% robot-assisted, 7.7% laparoscopic, and 41.3% were other, which includes codes that do not distinguish between robotic and laparoscopic procedures. 37.1% of our patients, treated prior to EHR implementation, were without an EHR note. UI was identified pre-surgery in 6.99% of patients and post-surgery in 9.66% of patients. Using only coded data, rates dropped to 0.24% pre-surgical and 0.21% post-surgical. In patients with an EHR clinical note (3,367 patients, 62.9%), PO-UI was identified in 22.6% of patients; 19.7% open, 12.7% robot-assisted, 21.5% laparoscopic, and 29.5% other surgeries (p<0.0001). 47% of all PO- UI were identified within 60 days of surgery. 20.8% of patients had documentation of no PO-UI. 44.2% of patients had pre-operative discussion of PO-UI documented as a possible complication. **Conclusions:** Using EHR to identify quality metrics is feasible, efficient and can capture patient-centered outcomes. Our results indicate that patient-centric events are not always coded in EHR and therefore not entered into administrative datasets; thus escaping quality assessment. Using EHRs for quality assessment promotes meaningful use of health information technology and allows quality measurement to move into the Big Data era.

**6613 General Poster Session (Board #76), Mon, 1:15 PM-5:00 PM**

**Improved access to tobacco cessation services for cancer patients using a statewide collaborative approach.** *Presenting Author: Jane Alcyne Severson, Michigan Oncology Quality Consortium, Ann Arbor, MI*

**Background:** The Michigan Oncology Quality Consortium (MOQC) collaborated with the Michigan Department of Community Health (MDCH) and Michigan Cancer Consortium (MCC) to implement a statewide Tobacco Cessation Demonstration Project to improve cancer patients' access to tobacco cessation services. **Methods:** Beginning in fall 2012, MOQC, MDCH, and MCC implemented a program to refer all cancer patients who use tobacco to the Michigan Tobacco Quitline. Referred patients were provided free counseling services and nicotine replacement therapy. A lean problem solving approach was deployed that included standard workflows, scripts, and visual management tools to support frontline staff in identifying all cancer patients who use tobacco and referring them to the Quitline. Eighteen oncology practices (63 physicians) participated in 3 learning sessions during which the following were provided: education by subject matter experts, data management and lean tools, and sharing of barriers and successes. **Results:** Between May and December of 2013, a total of 694 cancer patients were referred for cessation support and at least 1 contact attempt was made for 686 patients. A total of 308 patients (45%) were successfully contacted by the Quitline, only 3% were ineligible to participate, and 26% declined participation. Whereas total Michigan Quitline referrals increased by an average of 40% each month in this period, non-MOQC referrals decreased from 140 per month in May to 95 per month in December. In contrast, MOQC cancer patient referrals increased from 62 per month to 80-123 per month in the subsequent months representing an average of 43% of all Michigan Quitline referrals. Tobacco assessment rates for cancer patients were maintained above 95%, and an average of 61% of eligible cancer patients were referred to the Quitline, a four-fold increase from the baseline referral rate of 15%. **Conclusions:** Increasing access to dedicated statewide resources and providing oncology practices with lean resources including standardized workflows improves the tobacco cessation referral rate for oncology patients. Improvements in referral rates may significantly increase participation in dedicated tobacco cessation programs.

**6614 General Poster Session (Board #77), Mon, 1:15 PM-5:00 PM**

**Prevalence of prescribing errors resulting in administration of incorrect dosages of antineoplastic treatment.** *Presenting Author: Thea Otto Mattsson, University of Southern Denmark, Odense, Denmark*

**Background:** The prevalence of non-intercepted prescribing errors and the impact of computerized order entry systems (CPOE) in preventing such errors are not known. Our objective was to evaluate both prevalence and severity of non-intercepted prescription dose errors as well as the impact of a CPOE system on these in a setting of adult cancer patients. **Methods:** A prospective observational case control study in two clinical oncology units. One institution used a parallel CPOE system with no connection to the electronic patient chart data, while the other used paper based prescription forms. All standard prescriptions from both institutions were included and reviewed. Doses were recalculated according to the guidelines of each of the institutions using the patient data as documented in the chart, on the paper based form or in the CPOE system at the time of prescription. A non-intercepted prescription dose error was defined as ≥ 10% difference between the administered and the recalculated dose. Main outcome measures were prevalence and severity of prescription errors using validated harm categories. **Results:** Data were collected from November 1, 2012 til January 31, 2013. A total of 5,767 physician prescriptions were evaluated. 2,677 from the institution using CPOE and 3090 from the institution with paper based prescription forms. Crude analysis showed an overall risk of a prescription dose error of 1.73 per 100 prescriptions. CPOE resulted in 1.60 and paper based prescription forms in 1.84 errors per 100 prescriptions. OR = 0.87 (95%CI 0.59-1.29, P=0.49). Furthermore, no significant difference between institutions in severity of errors was observed. **Conclusions:** Non-intercepted prescribing dose errors are relatively common in clinical oncology units. Non integrated CPOE systems without decision support do not seem to significantly reduce the risk of prescription errors or affect severity of errors. Based on the results of this study strategies to prevent future prescription errors are highly warranted.

**6615 General Poster Session (Board #78), Mon, 1:15 PM-5:00 PM**

**Can we identify patients at risk for discordance in preferred and actual role in cancer treatment decision making?** *Presenting Author: Leah L. Zullig, Health Services Research and Development, Durham VA Medical Center, Durham, NC*

**Background:** Assuring treatment-related decision-making aligns with patients' preferences is a critical component of quality care. Yet often patients' preferred and actual treatment-related decision-making roles are discordant (i.e., patients may play a more or less active role in decision-making than was preferred). We examined whether patient characteristics predict discordant treatment decision-making roles. **Methods:** We surveyed adults receiving anti-cancer therapy. First, patients were asked to state their preferred role: to make treatment decisions with little or no input from their oncologists; to let their oncologists make the decision for them; or to engage in shared decision-making. Second, patients were asked about their actual role: the role they played when treatment decisions were actually made, using the same categories. A dichotomized variable measured discordance between preferred and actual decision-making roles. Multivariable regression examined the association between characteristics (age, gender, race, education, income, financial distress, employment, insurance, marital status, treatment intent, time on treatment, income, quality of life, out-of-pocket costs) and decision-making role discordance. **Results:** Of 300 respondents (86% response), 12% preferred to make decisions with little or no input, 7% preferred their doctor to make decisions, 25% preferred their doctor to make decisions after considering their input, and (55%) preferred shared decision-making between patients and their oncologists. The most common discrepancy was patients preferred a shared decision, but in actuality doctors made the decision after considering patients' opinion (5%). 81% reported decision making consistent with preferences. None of the examined patient characteristics were associated with decision-making role discordance. **Conclusions:** There was relatively little discordance between preferred and actual decision-making style.Readily identifiable patient characteristics were not associated with role discordance. Therefore, it may be important for clinicians to simply ask patients what role they would prefer to play in cancer treatment decision-making.

**6616 General Poster Session (Board #79), Mon, 1:15 PM-5:00 PM**

**Which formats for communicating patient-reported outcomes (PROs) work best?** *Presenting Author: Michael Donald Brundage, Queen's University, Kingston, ON, Canada*

**Background:** PROs provide patients' perspectives on health conditions and treatments. Both group-level PRO data (eg, clinical trial results) and individual-level PRO data (eg, charted symptoms) can inform clinical care. How to optimally present PROs to assist comprehension and use is unclear. **Methods:** We purposively sampled cancer patients (by cancer type, care setting, and education) and clinicians (by specialty and practice setting). Participants were randomized to evaluate either 6 formats for group-level data or 4 formats for individual-level data. For each format (eg, bar charts, line graphs), participants answered 2 questions testing comprehension and rated ease of understanding and usefulness (0 least-10 most). In follow-up qualitative interviews, participants described their interpretations of the formats and reported presentation elements that aided/hindered understanding. **Results:** We recruited 49 patients (median age 65, 44% <college graduate) and 20 clinicians (median age 42). Participants evaluating group-level formats rated line graphs highest for ease of understanding and usefulness (patients: median 8.0 and 8.0, respectively; clinicians: median 9.0 and 8.5, respectively). Accuracy of interpretation across formats ranged from 38%-100% for patients and 56%-100% for clinicians. The group-level qualitative data suggested clinicians value confidence intervals, normed scores, and p-values, but patients find this information confusing. Participants evaluating individual-level formats also rated line graphs highest for ease of understanding and usefulness (patients: median 8.0 and 8.0, respectively; clinicians: median 8.5 and 9.0, respectively). Accuracy of interpretation across formats ranged from 64%-96% for patients and 90%-100% for clinicians. The individual-level qualitative data suggested reference scores for comparison and highlighting issues requiring clinical attention are helpful. **Conclusions:** Participants preferred line graphs of trends over time for both group-level and individual-level PRO data. Given the variation in interpretation accuracy across formats, results regarding aspects that were helpful and confusing can inform best practices for presenting PRO data.

**6617 General Poster Session (Board #80), Mon, 1:15 PM-5:00 PM**

**NCI pilot intervention program to assist accrual for challenging late-phase clinical trials.** *Presenting Author: Andrea Denicoff, National Cancer Institute, Rockville, MD*

**Background:** Since 2010, the National Cancer Institute (NCI) has taken substantial efforts to compress the timelines for protocol review and trial activation (Abrams, JNCI, 2013). In 2012, NCI's Cancer Therapy Evaluation Program (CTEP) began a pilot in collaboration with NCI Cooperative Groups (CG) to support accrual to Phase 2-3 treatment trials identified as potentially challenging or at risk for insufficient accrual (Korn, JCO, 2010). Pilot program findings are reported. **Methods:** CG trials were identified for the pilot if accrual concerns were raised during the concept or protocol review or were at risk of not meeting CTEP's slow accrual guidelines after activation. In collaboration with CG study teams, each trial underwent the following evaluation and analyses: accrual feasibility/challenges; site activation data; tailored interventions to address challenges, track and report accrual changes. **Results:** To date, 18 trials are in the pilot (10 identified pre-activation, 8 post-activation). Nine received interventions and 9 are in process. Interventions included: trial-specific materials, outreach to investigators/sites, survey data to guide amendments, social media outreach. Accrual data are available for 5 trial interventions. Quarterly accrual rates (QAR) increased for all 4 post-activation trials: Trial 1 now exceeds projected QAR (18 patients) by 6% (pre-intervention=10; post=19); Trial 2 exceeds projected QAR (72 pts) by 6% (pre=52; post=76); projected QAR for Trial 3 (36 pts) and Trial 4 (84 pts) remain below goals but QAR did improve(Trial 3: pre=5, post=29; Trial 4: pre=44, post=63). The lone pre-activation trial (Trial 5) is 61% below its projected QAR (102) 2 yrs after activating. **Conclusions:** Improved QARs for 4 of 5 trials. No intervention appears generally applicable and most trials require very specific interventions. Monitoring of trials will continue as interventions are implemented. CTEP plans to expand the pilot to support the new NCI National Clinical Trials Network (NCTN) and Early Therapeutic Clinical Trials Network (ET-CTN) and assist both early and late phase trials with accrual challenges. The effect of future interventions will be continually assessed.

**6618 General Poster Session (Board #81), Mon, 1:15 PM-5:00 PM**

**Next steps for IBM Watson Oncology: Scalability to additional malignancies.** *Presenting Author: Andrew S. Epstein, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** We reported on the development of IBM Watson Oncology, a cognitive computing system designed to inform clinical decision making. The initial prototype demonstrated results (Bach, Proc ASCO 2013) in lung cancers, including the complexities of natural language processing. Here, we report the experience scaling the tool to additional cancers using an alternative method of attribute collection. **Methods:** Memorial Sloan Kettering and IBM's continued collaboration now includes the creation of electronic decision support prototypes for colon, rectal, bladder, pancreatic, kidney, ovarian, cervical and endometrial cancers. To date, each prototype has been created with IBM Watson and trained by Memorial Sloan Kettering physicians by identifying key attributes common to all cancers (e.g., stage, age) and specific to individual cancers (e.g., high risk features for stage II colon cancer), manually entering attribute and candidate treatment answer combinations, and ranking treatments as preferred, acceptable, or not recommended. Precision, defined as [(correct preferred treatments)/(correct preferred treatments + false positives (incorrect preferred treatments) + false negatives (missing preferred treatments))], was measured for each prototype. **Results:** To date, each cancer prototype has been created with dozens of training cases and candidate treatment answers. Average precision, retesting with the same training data, has improved from 5% to nearly 100% depending on the cancer type. Table 1 is provided as a descriptive summary and not a statement of statistical significance. **Conclusions:** IBM Watson Oncology's training is scalable to additional cancers and today covers the majority of solid tumors, including breast and lung. Future steps include using additional machine learning features and training cases to improve precision, testing using blind cases, and using natural language processing to automatically extract clinical attributes from electronic medical records.

**Average precision (%) by disease site.**

| | First run | Middle run | Latest run |
|---|---|---|---|
| **Colon** | 68 | 81 | 98 |
| **Rectal** | 61 | 88 | 96 |
| **Bladder** | 24 | 75 | 91 |
| **Pancreatic** | 5 | 91 | 94 |
| **Kidney** | 12 | 87 | 91 |
| **Ovarian** | 41 | 97 | 95 |
| **Cervical** | 6 | 100 | 100 |
| **Endometrial** | 12 | 83 | 89 |

**6619 General Poster Session (Board #82), Mon, 1:15 PM-5:00 PM**

**Impact of recent clinical trials on the use of chemotherapy for resectable non-small cell lung cancer in the United States.** *Presenting Author: Ravi Rajaram, Center for Healthcare Studies, Institute of Public Health and Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL*

**Background:** Multiple clinical trials have demonstrated chemotherapy combined with surgery improves survival in many patients with non-small cell lung cancer (NSCLC). Per NCCN Guidelines, for selected stage IB and II-IIIA patients there is level 2B and 1 evidence for use of chemotherapy, respectively. We sought to (1) evaluate changes in chemotherapy utilization in surgically treated NSCLC over time and (2) to identify factors predictive of chemotherapy administration in this population. **Methods:** Patients who had surgery for AJCC seventh edition stage IB-IIIA NSCLC (2002-2011) were identified from the National Cancer Data Base. Administration of chemotherapy (neoadjuvant or adjuvant) was assessed over time. Hierarchical regression models were developed to assess patient, hospital, and tumor characteristics predicting chemotherapy utilization separately for IB and II-IIIA tumors. **Results:** Overall, 112,049 patients had resection for stage IB-IIIA NSCLC. In 55,016 patients with stage IB disease, chemotherapy use increased from 5.3% to 15.1%, with adjuvant therapy specifically increasing from 2.4% to 14.4% (both $p < 0.01$). On multivariable analysis, stage IB patients were less likely to receive chemotherapy if they were older, treated at an academic or NCI center (vs. community), had more comorbidities, or had lower grade tumors (all $p \leq 0.01$). In 57,033 patients with stage II-IIIA disease, chemotherapy administration also significantly increased from 29.3% to 58.4%, with adjuvant therapy increasing from 18.0% to 43.4% (both $p < 0.01$). Predictors of decreased chemotherapy use in stage II-IIIA patients included increasing age, non-private insurance status, non-NCI academic treating facility, increased comorbidities, squamous histology, lower grade tumors, or sublobar resection (all $p < 0.04$). Stage IIIA (vs. IIA) disease (OR 2.82, 95% CI 2.56-3.11) was predictive of increased chemotherapy delivery. **Conclusions:** In patients with resected stage IB-IIIA NSCLC, use of chemotherapy has substantially increased since 2002. However, while many providers have adopted evidence-based recommendations into their practice, sizeable treatment gaps persist and are areas for targeted quality improvement.

**6620 General Poster Session (Board #83), Mon, 1:15 PM-5:00 PM**

**HIV and predictors of advanced cancer at presentation: Uganda.** *Presenting Author: Manoj Menon, Fred Hutchinson Cancer Research Center, Seattle, WA*

**Background:** The HIV epidemic has contributed to the increasing incidence of cancer in sub-Saharan Africa (SSA), where most patients with cancer present at an advanced stage. However, improved access to HIV care and treatment centers in SSA may facilitate earlier diagnosis of cancer among HIV+ patients. To test this hypothesis, we characterized the stage of cancer and evaluated predictors of advanced stage at presentation among patients in Uganda. **Methods:** We conducted a retrospective analysis of adult patients who presented for care at 1 of 2 tertiary care sites in Kampala, Uganda with any of 5 specific cancers between 2003 and 2010. Demographic, clinical and laboratory data were abstracted from the medical record along with the outcome measure of advanced stage of disease (clinical stage 3 or 4). We utilized bivariate analyses to identify measures with $p<0.20$ for inclusion in a multivariate logistic regression model. **Results:** We analyzed 802 patients with the following cancers: cervical (39%), breast (27%), NHL (17%), esophageal (9%) and HL (8%). Nearly 80% presented at an advanced stage and 34% had HIV infection. The median age was 44 years. Over 90% of patients were symptomatic and the median duration of symptoms prior to presentation was 5 months. The median hemoglobin (hgb) level at presentation was 11.1g/dl (IQR 4.4 g/dl). In bivariate analyses of all cancer types, higher hgb, fewer symptoms, shorter symptom duration, younger age and HIV infection were associated with less advanced cancer. The association between HIV infection and less advanced stage of cancer was significant at $p<0.01$ for only the AIDS-defining cancers (i.e. cervical cancer and NHL). In the multivariate model, HIV+ patients were less likely ($p=0.01$) to present at an advanced stage, as were patients with higher hgb ($p=0.03$) and fewer symptoms ($p<0.01$). **Conclusions:** Patients with limited access to primary care may present with advanced cancer due to a delay in diagnosis. However, patients with HIV now have better access to clinical care. Utilization of this growing infrastructure to increase cancer screening and referral is promising and deserves continued support, as the prognosis of HIV+ patients with advanced cancer is characterized by poor survival, even in resource-abundant regions.

**6621 General Poster Session (Board #84), Mon, 1:15 PM-5:00 PM**

**Relationship between type of therapeutic intervention and funding source in randomized clinical trials (RCTs) in oncology.** *Presenting Author: Fernando Costa Santini, Hospital Sirio Libanes, Sao Paulo, Brazil*

**Background:** Pharmaceutical companies play an important role in drug development and approval in an environment where performing RCTs has become increasingly costly and complex. However, myriad questions about the impact of surgical and radiotherapy interventions equally require adequate hypothesis testing in RCTs. A potential lack of funding for non-drug related RCTs may lead to important gaps in clinical knowledge. **Methods:** We searched PubMed for all RCTs published between 01/2009 and 12/2013 in breast, prostatic, lung and colorectal cancers. All articles published in this period were manually screened for eligibility. We included only RCTs with clinical endpoints such as TTP, PFS, OS and response rate. Two investigators independently selected phase 2 and phase 3 RCTs with at least 50 patients published in English. We classified eligible trials according to the type of intervention (drugs, radiotherapy or surgery) and the stated funding source (industry versus nonprofit). **Results:** We retrieved 4,416 RCTs studies of which 709 (16%) were eligible. 578 (82%) of the RCTs evaluated drugs, 74 (10%) radiotherapy and 57 (8%) surgery. There was a significantly greater number of RCTs evaluating radiotherapy or surgery performed in colorectal and prostatic cancers compared to lung and breast. Overall, 470/709 (66%) RCTs were funded entirely or partially by industry (pharmaceutical and device companies) and 239/709 (34%) by nonprofit organizations (government, academic centers or foundations). There was a significant association between source of funding and type of intervention: 448/578 RCTs (77,5%) evaluating drugs were funded by industry, in comparison to only 22/131 (17%) of surgical and radiotherapy RCTs ($p<0.0001$). **Conclusions:** The vast majority of RCTs in oncology relates to drug development and is being funded by industry, while 83% of RCTs evaluating surgical or radiotherapy related questions are not industry funded. Even though drug development is of paramount importance, the extent to which clinically relevant issues are not being properly addressed by RCTs, at least in part due to lack of funding, should be considered and further evaluated.

**6622 General Poster Session (Board #85), Mon, 1:15 PM-5:00 PM**

**Permanent stoma use in rectal cancer surgery in Canada: A population-based analysis.** *Presenting Author: Geoffrey A. Porter, Canadian Partnership Against Cancer, Toronto, ON, Canada*

**Background:** Sphincter preservation is important for many patients with rectal cancer; avoidance of a permanent stoma (either colostomy or ileostomy) is a well-accepted quality indicator of rectal cancer care. This study describes, at a population level, the frequency of permanent stoma (PS) use in rectal cancer surgery in Canada. In addition, this study examines potential disparities in PS use related to income, geography and immigration status. **Methods:** Patients undergoing resection for primary adenocarcinoma of the rectum in Canada during fiscal years 2007/08-2011/12 with a valid postal code were included; procedure codes from the discharge abstract database were used to categorize surgery as involving either a permanent stoma (PS), temporary stoma (TS) or no stoma (NS). Income for urban Canada was categorized according to neighbourhood income quintile, and immigration density represented the percentage of immigrant/non-permanent populations living in a dissemination area based on census information. Geography was examined according to province of residence, statistical area classification (SAC) of urban/rural, and travel time (in minutes) to nearest hospital **Results:** Among the 10,559 patients undergoing rectal cancer resection, 3,895 (36.9 %) underwent a PS, 3,501 (33.2 %) a TS, and 3,163 (30.0%) had NS. Significant variation in PS rates was identified among 9 Canadian provinces (range 35.1%- 51.4%; $p<0.0001$). The table below shows increased rates of PS among patients living in rural/remote areas, low income neighbourhoods, and those with longer travel time to hospital. Lower rates of PS were seen among patients residing in areas of higher immigration density. **Conclusions**: Significant variation exists in the use of PS for rectal cancer in Canada, particularly related to geography. Better understanding of root causes of such variation will be important to guide targeted initiatives aimed at optimizing the quality of rectal cancer care at a population level.

| | % with PS | P value |
|---|---|---|
| **SAC** | | 0.0003 |
| **Urban** | 35.9 | |
| **Rural** | 36.1 | |
| **Rural - remote** | 40.1 | |
| **Rural - very remote** | 41.9 | |
| **Travel time (minutes)** | | <0.0001 |
| **0-39** | 35.9 | |
| **40-179** | 41.9 | |
| **≥ 180** | 42.6 | |
| **Immigrant density** | | <0.0001 |
| **Low** | 37.9 | |
| **Middle** | 35.7 | |
| **High** | 30.3 | |
| **Income** | | 0.003 |
| **Lowest quintile** | 38.5 | |
| **Highest quintile** | 35.4 | |

**6623 General Poster Session (Board #86), Mon, 1:15 PM-5:00 PM**

**Standardized criteria for required palliative care consultation on the solid tumor oncology service.** *Presenting Author: Kerin Adelson, Icahn School of Medicine at Mount Sinai, New York, NY*

**Background:** Studies have shown that for patients with advanced cancer, integration of Palliative Care (PC) is associated with improved symptom control, clearer understanding of prognosis, lower utilization of health care resources, and increased hospice use. The 2012 ASCO guidelines call for incorporation of PC for any patient with metastatic cancer and/or high symptom burden. Despite a top-rated PC division at Mount Sinai, our Solid Tumor (ST) Division utilized PC and hospice less than other centers. Our inpatient ST service demonstrated poor quality metrics. Our 2011-2012 UHC statistics were: mortality index, 1.35 (target <1), 30-day readmission rate, 21.7%, (target < 10.3%) and length of stay (LOS) index, 1.23 (target <1). We hypothesized that implementing standardized criteria for PC consultation would improve these metrics. **Methods:** During this 3-month pilot, criteria for PC consultation included patients with one or more of the following: stage IV disease, Stage III lung or pancreatic cancer, hospitalization within prior 30 days, >7 day hospitalization, uncontrolled symptoms (pain, nausea, dyspnea, delirium, distress). We looked at two baseline groups for comparison: 1) patients who met eligibility in a six week period prior to the intervention 2) For UHC index data, we used the hospital dashboard average over a 1-year period prior to the intervention. Primary outcomes were: hospice utilization, ST mortality index, 30-day readmission rate and LOS. **Results:** Comparing group 1 to the pilot group, palliative care consultation doubled from 41% to 82%, 30-day readmission decreased from 36% to 17% ($p = 0.022$), and hospice utilization increased from 14% to 25% ($p = 0.146$). UHC data (Group 2 vs. Pilot) showed: mortality index improved (1.35 to 0.59) and 30-day readmission rates decreased (21.7% to 13.5%, $p = 0.026$). LOS was unchanged (1.23 to 1.25). **Conclusions:** Mandating palliative care consults for patients at the highest risk for in hospital death and readmission improved hospice utilization, 30-day readmission, oncology service mortality and adherence with ASCO guidelines. Mount Sinai has funded an extra palliative care team; use of these criteria have become our standard of care.

**6624 General Poster Session (Board #87), Mon, 1:15 PM-5:00 PM**

**Development of a new oncology quality metric: The rate of evidence-based adherence.** *Presenting Author: Kerin B. Adelson, Division of Hematology and Medical Oncology, The Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY*

**Background:** The degree to which electronic health records enhance the quality of patient care depends on how the system is used to monitor and improve practice. In planning the transition to Epic's electronic chemotherapy ordering platform, we saw an opportunity to increase evidence-based practice. **Methods:** Our Chemotherapy Council vetted more than 600 electronic protocols based entirely on published clinical trials and NCCN guidelines; modifications made to these protocols represent a divergence from clinical evidence. We examined the number of times the chemotherapy section of a protocol was modified before the first cycle to avoid counting dose modifications made for toxicities. To get the rate for the cancer center we calculated the # of discrete times all protocols were used (denominator) and the number of times all protocols were modified (numerator). We subtracted the ratio from 1 to reflect the proportion of protocols that were not modified. This ratio serves as a new quality metric – the Rate of Evidence-Based Adherence (REBA). $REBA_{institution} = 1$ - Total # of modifications prior to first cycle for each protocol / Total # of uses of all protocols. Additionally, REBA can be used to examine disease group rates ($REBA_{group}$), individual provider rates ($REBA_{provider}$) and rates for individual protocols ($REBA_{protocol}$). Institutions that have implemented evidence-based clinical pathways have strived for 80% (.80) adherence. We set this as our REBA benchmark. **Results:** The $REBA_{institution}$ was .86, higher than our pre-defined goal ($p<0.001$). There was wide variation in the $REBA_{group}$ (range 0.50-0.95). The $REBA_{protocol}$ identified two protocols (rates of .33 and .42 respectively) that were dose reduced the majority of the time. In the example of our Breast Group, the $REBA_{provider}$, ranged from (.78 to .97) reflecting differing practice among 4 physicians. **Conclusions:** The REBA can identify faculty and disease groups who underutilize clinical evidence, facilitating feedback for quality improvement. The $REBA_{protocol}$ is a useful tool to identify specific chemotherapy templates that may need modification. The REBA is a powerful electronic tool, which can be utilized to monitor and enhance the rate of evidence-based practice in oncology.

**6625 General Poster Session (Board #88), Mon, 1:15 PM-5:00 PM**

**Associations among socioeconomic status (SES), patterns of care and outcomes in breast cancer (BC) patients (pts) in a universal health care system: Ontario's experience.** *Presenting Author: Alexander Kumachev, University of Toronto, Toronto, ON, Canada*

**Background:** The Canadian health care system was designed to provide equitable access to equivalent standards of care. We aim to examine if BC pts with different SES received different care and had different overall survival (OS) in Ontario, Canada's largest province. **Methods:** Female pts diagnosed with BC between 2003-2009 were identified from the Ontario Cancer Registry and linked to databases related to physician claims, hospital and emergency visits and provincial funding programs to ascertain demographics, cancer stage (CS), comorbidities, mammography use, surgery type, adjuvant chemotherapy (chemo), radiation (RT), and vital statistics. SES was defined as neighbourhood income by postal code attained from Statistics Canada and divided into income quintiles (Q1-Q5; Q5=highest). Univariate and multivariable analyses were used to examine the association between i) SES and mammogram screening and BC treatments, and ii) SES and OS. **Results:** 34,446 BC pts with CS available were identified. 76.0% were > 50 years old. The proportion of CS I, II, III and IV were, 41.4, 38.8, 14.9, & 4.9%, respectively. Screening mammograms (1-5 years prior to diagnosis) rates were significantly higher with higher SES (Q5 = 50.1% and Q1=41.7% (OR = 1.43, 95% CI: 1.32-1.56, $p<0.0001$)) for pts age >55. Pts with higher SES were more likely to be diagnosed at an earlier CS ($p<0.0001$, Q5=44.3% & Q1=37.7% were diagnosed with CS (OR = 1.31, 1.23-1.41)). Pts with higher SES were more likely to receive adjuvant chemo ($p<0.0001$, Q5 vs. Q1 OR = 1.18, 1.10-1.26) and RT ($p<0.0001$, Q5 vs. Q1 OR = 1.24, 1.15-1.33). There were no obvious differences in adjuvant trastuzumab (T-mab) use ($p=0.62$), breast conserving surgery ($p=0.057$) and time between surgery and adjuvant chemo ($p=0.15$) based on SES. The 5 year OS rates for Q1-Q5 were 80.0, 81.0, 82.2, 83.9 & 85.7%, respectively ($p<0.0001$). After adjusting for age, CS, comorbidities, rural residence, use of adjuvant chemo, T-mab, RT and surgery type, higher SES remained associated with better OS ($p=0.0017$). **Conclusions:** Higher SES is associated with more use of screening and treatments, and better OS in BC pts in a universal health care system.

**6626 General Poster Session (Board #89), Mon, 1:15 PM-5:00 PM**

**Practice of venous thromboembolism (VTE) prophylaxis in hospitalized cancer patients at a comprehensive cancer center.** *Presenting Author: Maria Alma Rodriguez, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background**: VTE prophylaxis measures are endorsed by the National Quality Forum in alignment with quality indicators from the Centers for Medicare and Medicaid Services. Accordingly, documentation of VTE risk, prophylaxis measures, and contraindications are recommended for hospitalized patients. To standardize practice we embedded a VTE risk assessment and prophylaxis module into admission and post-surgical order sets (OS), starting August 15, 2011. **Methods**: A retrospective study of 9,065 cancer patients (≥18 years) admitted to The University of Texas MD Anderson Cancer Center between June 01, 2013, through September 30, 2013**.** Pharmacological prophylaxis was executed with low-molecular-weight heparin or unfractionated heparin. Mechanical prophylaxis was executed with graduated compression stockings and/or sequential compression devices. *Chi*-square testing was used to determine the association between categorical variables. **Results**: 7,366 (81%) of all hospital admissions had documented VTE risk assessment and prophylaxis through the standardized VTE module. Before implementation of the new OS, only 40% of eligible patients received an order for VTE prophylaxis**.** The majority of patients were designated high or moderate risk (91.1%). Patients with high risk were more likely to receive pharmacological prophylaxis than those with moderate risk (74.1% vs. 38.2%, $P<0.01$). The most frequent contraindications to pharmacological prophylaxis were major surgery with risk of bleeding and thrombocytopenia. Results are shown in Table. **Conclusions**: Most patients received VTE prophylaxis based on VTE risk levels presented in a standardized OS. Because there is limited information in the clinical literature about the impact of VTE prophylaxis on outcomes among cancer patients, we plan to monitor and analyze anticoagulation-related outcomes as well as mortality and morbidity related to thrombosis and bleeding in this cohort of patients.

**VTE risk assessment and prophylaxis (n=7,366).**

| | | % of prophylaxis | | |
|---|---|---|---|---|
| VTE risk level | No (%) | Pharmacological | Pharmacological contraindication | Mechanical |
| High | 1,021 (13.9%) | 74.1 | 20.1 | 99.7 |
| Moderate | 5,689 (77.2%) | 38.2 | 56.3 | 35.4 |
| Low | 656 ( 8.9%) | N/A | N/A | 97.6 |

**6627 General Poster Session (Board #90), Mon, 1:15 PM-5:00 PM**

**An electronic prompt prior to myelosuppressive therapy to improve hepatitis B virus screening.** *Presenting Author: Jordan J. Feld, University Health Network, University of Toronto, Toronto, ON, Canada*

**Background:** Hepatitis B virus (HBV) reactivation is a potentially fatal and yet preventable complication of myelosuppressive therapy. However, HBV screening rates have been low despite the recommendation from the Centre of Disease Control (CDC) to screen all patients prior to myelosuppressive therapy. We evaluated the effectiveness of an electronic prompt on HBV screening rates. **Methods:** An electronic prompt was established in Nov 2010 at a large academic oncology centre in Toronto (study centre). The electronic prompt reminded ordering physicians to order HBV surface antigen (HBsAg) at the time of booking a new patient's first chemotherapy electronically. For physicians who agreed, HBsAg was automatically ordered. The prompt was not implemented at another large academic oncology centre in Toronto (control centre). Both centres received the same educational rounds in Nov 2010. The primary endpoint was the rate of HBV screening. Actual HBV screening rates were determined in both centres both prior to the intervention (Nov 2009 to Oct 2010) and during the intervention (Nov 2010 to Oct 2011). Multivariable logistic regression with random effects was conducted to assess the effect of the electronic prompt adjusting for potential confounders and clustering of patients by physicians. **Results:** 6,116 patients received first chemotherapy during the study period (2,095 study centre, 4,021 control center). In the pre-prompt period, the screening rate was 17% in the study centre and 25% in the control centre. In the prompt period, the screening rate increased to 61% in the study centre and was unchanged at 25% in the control centre. The overall screening rate for patients with hematological (heme) malignancies was higher (62.3% vs. 20.4% in non-heme patients, $p<0.0001$). After adjusting for study period, centres and heme malignancies, the electronic prompt improved the HBV screening rate significantly (odds ratio 11.0, 95% CI 8.3-14.7, $p<0.0001$), which remained significant adjusting for clustering of patients by physicians ($p<0.0001$). **Conclusions:** An electronic prompt increased the rate of HBV screening, however screening rates remained relatively low. Educational rounds did not appear to improve the HBV screening rate.

**6628 General Poster Session (Board #91), Mon, 1:15 PM-5:00 PM**

**Coordinating cancer care: What organizations do to deliver high-quality breast cancer care.** *Presenting Author: Nina A. Bickell, Icahn School of Medicine at Mount Sinai, New York, NY*

**Background:** Hospitals are reorganizing how they coordinate care. Little is known about how cancer care is effectively coordinated particularly for patients at high risk of underuse. **Methods:** We interviewed 75 key informants (48 clinical; 14 administrative; 11 clerical; 2 other) from 9 inner-city safety net hospitals with a high proportion of minority breast cancer patients. We used fuzzy set Qualitative Comparative Analysis focusing on defined coordination approaches, calibrating each approach between 0 and 1 based on sites' coordination processes and assessed their relationship to adjuvant underuse. **Results:** Five organizational factors appear salient to coordinating adjuvant breast cancer care: 1) better performing sites had someone designated to track and re-contact *no-shows*; 2) *handoffs* include exchange of clinical information (drs speaking directly to drs) as well as clerical transfer of responsibility (clerks scheduling appointments); 3) *organizational attention to clinic patients:* some sites separated private & clinic patients tolerating hectic, understaffed clinics; 4) all high quality sites had *integrated Electronic Medical Records* - doctors could see patients' tests and treatments across specialties; 5) organizations with a *culture of patient-centeredness* worked for their patients, not vice-versa. **Conclusions:** Organizational factors can affect care coordination & cancer care quality. Higher quality sites had a fully integrated EMR, were better at tracking no shows, managing handoffs, paying attention to clinic patients & fostering a patient-centered culture. As care coordination across sites and specialties is encouraged by federal law and regulation, specialty care silos and rigid communication systems still pose barriers to change. Improving organizational factors may increase appropriate delivery of adjuvant breast cancer therapies, particularly for vulnerable women.

| Site: adj underuse (%) | No-show tracking | Handoffs | Org. attn. to clinic | Integrated EMR | Culture |
|---|---|---|---|---|---|
| **A (7.7)** | 1.0 | 0.9 | 0.9 | 1.0 | 1.0 |
| **B (8.3)** | 0.8 | 0.6 | 0.8 | 0.7 | 1.0 |
| **C (9.7)** | 1.0 | 1.0 | 0.7 | 0.7 | 1.0 |
| **D (10.5)** | 0.6 | 0.4 | 0.2 | 0.5 | 0.6 |
| **E (11.8)** | 0.8 | 0.6 | 0.4 | 0.6 | 0.6 |
| **F (14.3)** | 1.0 | 1.0 | 0.6 | 0.9 | 0.8 |
| **G (15.2)** | 0.0 | 0.3 | 0.2 | 0.2 | 0.2 |
| **H (20.7)** | 0.4 | 0.8 | 0.2 | 0.2 | 0.6 |
| **I (25.5)** | 0.7 | 0.5 | 0.2 | 0.3 | 0.4 |

**6629 General Poster Session (Board #92), Mon, 1:15 PM-5:00 PM**

**An international survey of health care providers involved in the management of cancer patients exposed to cardiotoxic therapies.** *Presenting Author: Susan Faye Dent, The Ottawa Hospital Cancer Center, University of Ottawa, Ottawa, ON, Canada*

**Background:** Targeted agents used in cancer therapy may negatively impact cardiovascular health. There is increasing interest by health care providers (HCPs) in developing multidisciplinary approaches to manage these patients (pts). The objective of this international survey was to gain better understanding of current knowledge and practice patterns among HCPs involved in the management of cancer pts exposed to potentially cardiotoxic drugs. **Methods:** HCPs involved in the management of cardiac disease in cancer pts were surveyed using email lists from the Canadian Association of Medical Oncologists, Canadian Cardiovascular Society, Canadian Cardiac Oncology Network and International CardiOncology Society. The survey consisted of 14 questions related to cancer treatment-induced cardiotoxicity. Canadian HCP's were asked to comment on treatment strategies for 3 case scenarios. Descriptive data was collected and summarized. **Results:** 393 survey responses were received (response rate of 25%). The majority of respondents were cardiologists (47%, 185/393), or medical oncologists (40%, 158/393). 55% of respondents were in academic practice (212/383). The majority agreed that cardiac issues are important to cancer pts (97%, 381/393); 94% felt that the diagnosis of cardiac disease had an impact on cancer prognosis (349/383), and 77% agreed that chemotherapy or radiation is an important risk factor for cardiac disease (301/393). Only 36% of respondents felt there is an accepted definition of cardiotoxicity (109/383). 78% of respondents felt cardiac medications are protective during active cancer treatment (307/393), however only 51% would consider prescribing these medications upfront in cancer pts (199/393). While the majority of Canadian HCP's ($n=77$) agreed on pt care strategies, there was marked discrepancy in the cardiac management of metastatic breast cancer pts with asymptomatic heart failure. **Conclusions:** There is a high level of concern for cardiac safety among HCP's regarding active cancer therapy for pts; however, there is a lack of consensus on the definition of cardiotoxicity and uncertainty remains for optimal management in this new field of cancer care.

**6630 General Poster Session (Board #93), Mon, 1:15 PM-5:00 PM**

**Combining survival and toxicity effect sizes from clinical trials into an interpretable, quality-adjusted survival effect size estimate of treatment efficacy.** *Presenting Author: Jeff A. Sloan, Mayo Clinic, Rochester, MN*

**Background:** How can a clinician combine survival and toxicity data to interpet treatment benefit? Quality adjusted life years (QALYs) attempts to account for both the quality and quantity of life lived but interpretation and power considerations are barriers to implementation. We developed a new method by extending the ½ standard deviation approach to assessing clinical significance to combine survival and toxicity clinical trial data into a single quality-adjusted survival effect size (QASES). **Methods:** QASES is a weighted combination of the survival and toxicity effect sizes based on differences in survival and toxicity using the ½ standard deviation method. We demonstrate the QASES method on 20 exemplary oncology clinical trials involving brain, breast, colorectal, lung, melanoma and pancreatic tumors. One example is a phase III clinical trial carried out by the North Central Cancer Treatment Group, NCCTG 89-20-52 (Alliance), which randomized patients to once-daily thoracic radiotherapy (ODTRT) versus twice-daily treatment of thoracic radiotherapy (TDRT) for the treatment of lung cancer. **Results:** The ODTRT (TDRT) arms had non-significantly different median survival times of 22 (20) months.($p=0.49$) but strikingly different toxicity rates of 39% (54%), ($p<.05$). The combined QASES of 0.18 standard deviations is equivalent to a significant 5.7 months advantage in quality-adjusted survival for the ODRT arm over the TDRT treatment arm (22 (16.3) months, $p<0.05$). Similar results will be presented for the four possible case combinations of significant/non-significant differences in survival and toxicity data using 20 completed clinical trials including the CLEOPATRA and FLAGS trials. **Conclusions:** The QASES approach allows for an intuitively appealing and mathematically simple and robust approach to combining survival and toxicity data. Clinicians can use QASES to interpret and communicate the findings of oncology clinical trials to patients by weighing both the survival and toxicity information into a single quality-adjusted estimate of survival.

**6631 General Poster Session (Board #94), Mon, 1:15 PM-5:00 PM**

**Abnormal screening mammogram follow-up: Improving time and timeliness benchmarks.** *Presenting Author: Seyed S. Pairawan, Loma Linda University School of Medicine, Loma Linda, CA*

**Background:** Abnormal screening mammograms cause significant patient distress. Current benchmarks for timeliness of care for additional imaging after abnormal screening assess the time interval from screening to initial follow-up imaging. We sought to investigate the overall length of time required for imaging resolution after abnormal screening mammogram. **Methods:** We performed a retrospective review of women undergoing screening mammograms during a two month period at a tertiary-care institution. The main outcome measure was calendar days (d) between dates of screening mammogram and imaging resolution (final additional imaging or percutaneous biopsy). **Results:** From 1,133 sequential screening mammograms, 237 (20.9%) patients required at least one recall study. Median patient age was 55 years (28-92). Of patients requiring call back exams, 68.7% required only one recall; however, 23.6% required two; 6.3% required three; 0.8 % required four; and 0.04% required five. The overall median time for resolution of abnormal screening mammogram was 22 d (range 0-405). The time for resolution was significantly longer for women with a prior history of breast cancer than those without (35.5 d vs. 21 d, p=0.04), and in women with mass lesions compared to those with calcifications or a focal asymmetry (34 d vs. 22 d and 20 d, respectively, p=0.01). Time to resolution for patients requiring one recall was 14 d, two recalls was 42.5 d, three recalls was 49 d, four recalls was 68 d, and five recalls was 203 d (p<0.0001). There was no significant difference in time to resolution of abnormal screening mammogram based on patient age, race/ethnicity, BMI, insurance type, breast density, or individual radiologist. **Conclusions:** While most patients with abnormal mammograms had a single call back and resolution of imaging findings within two weeks of screening, a significant proportion of women required more prolonged imaging follow up. Patients with a history of breast cancer and those who present with mass lesions should be targeted for quality improvement. Benchmarks evaluating the overall time required for resolution of imaging findings may better represent the patient experience.

**6632 General Poster Session (Board #95), Mon, 1:15 PM-5:00 PM**

**Defining quality and value in a prospective study of an emergency department (ED) febrile neutropenia pathway (FNP).** *Presenting Author: Michael Kenneth Keng, Leukemia Program, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH*

**Background:** Febrile neutropenia (FN) is an oncologic emergency and delays in antibiotic (ABX) administration lead to worse outcomes. We instituted a FNP in the Cleveland Clinic (CC) ED to reduce ABX delays. **Methods:** This is a prospective study comparing ED FNP patients (pts) (06/12-06/13) to historical (H) pts (02/10-05/12) and direct admit (DA) FN pts (06/12-06/13). Interventions included: providing pts with FN ID cards, recognizing FN as a distinct chief complaint, revising ED triage level for FN, creating ED-specific electronic FN order sets, administering ABX prior to return of neutrophil count, and relocating all FN ABX to ED automated drug dispensing machines. The primary goal of the FNP was empiric broad-spectrum ABX administration within 90 minutes of ED presentation. Group comparisons were made using the chi-square and Kruskal-Wallis tests, as appropriate. **Results:** In total, 276 consecutive FN episodes in 217 FNP pts occurred during the 12 month study period, 107 episodes in 87 pts and 114 episodes in 101 pts in the H and DA cohort respectively. All ED FN pts were triaged and treated using the ED FNP, but use of the specific FN order set was variable: episodes were classified as treated per order set (n=103) or not (n=173). In addition to hospital stay, the ED FNP improved all identifiable metrics (all p <.0005), depicted in Table 1. Other factors increasing hospital stay were primary hematologic malignancy and degree of neutropenia (p <.05). **Conclusions:** The CC ED FNP is a significant quality initiative, and was able to demonstrate value by decreasing time to ABX administration and length of hospital stay compared to both H and DA controls in cancer pts presenting to the ED with fever. ICU admission rate and ICU length of stay were also decreased. Usage of the ED FNP FN order set further improved these metrics.

| | ED FNP | | | H | DA | p value |
|---|---|---|---|---|---|---|
| Episodes (n) | Total, 276 | Order set, 103 | No order set, 173 | 107 | 114 | |
| Time to (median minutes) | | | | | | |
| Physician evaluation | 43 | 43 | 43 | 73 | 57 | <.0001 |
| ABX order | 35 | 35 | 48 | 141 | 72 | <.0001 |
| ABX administration | 81 | 68 | 96 | 235 | 168 | <.0001 |
| Admission | 263 | 252 | 276 | 360 | | <.0001 |
| Length of stay (median days) | | | | | | |
| Hospital stay | 3.3 | 3.1 | 3.4 | 4.3 | 5.6 | .0005 |
| ICU admission rate (n(%)) | 18(6%) | 4(4%) | 14(8%) | 8(8%) | 5(4%) | .39 |
| ICU stay | 1.9 | 3.1 | 1.8 | 2.2 | 4.4 | .19 |

**6633 General Poster Session (Board #96), Mon, 1:15 PM-5:00 PM**

**Risk of hematologic malignancies following radiation treatment for well-differentiated thyroid cancer in the United States over 37 years.** *Presenting Author: Surbhi Sidana, Department of Internal Medicine, Cleveland Clinic Foundation, Cleveland, OH*

**Background:** Radiation therapy (XRT) including radioisotopes (RI), radioactive implants (RAI) and external beam radiation (EBRT) are commonly used for treatment of well differentiated thyroid malignancies (WDTMs) – papillary and follicular. We investigated the risk of all secondary hematologic malignancies (SHMs) in a population-based cohort of patients (pts) with WDTMs treated with XRT. **Methods:** Surveillance, Epidemiology, and End Results (SEER) 17 registries were queried to identify a cohort of 52,121 adult pts with WDTM as the first primary cancer between 1/1973 and 12/2010 who had adequate follow up. To determine the risk of development of SHM at least one year after the diagnosis of WDTM, pts who received XRT were compared to those who did not. SHMs included leukemias, lymphomas and Multiple Myeloma (MM). Fine and Gray competing risk regression analysis was performed with SHM as a time-dependent endpoint and death from any cause, development of non-hematologic malignancy as the competing events. Hazard ratios (HR) with 95% confidence intervals (CIs) are reported. **Results:** The median age at WDTM diagnosis was 45 (range 18 - 100) years (yrs); most pts were Caucasian (82.4%); female (77%). 45% of patients were treated with XRT; of them 85% received RI or RAI, 4.9% received EBRT, 16.9% both and in 9.3% details were not specified. In total, 371 pts developed SHM after a median interval of 7.6 yrs (range 1- 37.2) from WDTM diagnosis: 178 pts developed lymphoma [Non-Hodgkin's Lymphoma (n=163); Hodgkin's Disease (n=15)]; 124 pts developed leukemia [Acute Myeloid Leukemia (n=44); Chronic Lymphocytic Leukemia (n=34); Chronic Myeloid Leukemia (n=23)] and 68 developed MM. In multivariate analysis, XRT was associated with an increased risk of developing SHM vs. no XRT (HR=1.27; CI, 1.01 – 1.60, p=0.038). Among the XRT modalities, RAI or RI were associated with 32% increased risk (HR=1.32; CI, 1.02 – 1.71, p=0.037) vs. no XRT. Age (HR=1.39, p<0.0001), male gender (HR=1.39, p=0.004) and papillary histology (HR=1.43, p=0.044) were additional risk factors. **Conclusions:** XRT increases the risk for developing SHM by 27% in pts with WDTM, which is mainly attributable to 32% increased risk with RAI/RI.

**6634 General Poster Session (Board #97), Mon, 1:15 PM-5:00 PM**

**Implementation of a written chemotherapy consent form with explicit goals of treatment in a university center.** *Presenting Author: Brendan F. Curley, Mary Babb Randolph Cancer Center at West Virginia University, Morgantown, WV*

**Background:** The American Society of Clinical Oncology (ASCO) has stated that consent to treatment with chemotherapy is an important part of the delivery of quality cancer care. Best practices dictate that consent conversations should be well documented in the patient record. Discussion of goals of treatment can be difficult for physicians and patients, however research has shown that patients often mistakenly believe that therapy with palliative intent is in fact curative. The implementation of a written consent form with goals of care in an academic practice has not been studied. **Methods:** As part of the inaugural ASCO Quality Training Program, a quality improvement project that focuses on the implementation of a written chemotherapy consent with incorporated goals of treatment was designed and implemented. Chemotherapy consent documentation and goals of therapy were retrospectively collected on all patients receiving a new line of chemotherapy. The written chemotherapy consent form was implemented on July 1, 2013; patient data was collected for the duration of 2013, and divided into pre and post intervention data. Patients on clinical trials were excluded from analysis, as written consent is required on protocol. **Results:** Data was collected from 546 patients, with 224 in the pre-intervention group and 322 in the post-intervention group. Documentation of chemotherapy consent decreased from 63% to 52% (p =0.011) when written consent was required. However, documentation of goals of care improved dramatically with 95% of patients having explicit goals of care documented with written chemotherapy consent, compared to 48% of those that consented orally (p<0.0001). **Conclusions:** Implementation of written consent that is reviewed and signed by the patient may initially reduce compliance with the consent process when compared to documenting an oral consent in the patient's chart. However, written consent appears to drastically improve documentation of treatment goals.

**6635 General Poster Session (Board #98), Mon, 1:15 PM-5:00 PM**

**Impact of pretreatment variables on overall survival of patients with stage IV NSCLC: An analysis of the Veterans Affairs Central Cancer Registry.** *Presenting Author: Danielle M. File, Medical College of Wisconsin, Milwaukee, WI*

**Background:** The aim of this study was to utilize a large database of patients treated in the VA to identify prognostic factors that influence survival in patients with stage IV NSCLC. **Methods:** Patients diagnosed with stage IV NSCLC from 2001 to 2008 who received chemotherapy within 4 months of diagnosis were identified using the VA Central Cancer Registry. We augmented the VACCR database with data regarding clinical variables, comorbid conditions and vital signs from several VA databases. The 2009 Area Resource File was used to identify area level surrogates for socioeconomic status. Multivariate analysis was performed using a standard Cox proportional hazard model with a stepwise selection procedure with a p value of 0.25 to enter the model and a p value of 0.10 to remain in the model. **Results:** We identified 20,172 individuals with metastatic NSCLC during the study time period; 4,352 patients met our inclusion criteria. The median overall survival (OS) was 8.1 months with 32% alive at one year and 11% alive at two years, which mirrors what was found in the landmark ECOG 1594 study. In a multivariate analysis prior hospitalizations (HR 1.09, 95% CI 1.05-1.13), a higher percentage of weight loss (HR 1.02, 95% CI 1.02-1.03), chronic kidney disease (HR 1.14, 95% CI 1.03-1.59), baseline anemia (HR 1.21, 95% CI 1.11-1.32), thrombocytopenia (HR 1.49, 95% CI 1.05-2.11) and hypoalbuminemia (HR 1.46, 95% CI 1.34-1.59) were all independently associated with decreased survival. The OS for stage IV NSCLC in patients with pretreatment Hgb $<$12g/dl was 6.5 versus 9.2 months in patients with Hgb $>$12g/dl. A pretreatment albumin of $<$3.5g/dl was associated with a 6 month OS compared to a 10.2 months if albumin was $>$3.5g/dl. The OS of patients with a GFR $<$60ml/hr was 7.7 versus 8.0 months in those with a GFR $>$60ml/hr. Presence of a platelet count of $<$100,000 was associated with a OS of 3.7 months compared to 8.0 months in those with a higher platelet count. **Conclusions:** The outcomes of patients treated with a platinum doublet within the VA system mirror those reported in clinical trials. Several pretreatment factors present at the time of initial treatment can be used to determine prognosis in patients with NSCLC.

**6636 General Poster Session (Board #99), Mon, 1:15 PM-5:00 PM**

**Outcomes of in-hospital cardiopulmonary resuscitation in patients with metastatic cancer.** *Presenting Author: Touqir Zahra, Massachusetts General Hospital, Boston, MA*

**Background:** Patients with metastatic cancer are increasingly availing the use of palliative care services. However, most of them also enroll in clinical trials of novel chemotherapeutic agents. The occurrence of an episode of cardiopulmonary resuscitation (CPR) while these patients are hospitalized may significantly affect their performance status and subsequent treatment. The data with regards to outcome of CPR in patients with metastatic disease is very limited. **Methods:** Using the Healthcare Cost and Utilization Project – California State Inpatient database 2005-2011, patients undergoing in hospital CPR were identified using appropriate ICD-9-CM. Chi square test and Wilcoxon rank test were used to compare discrete and continuous variables respectively. Significance was defined as p value set at $<$0.05. Bonferroni's correction was applied for multiple comparisons. **Results:** There were 110,581 patients who underwent CPR from 2005 to 2011. Of these 5828 (5.3%) had metastatic cancer. After adjusting for age, the odds of mortality were 3.64 times higher (95% confidence interval 1.99-6.67) when compared to those without any cancer. Age was not associated with better outcomes in those with metastatic cancer undergoing CPR. The outcomes of patients who underwent CPR are shown below (see Table). **Conclusions:** The resource utilization in patients who underwent CPR is similar regardless of metastatic disease. The mortality however, is significantly higher in those with metastatic disease. Patients with metastatic cancer may benefit from early palliative care services if they undergo CPR and their functional status significantly deteriorates during hospitalization.

| | No cancer | Solid organ cancer | Metastatic solid organ cancer |
|---|---|---|---|
| **Mortality (%)** | 69.7 | 78.6* | 85.7* |
| **Invasive mechanical ventilation (%)** | 68.6 | 61.9* | 63.3* |
| **Tracheostomy (%)** | 6.0 | 6.0 | 5.4 |
| **Disposition of survivors** | | | |
| **Home** | 34.7 | 31.8* | 29.6* |
| **Home healthcare** | 12.5 | 17.0* | 20.5* |
| **Nursing home** | 50.7 | 49.3 | 46.4* |
| **Others** | 2.1 | 1.9 | 3.5 |
| **Median LOS in survivors, days(IQR)** | 11(5-23) | 13(7-22)* | 14(7-25)* |
| **Median time to death** | 4(1-10) | 5(1-11)* | 6(2-13)* |
| **Median hospital charges, USD** | 97,283 | 89,916* | 95,633 |

* p$<$0.025 when compared with patients with no cancer.

**6637 General Poster Session (Board #100), Mon, 1:15 PM-5:00 PM**

**Enhancing pathway adherence in a quality initiative for breast cancer.** *Presenting Author: Johnathan M. Lancaster, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

**Background:** Clinical pathways are associated with improved outcomes and reduced health care costs. However, physician adherence to clinical pathways remains a challenge for cancer centers across the country. Moffitt Cancer Center (MCC) has developed and implemented clinical pathways across disease-focused programs. We performed a series of measurements of adherence to evidence-based clinical pathways, which included subsequent educational feedback on performance. **Methods:** Using Clinical Performance and Value (CPV®) vignettes, a validated *in silico*simulation measurement tool, we evaluated breast cancer clinical pathway adherence every 4 months. 18 providers completed two BC cases each at months 1, 5 and 9. For each case completed, an overall CPV score was generated with scores calculated as a percentage of the items that the physician correctly completed against all necessary elements of care for that case. Clinicians then received confidential individualized feedback for each case, with quantitative feedback benchmarked to their peers and qualitative individual feedback with suggestions on how they could improve pathway adherence. **Results:** At baseline, measurement revealed wide variance levels of adherence to pathways across the clinician cohort. With serial measurement and feedback, mean CPV scores increased significantly from 55.4% at round 1 to 68.8% at round 3 (p $<$0.01). Particular categories of pathway compliance also improved after the three rounds. Chemotherapy pathway compliance increased from 40% to 65%; appropriate diagnostic work up from 31 to 93% and surgery pathway compliance from 69% to 86%. **Conclusions:** We found that adherence to clinical pathways can be improved with a serial measurement and feedback tool. Future studies will link these changes to utilization and costs. Consistent feedback at the individual and group level engages and aligns providers around pathways and common practice standards.

**Breast pathway adherence improvement over time, by treatment category.**

| | Round 1 (M1) | Round 2 (M5) | Round 3 (M9) |
|---|---|---|---|
| **Surgery** | 69% | 57% | 86% |
| **Work-up of the axilla** | 31% | 31% | 93% |
| **Radiation therapy** | 83% | 83% | 77% |
| **Chemotherapy** | 40% | 50% | 65% |
| **Hormonal** | 79% | 64% | 100% |

**TPS6638 General Poster Session (Board #101A), Mon, 1:15 PM-5:00 PM**

**Simone-simulation in medical oncology education: Part I—Pilot feasibility study.** *Presenting Author: Shelly Sud, Division of Medical Oncology, The Ottawa Hospital Cancer Centre, Department of Medicine, University of Ottawa, Ottawa, ON, Canada*

**Background:** Advances in medical oncology therapeutics have led to increasingly challenging cancer scenarios (CCS), including an expanding spectrum of treatment side effects and chronic cancer complications. There is no defined curriculum addressing CCS management. Simulation based training with debriefing (SBTD) is an educational method utilizing a virtual medium to mimic clinical scenarios. We hypothesize that SBTD, as an educational tool, is better than traditional didactic teaching of CCS management. This unique study tests the feasibility of high-fidelity SBTD in medical oncology education. We eventually aim to develop a national standardized oncology SBTD curriculum to train oncologists in CCS management **Methods:** With ethics approval, a curriculum highlighting CCS topics was created. Three clinical scenarios were developed and programmed using the high-fidelity SimMan mannequin. Scenarios last 10 minutes, and participants' decisions determine the course of the scenario. Participants are recruited from medical oncology and internal medicine. After receiving the curriculum, participant demographics are collected and they are randomized 1:1 to intervention Arm A or B. Both arms perform three simulation scenarios. After scenario #1, all participants take a quiz testing CCS-relevant knowledge. Then, Arm A receives an expert-facilitated debriefing; Arm B receives a didactic lecture covering CCS management. The next day all participants perform simulation and quiz #2, with simulation and quiz #3 planned for 8 weeks later. Each simulation is videotaped for two independent reviewers to grade performance using the validated Ottawa Crisis Resource Management Global Rating Scale. Beyond feasibility, outcomes include change in performance and quiz scores, and participants' satisfaction with educational method as assessed by questionnaire after simulation #2-3. Differences between the three simulation scores in both arms will be calculated, and assessed using independent t-test. At this time, eleven participants have been enrolled and all participants have completed two simulations. Data will be analyzed after the third simulation.

**TPS6639 General Poster Session (Board #101B), Mon, 1:15 PM-5:00 PM**

**Prospective survey on patient satisfaction and quality-of-life impact concerning the administration of fentanyl pectin nasal spray for breakthrough pain in cancer: Qualipec study.** *Presenting Author: Ignacio Delgado, Hospital Infanta Cristina, Badajoz, Spain*

**Background:** Previous clinical trials have confirmed the efficacy and safety of fentanyl pectin nasal spray (PFNS), as a rapid analgesic agent in cases of Breakthrough pain in cancer (BTPc), characterized by intermittent episodes of intense pain of limited duration. Here we present two QUALIPEC studies aimed to assess patient satisfaction after early administration and dose titration of PFNS for BTPc. The surveys intend to describe patients' quality of life improvement along the four week observational period and the effects of PFNS treatment on their everyday activities. Concurrently, they expect to analyze the clinicians' therapeutic management in real practice. **Methods:** These are two multicenter, open-label, prospective, observational studies conducted in different hospitals in France and Spain. The current numbers of enrolled patients are 253 and 42 patients, for France and Spain, respectively. Major eligibility criteria were patients over 18 that were taking at least 60 mg/day morphine (or equivalent) for chronic background pain in cancer. The BTPc diagnosis was evaluated through patient medical interrogation and/or visual analog scale (VAS). Patients started PFNS treatment during the inclusion visit. The first criterion for prescribing PFNS treatment was the BTPc intensity, associated with the daily number and/or duration of the episodes. Patients initially entered a dose-titration training phase which was primarily done during the first treatment prescription and evaluated during the following medical consultation. The primary objective was the measurement of early treatment satisfaction after PFNS titration. Also additional quality of life criteria were evaluated and the effect on daily activities. Clinical trial information: NCT01693328 (France) and NCT01698645 (Spain).

**7002 Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**Randomized multicenter phase II trial of timed-sequential therapy with flavopiridol (alvocidib), cytarabine, and mitoxantrone (FLAM) versus "7+3" for adults with newly diagnosed acute myeloid leukemia (AML).** *Presenting Author: Joshua F. Zeidner, The Johns Hopkins Hospital and The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

**Background**: Serial studies have demonstrated that induction therapy with flavopiridol (50 mg/m$^2$ days 1-3), a multi-serine-threonine cyclin-dependent kinase inhibitor, followed by cytarabine (667 mg/m$^2$/days 6-8) and mitoxantrone (40 mg/m$^2$ day 9) yields complete remission (CR) rates of nearly 70% in pts with newly diagnosed, poor-risk AML. This trial compares "FLAM" with 7+3 in newly diagnosed AML pts. **Methods**: Between May 2011-July 2013, 165 (FLAM, n=109; 7+3, n=56) newly diagnosed AML pts (18-70 years) with non-favorable cytogenetics were randomized 2:1 to receive FLAM or 7+3 (cytarabine 100 mg/m$^2$/day, daunorubicin 90 mg/m$^2$) across 10 institutions. Randomization was stratified by age, secondary AML and leukocyte count. Pts with residual leukemia on day 14 received 5+2 on the 7+3 arm, whereas pts treated with FLAM were not retreated on day 14. The primary endpoint was to compare CR rates between 1 cycle of FLAM and 1 cycle of 7+3. Secondary endpoints were safety, CR rates after 1 cycle of FLAM vs 7+3 + 5+2, overall survival (OS), and disease-free survival (DFS). **Results**: The majority of pts on both arms had at least 1 poor-risk feature, excluding age (FLAM=77%, 7+3=68%). FLAM resulted in higher CR rates compared to 7+3 (70% vs 46%, p=0.003), though this difference was less when compared to 7+3 + 5+2 (70% vs 57%, p=0.08). FLAM also produced higher CR rates in pts with secondary AML (60% vs 35%, p=0.05), pts with >1 poor-risk feature (61% vs 34%, p=0.01), pts without poor-risk features (100% vs 72%, p=0.009), and pts <60 years (79% vs 52%, p=0.02). Relapse rates as of this analysis were similar (FLAM: 36% vs 7+3: 38%). Toxicities were similar between both arms, including grade >3 toxicities, early treatment-related mortality, and time to count recovery. **Conclusions**: FLAM induction results in significantly higher CR rates compared with 7+3 without increased toxicity. FLAM appears to be more active than 7+3 in pts <60 years of age and those with poor-risk features. Although follow-up is too early to assess OS and DFS, these results are promising and a phase 3 comparison of FLAM vs 7+3 is being explored. Clinical trial information: NCT01349972.

**7003 Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**Efficacy of HSV-TK$^+$ suicide gene donor lymphocytes after haploidentical transplantation (haplo-HSCT): Preliminary results of randomized TK008 study.** *Presenting Author: Fabio Ciceri, Hematology and BMT Unit, Department of Onco-Hematology, San Raffaele Hospital, Milan, Italy*

**Background:** Haploidentical family donors represent the ideal solution to offer for every patient with high risk leukemia the potential cure of hematopoietic stem cell transplantation. Extensive application of haplo-HSCT is limited by high rate of late transplant related mortality (TRM) and relapse associated with the inadequate immune reconstitution (IR) due to ex vivo T cell depletion or in vivo post-transplant cyclophosphamide administration for severe graft-vs-host disease (GvHD) prevention. **Methods:** In a haplo-HSCT phase III trial (TK008, NCT00914628), we infuse donor lymphocytes genetically engineered to express the suicide gene herpes simplex thymidine kinase (TK cells) to induce early IR after a T cell depleted graft. Key inclusion criteria are acute leukemia at high risk in patients lacking an HLA-matched donor. Control arms include T cell depleted or post HSCT cyclophosphamide haplo-HSCT. We enrolled 25 patients in 8 centres in Europe and US; 17 were assigned to experimental arm, 15/17 were in complete remission at HSCT. Hypothesis testing: 1-year disease free survival (DFS) 30% (control) vs 52% (TK arm). **Results:** Results are presented only for patients enrolled in the experimental arm at November 2013 last follow-up. TK cells were given to 13 patients; IR was obtained in 9/13 patients after a median of 2 TK cell monthly infusions; median time from last infusion to IR (CD3$^+$>100/$\mu$L) was 28 days (95% CI 24-41). Six pts developed GvHD (2 grade I, 2 grade II and 2 grade III) that was always abrogated by suicide gene induction; no progression from acute to chronic GvHD and no GvHD-related death occurred. IR obtained with TK cell infusion correlated with rapid development of a wide T cell repertoire and detection of high frequencies of T-cells specific for opportunistic pathogens. At a median follow-up of 473 days, by ITT analysis, 1-year overall survival is 89% (+ 10), DFS and immunosuppression-free survival is 80% (+ 10), 1-year TRM is 11% and relapse incidence is 8%. **Conclusions:** Preliminary results of this ongoing phase III trial confirm safety and potential benefit in improving survival of the T-cell gene transfer technology integrated with T cell depleted haplo-HSCT. Clinical trial information: NCT00914628.

**7004 Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**Haplo+cord transplantation: Neutrophil and platelet recovery and long-term survival compared to double umbilical cord blood (UCB) transplantation—A case-cohort analysis.** *Presenting Author: Koen Van Besien, Weill Cornell Medical College, New York, NY*

**Background:** Double UCB (dUCB) SCT can result in long-term survival and low rates of chronic GVHD. Limitations are delayed engraftment and early TRM. We previously reported that co-infusion of CD34-selected SCT from a haplo-identical relative, with a single UCB graft (haplo+cord ) results in rapid count recovery and durable engraftment from the UCB graft. In the current study we compared the outcomes of haplo+cord to dUCB transplantation. **Methods:** As of October 2013, 99 pts have been treated with haplo+cord at two institutions. Their outcomes were compared with those of 737 adults undergoing dUCB during the same period and reported to CIBMTR. Haplo-cord pts were older, more of minority descent, and had higher risk disease. Haplo+cord cases were matched to 4 dUCB controls based on age, gender, race, disease type, disease stage pre-transplant, KPS and year of transplant. The final control group had 344 pts. Despite matching, a higher percentage of haplo+cord pts had high-risk disease, (44% vs 34%, p=0.06). **Results:** In multivariate analysis, engraftment of neutrophils and platelets was faster after haplo+cord than after dUCB SCT. By day 30, 91% of haplo-cord pts had neutrophil recovery (median 12 d) and 53% had platelet recovery (median 24 d) vs 72% (median 21 d) and 6% (median 45 d) of dUCB respectively (P<0.0001). Haplo+cord survival was superior at all time points (Table). At 4 years, 43% of haplo+cord pts were alive vs 21% of dUCB (p=0.0053). **Conclusions:** Haplo+cord results in much faster engraftment than dUCB transplantation. The trend toward improved survival, that becomes more significant with prolonged follow up, justifies further prospective studies.

| Event | Haplo-cord (n=99) P1 | dUCB (n=344) P2 | P |
|---|---|---|---|
| **ANC recovery** | | | |
| 30 Day | 91 % | 72 % | <0.0001 |
| 60 Day | 96 % | 86 % | 0.0001 |
| 90 Day | 96% | 87 % | 0.0001 |
| 120 Day | 96 % | 87 % | 0.0001 |
| **Platelet recovery** | | | |
| 30 Day | 53% | 6 % | <0.0001 |
| 60 Day | 75 % | 54 % | <0.0001 |
| 90 Day | 79 % | 64 % | 0.0014 |
| 120 Day | 80 % | 66 % | 0.0019 |
| **Overall survival** | | | |
| 1 Year | 52 % | 44 % | 0.2277 |
| 2 Year | 43 % | 38 % | 0.3846 |
| 3 Year | 43 % | 33 % | 0.1219 |
| 4 Year | 43 % | 21 % | 0.0053 |

**7005^ Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**Confirmatory open-label, single-arm, multicenter phase 2 study of the BiTE antibody blinatumomab in patients (pts) with relapsed/refractory B-precursor acute lymphoblastic leukemia (r/r ALL).** *Presenting Author: Max S. Topp, Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Würzburg, Germany*

**Background:** Blinatumomab, an investigational bispecific T-cell engaging (BiTE) antibody that directs cytotoxic T-cells to CD19-expressing target cells, has shown antileukemia activity in an exploratory study in adult r/r B-precursor ALL. We evaluated blinatumomab efficacy and toxicity in a large confirmatory phase 2 study. **Methods:** Pts (≥18 yrs) with Ph-negative r/r ALL (refractory; 1$^{st}$ relapse <12 mo; relapse post HSCT <12 mo; ≥2$^{nd}$salvage) were eligible. Blinatumomab was given by continuous IV infusion (4 wks on/2 wks off) for up to 5 cycles (cycle 1 only: 9 $\mu$g/d days 1-7; then 28 $\mu$g/d). The primary endpoint was complete remission (CR) or CR with partial hematological recovery (CRh*) within the first 2 cycles. **Results:** 189 pts were enrolled and received blinatumomab for a median (range) of 2 (1–5) cycles. Median age was 39 (18–79) yrs. As of Jan 2014 (primary analysis in Feb 2014), 43% of pts achieved CR/CRh*; 80% of responses occurred within cycle 1. CRs/CRh* were seen in all subgroups (Table). Regardless of causality, the most frequent adverse events (AEs) were pyrexia (59%), headache (35%) and febrile neutropenia (29%). The most frequent gr ≥3 AEs were febrile neutropenia (26%), anemia (15%) and neutropenia (15%); 2% had gr ≥3 cytokine release syndrome. The most common gr ≥3 nervous system disorders were headache (4%), encephalopathy (3%) and ataxia (2%). 3 (2%) pts had gr 5 AEs considered treatment-related (sepsis, n=2; candida infection, n=1). **Conclusions:** This large phase 2 study confirmed the antileukemia activity of single-agent blinatumomab in a difficult-to-treat population with r/r ALL. Clinical trial information: NCT01466179.

| Endpoint | All patients N=189 |
|---|---|
| **Primary** | |
| CR/CRh*, n (%)[a] | 82 (43) |
| Prior aHSCT (n=64) | 95% CI, 36%–51% |
| No prior aHSCT: | 30 (47) |
| No prior salvage (n=25) | 10 (40) |
| 1 prior salvage (n=47) | 24 (51) |
| ≥2 prior salvages or primary refractory (n=53) | 18 (34) |
| **Secondary** | |
| CR, n (%)[a] | 64 (34) |
| CRh*, n (%)[a] | 18 (10) |
| Median relapse-free survival, mo (95% CI) | 5.9 (5.0–8.4) |
| Median OS, mo (95% CI) | 6.1 (4.2–7.5) |
| **Exploratory** | Responders n=82 |
| Minimal residual disease (MRD) response, n (%)[a] | 61 (74) |

Abbreviation: aHSCT, allogeneic stem cell transplantation. [a] First two cycles (central review).

**7007 Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**Phase 2 trial of GS-9973, a selective Syk inhibitor, in chronic lymphocytic leukemia (CLL).** *Presenting Author: Jeff Porter Sharman, Willamette Valley Cancer Institute and Research Center/US Oncology Research, Springfield, OR*

**Background:** Spleen tyrosine kinase (Syk) is a mediator of B-cell receptor signaling in normal and transformed B-cells. GS-9973 is an orally bioavailable, selective inhibitor of Syk (Kd 7.6 nM, no other kinase $<$ 100 nM). **Methods:** This Phase 2 trial enrolled 44 subjects with CLL treated with GS-9973 800 mg BID. Tumor imaging occurred at weeks 8, 16, 24 and then every 12. Response was independently evaluated according to Hallek 2008 as modified by Cheson 2012. GS-9973 plasma levels were obtained concurrently with plasma chemo/cytokine levels and phospho flow analysis of circulating leukemic cells. **Results:** 27 subjects are still on treatment (Rx) for a median of 22 weeks. Median age was 73 (range 51 - 89), 66% were male. The median number of prior Rx regimens was 3 (range 1-8). Prior Rxs included anti-CD20 antibodies (95%), alkylating agents (86%; bendamustine 64%) and fludarabine (68%); 9 subjects had 17p deletions/TP53 mutations and 17 had other poor prognosis mutations/deletions. Results: 41 subjects were treated for at least 8 weeks and had $\geq$ 1 efficacy assessment. Per investigator, 40 (91%) subjects experienced reduced tumor bulk; 28 (64%) achieved a decrease of $\geq$ 50%. Results of the independent response assessments are pending and will be presented. GS-9973 was generally well tolerated. Rx emergent adverse events occurring in $\geq$ 10% of subjects are listed in the Table. Reversible Grade 3 or 4 ALT/AST elevations occurred in 2 (4.5%) subjects. 2 subjects died while on study: 1 from progressive disease, 1 from sepsis. The mean absolute lymphocyte count increased from 46,410 to 68,850/uL by day 8 and then declined; in 38 paired samples, mean leukemic cell pSyk MdFI levels decreased from 222 (D1) to 186 (D8). **Conclusions:** GS-9973 given on this dose and schedule was generally well tolerated and demonstrated substantial activity in subjects with CLL, including those with poor prognostic features. Clinical trial information: NCT01799889.

| | Grade | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | All |
| Diarrhea | 18 | 2 | 1 | | 21 (48%) |
| Fatigue | 9 | 9 | 2 | | 20 (45%) |
| Nausea | 11 | 3 | 1 | | 15 (34%) |
| Headache | 11 | 2 | | | 13 (30%) |
| Dizziness | 12 | | 1 | | 13 (30%) |
| Anemia | 1 | 6 | 3 | 1 | 11 (25%) |
| Decreased appetite | 7 | 3 | | | 10 (23%) |
| Pyrexia | 6 | 4 | | | 10 (23%) |
| Constipation | 8 | 1 | | | 9 (20%) |
| Cough | 5 | 3 | | | 8 (18%) |
| Peripheral edema | 5 | 1 | | | 6 (14%) |
| Vomiting | 5 | | 1 | | 6 (14%) |
| Chills | 6 | | | | 6 (14%) |
| Upper respiratory tract infection | 1 | 5 | | | 6 (14%) |
| Neutropenia | | | 3 | 2 | 5 (11%) |

**LBA7008 Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**Randomized comparison of ibrutinib versus ofatumumab in relapsed or refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma: Results from the phase III RESONATE trial.** *Presenting Author: John C. Byrd, The Ohio State University, Columbus, OH*

**The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, May 31, 2014, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2014, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.**

**7009 Poster Highlights Session (Board #1), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**A phase 1b/2 study evaluating activity and tolerability of the BTK inhibitor ibrutinib in combination with ofatumumab in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and related diseases.** *Presenting Author: Samantha Mary Jaglowski, The Ohio State University, Columbus, OH*

**Background:** Ibrutinib (Ib), an oral covalent BTK inhibitor, has significant activity in relapsed/refractory (R/R) CLL. Adding ofatumumab (O), an anti-CD20 antibody, to chemotherapy in CLL can improve response and progression free survival (PFS). Here, Ib was given with O in 3 different administration sequences. **Methods:** Patients (pts) with R/R CLL/SLL, PLL or Richter's transformation (RT) after $\geq$2 prior therapies including a purine analog were treated with 420 mg Ib daily and 300/2000 mg O (8 x weekly/then 4 x monthly) in 28-day cycles until progressive disease (PD). Group (G) 1 had 1 cycle of Ib monotherapy, then O was added. G2 started O on Day (D) 1/Cycle (C) 1 and Ib on D2/C1. G3 had 2 cycles of O monotherapy, then Ib was added on D1/C3. **Results:** 71 pts (27, 20, 24 in G1, 2, 3) were enrolled. Median age was 64 y; 61% had Rai stage III/IV; 65 pts had CLL, 1 SLL, 2 PLL and 3 RT; 75% had lymph nodes $\geq$5 cm; 44% had del(17p); 31% had del(11q). The most frequent AEs were diarrhea (68%), infusion-related reaction (IRR, 45%), peripheral sensory neuropathy (42%) and stomatitis (37%). In all, 61% had $\geq$1 AE $\geq$grade (g) 3; most common g 3-4 AE was neutropenia in 17%. 39% had SAEs including: 1 pt in G2 with $\geq$g 3 IRR; 6 pts with AEs leading to Ib discontinuation; 9 pts died within 30 days of last dose and 2 within f/u period. Overall response rate in CLL/SLL was 100% in G1, 79% in G2, and 71% in G3. 2 additional pts achieved a partial response with lymphocytosis. 4 pts in G3 progressed before starting Ib. At study end, 52/58 responders (90%) remained progression-free with f/u of 16, 12 and 11 months for G1, 2 and 3, respectively. Three RT pts had disease control followed by PD on Day 471, 168, and 137. At 12 months, PFS was 89%, 85%, and 90% in G1, 2 and 3, respectively; 76% continued on Ib in a long-term extension study; 2 pts had a transplant. **Conclusions:** Ib combined with O is well tolerated and highly active (83% ORR) in pts with R/R CLL/SLL in all 3 dosing sequences investigated. Because of these compelling results, randomized trials evaluating anti-CD20 antibodies in combination with Ib with a PFS endpoint are ongoing. Clinical trial information: NCT01217749.

**7010 Poster Highlights Session (Board #2), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Association of disease progression on ibrutinib therapy with the acquisition of resistance mutations: A single-center experience of 267 patients.** *Presenting Author: Jennifer Ann Woyach, The Ohio State University, Columbus, OH*

**Background:** The Bruton's Tyrosine Kinase (BTK) inhibitor ibrutinib (I) is very effective in chronic lymphocytic leukemia (CLL), with progression free survival of 76% at 26 months (mo) for patients (pts) with relapsed disease (Byrd J et al, NEJM 2013). We evaluated pts treated with I to explore features associated with progressive disease (PD) and subsequent outcomes. **Methods:** 267 pts from The Ohio State University Comprehensive Cancer Center participating in 3 previously reported Institutional Review Board approved trials of I were included; 196 pts received single agent I and 71 received I plus ofatumumab. A subset of pts with PD had Ion Torrent deep sequencing (DS) performed on peripheral blood at baseline and relapse. **Results:** With a median follow-up of 16 mo ($<$1 mo-42 mo), 201 pts remain on I, and 66 have discontinued due to PD (24), infection (22), toxicity (8), transplant (4), or other (8). PD includes Richter's transformation (RT; n=16) or progressive CLL(n=8). RT tended to occur early, with 10 pts transforming prior to 12 mo of I. CLL progression tended to occur later, with 1 pt relapsing prior to 12 mo of I. 9 RT pts have died, with 6 deaths occurring within 1 mo without further therapy. Of pts with CLL PD, only 3 of 8 have died at day 25, 142, and 180 after going off study. 3 patients have survived $>$1 year after PD. 6 pts with CLL PD received further therapy $<$2 mo post PD, most in $\leq$ 2 weeks. DS on 4 pts with RT revealed 2 with mutations in BTK and 2 without mutations in BTK or PLC$\gamma$2. DS on 6 pts with CLL PD revealed BTK or PLC$\gamma$2 mutations in all. 1 pt had both BTK C481S and 3 mutations of PLC$\gamma$2, 2 had BTK C481S (1 previously reported; Chang B et al, ASCO 2013), 1 had BTK C481F, and 1 had PLC$\gamma$2 R665W (previously reported). An additional 2 pts who have relapsed outside of these studies both have BTK C481S. **Conclusions:** This single institution experience with I confirms it to be a well tolerated and effective therapy. Patients with PD require therapy quickly due to rapid disease progression. These DS confirm initial reports associating mutations in BTK and PLC$\gamma$2 with PD, and require further study in larger populations.

**7011^ Poster Highlights Session (Board #3), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Efficacy of idelalisib in CLL subpopulations harboring del(17p) and other adverse prognostic factors: Results from a phase 3, randomized, double-blind, placebo-controlled trial.** *Presenting Author: Jeff Porter Sharman, Willamette Valley Cancer Institute and Research Center/US Oncology Research, Springfield, OR*

**Background:** Idelalisib (IDELA) is a potent and selective inhibitor of PI3K$\delta$, which is critical for activation, proliferation and survival of B cells and their homing and retention in lymphoid tissues. An unmet need exists for effective therapies in patients with CLL positive for del(17p) and other adverse prognostic factors. This report describes the efficacy of IDELA in combination with rituximab (R) in such high-risk relapsed patients. **Methods:** Samples for del(17p), del(11q), TP53mut, IGHVmut, ZAP70 and CD38 expression, and $\beta$2-microglobulin were collected prospectively and tested using standard methods. Patients were stratified based on presence of del(17p) and/or TP53mut, and on IGHV mutational status. The endpoints evaluated in the high-risk subpopulations in the preplanned 1st interim analysis include progression-free-survival (PFS) and overall response rate (ORR). The primary study analysis was reported in NEJM 2014. **Results:** IDELA+R retained robust efficacy across all high-risk subpopulations (see Table). Importantly, IDELA+R achieved 76.5% ORR and PFS HR 0.13 in the highest risk patients who were positive for both del(17p) and TP53mut, compared to 80.4% ORR and PFS HR 0.17 in those who had neither present. **Conclusions:** These results confirm the retained robust efficacy of IDELA in high-risk CLL subpopulations and support IDELA as a potentially important novel treatment for patients with CLL positive for del(17p) and other adverse prognostic factors. Clinical trial information: NCT01539512.

| | PFS | | ORR | | | |
|---|---|---|---|---|---|---|
| | IDELA+R | | IDELA+R | | Placebo+R | |
| | HR | 95%CI | n | %ORR | n | %ORR |
| **Overall** | 0.15 | 0.08,0.28 | 88 | 80.7 | 88 | 12.5 |
| **Rai stage III or IV** | 0.12 | 0.05,0.27 | 52 | 75.0 | 60 | 11.7 |
| **Binet Stage C** | 0.13 | 0.06,0.30 | 47 | 74.5 | 51 | 13.7 |
| **Del(17p)** | 0.14 | 0.04,0.47 | 20 | 80.0 | 24 | 0.0 |
| **TP53mut** | 0.11 | 0.04,0.31 | 34 | 79.4 | 30 | 10.0 |
| **Del(17p) and/or TP53mut** | | | | | | |
| **: Both** | 0.13 | 0.04,0.47 | 17 | 76.5 | 15 | 0.0 |
| **: Either one alone** | 0.09 | 0.02,0.42 | 20 | 85.0 | 24 | 12.5 |
| **: Neither** | 0.17 | 0.07,0.43 | 51 | 80.4 | 49 | 16.3 |
| **Del(11q)** | 0.10 | 0.02,0.46 | 28 | 82.1 | 29 | 6.9 |
| **IGHV unmutated** | 0.13 | 0.06,0.27 | 71 | 78.9 | 72 | 12.5 |
| **ZAP70+** | 0.13 | 0.06,0.26 | 77 | 79.2 | 74 | 12.2 |
| **CD38+** | 0.13 | 0.05,0.34 | 43 | 83.7 | 34 | 17.6 |
| **$\beta$2-microglobulin > 4mg/L** | 0.14 | 0.07,0.27 | 75 | 77.3 | 68 | 10.3 |

**7012 Poster Highlights Session (Board #4), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Second interim analysis of a phase 3 study evaluating idelalisib and rituximab for relapsed CLL.** *Presenting Author: Steven E. Coutre, Stanford Cancer Center, Stanford University School of Medicine, Stanford, CA*

**Background:** Idelalisib (IDELA), an oral inhibitor of PI3K$\delta$, is highly active in heavily pretreated patients with CLL as single agent or combined with rituximab (R) as demonstrated in Phase 1 trials. **Methods:** A Phase 3 study evaluated IDELA+R vs placebo (PBO)+R in pts with CLL requiring therapy after progression <24 mos since completion of last therapy and considered unfit to receive cytotoxic therapy. Primary endpoint PFS was assessed by IRC and standard criteria (Hallek 2008/2012, Cheson 2012). After progression, pts could enroll into a blinded extension study to receive IDELA at 150 mg BID (prior PBO+R) or 300 mg BID (prior IDELA+R). The first interim analysis (Furman et al, 2014) led to a decision of early stop for overwhelming efficacy. **Results:** 220 pts (110/group) with median age of 71 yrs (78% ≥65 yrs), median time since diagnosis of 8.5 yrs, and median number of 3 prior therapies (range: 1-12) were randomized. 44% of pts had del17p/*TP53* mutation, 84% had unmutated *IGHV*. Table 1 summarizes efficacy and safety. **Conclusions:** Similar to the first interim analysis, IDELA+R demonstrated significant improvement in PFS, ORR, and LNR compared to control, with acceptable safety. OS of pts on IDELA+R remains superior, including pts that crossed over into the extension study. Clinical trial information: NCT01539512.

| | | Group | | |
|---|---|---|---|---|
| **Efficacy** | | **IDELA+R** | **PBO+R** | **Stats** |
| **PFS, all** | Median | NR | 5.5 mos | HR=0.18<br>95% CI: 0.10-0.32<br>p<0.0001 |
| | At 24 wks | 90% | 50% | - |
| **Overall response rate, all** | | 75% | 15% | OR=17.3<br>p<0.0001 |
| **Lymph node response rate, all** | | 92% | 6% | OR=165.5<br>p<0.0001 |
| **Overall survival (incl. extension study)** | Median | NR | NR | HR=0.28<br>95% CI: 0.11-0.69<br>p=0.003 |
| | At 24 wks | 96% | 86% | - |

| **Safety Category** | **Term** | **Group (any Grade/Grade ≥3, %) IDELA+R** | **PBO+R** |
|---|---|---|---|
| | Any AE | 96/64 | 98/52 |
| | Pyrexia | 35/3 | 17/1 |
| | Fatigue | 26/5 | 28/3 |
| | Nausea | 26/0 | 21/0 |
| **AEs in ≥20% of pts** | Chills | 21/2 | 16/0 |
| **Infusion-related reaction** | | 19/0 | 30/4 |
| **Cough** | | 17/1 | 28/2 |
| **Select AEs** | Diarrhea* | 19/4 | 15/0 |
| | Bleeding** | 14/1 | 19/1 |
| | Pneumonia | 10/8 | 13/9 |
| | Rash | 10/1 | 5/0 |
| | Pneumonitis | 6/4 | 1/1 |
| | Colitis* | 5/3 | 1/0 |
| **Select labs** | ALT elevation | 35/8 | 10/1 |
| | Creatinine increased | 13/0 | 9/1 |
| | Neutropenia | 60/37 | 51/27 |
| | Anemia | 29/7 | 32/17 |
| | Thrombocytopenia | 19/11 | 32/18 |

*3/5 pts w/colitis on IDELA+R also reported diarrhea; **Includes 16 preferred terms.

**7013 Poster Highlights Session (Board #5), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**ABT-199 (GDC-0199) combined with rituximab (R) in patients (pts) with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): Interim results of a phase 1b study.** *Presenting Author: Shuo Ma, Northwestern University Medical School, Chicago, IL*

**Background:** ABT-199 is a selective, orally bioavailable Bcl-2 antagonist that induces rapid apoptosis of CLL cells and > 80% response rate as monotherapy in pts with R/R CLL. R synergizes with ABT-199 in preclinical models of CD20+ve lymphoid cancers. **Methods:** Objectives were to assess safety, pharmacokinetics (PK) and preliminary efficacy of ABT-199 + R and to determine a recommended phase 2 dose. Daily ABT-199 began at 50mg (modified to 20mg), with weekly increases to a final cohort dose (200-600mg). R was then initially dosed at 375 mg/m$^2$ then 500mg/m$^2$ monthly for 6 months (cohort 1-2 had 8 doses) with daily ABT-199 until progressive disease (PD). **Results:** As of Jan 17, 2014, 37 pts were enrolled in 5 cohorts (median age 68, 14/23 F/M) with a median time on study: 4.8 (range 0 - 15.2) months, median number of prior therapies: 2 (range 1 - 5); 9 pts were fludarabine-refractory, 9 R-refractory, and 9 had del(17p). Six pts discontinued: 4 due to PD (3 Richter's transformation, 1 CLL), 1 withdrew consent (WC), 1 due to fatal hyperkalemia in the setting of tumor lysis syndrome (TLS) at 1st dose (50mg). The most common treatment-emergent adverse events (AEs, >25% pts) were neutropenia (43%), nausea (38%), diarrhea (30%). The most common grade 3/4 AEs were neutropenia (43%), thrombocytopenia (16%), and anemia (11%). Two dose limiting toxicities occurred with ABT-199 + R: thrombocytopenia (300mg/375mg/m$^2$) and hemophagocytic syndrome (300mg/500mg/m$^2$). Preliminary PK data suggest a negligible effect of R on ABT-199 exposure. Of 18 pts who have completed combination therapy or discontinued prior to completion, 7 (39%) achieved CR/CRi and 7 (39%) PR, 2PD, 1WC, 1 fatal event. Minimal Residual Disease (MRD) was quantified locally in 6/7 CR pts: 5 pts were MRD negative. Of the 19 yet to complete combination therapy, 4 have confirmed PR, 9 have unconfirmed PR, and 6 are not yet evaluable. **Conclusions:** To date, the addition of R to ABT-199 has identified no new toxicities. The combination is active in R/R CLL with a substantial CR rate. A fatal episode of TLS occurred during the ABT-199 lead-in period; with dosing modifications and increased monitoring no further TLS events occurred. Clinical trial information: NCT01682616.

**7014 Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**Independent evaluation of ibrutinib efficacy 3 years post-initiation of monotherapy in patients with chronic lymphocytic leukemia/small lymphocytic leukemia including deletion 17p disease.** *Presenting Author: Susan Mary O'Brien, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** CLL/SLL is generally very responsive to chemoimmunotherapy. However, relapses occur and resistance develops. In particular, del(17p) is associated with poor outcomes using all currently available treatments. Effective targeted therapies are needed. Ibrutinib, a first-in-class covalent inhibitor of Bruton tyrosine kinase, showed single-agent activity and mild toxicity in treatment-naïve (TN) (Lancet Oncology 2013) and relapsed/refractory (R/R) CLL (NEJM 2013) in the phase 1b/2 study (PCYC-1102). We present independent assessment of efficacy data 3 years following initiation of therapy to confirm and further characterize the durability of response. **Methods:** Analyses are based upon all patients (pts) treated from first dose on PCYC-1102 until data cut-off on the long-term follow-up study PCYC-1103. Patients received 420 or 840 mg ibrutinib daily. Best overall response rate (ORR) was assessed using iwCLL criteria. **Results:** Of 132 CLL/SLL (31 TN, 101 R/R) pts evaluated, the median age was 68 years (range, 37–84), with 61% aged ≥ 65 years; 36 (27.3%) pts (2 TN, 34 R/R) had del(17p) and 36 (27.3%) had del(11q). R/R pts including 34 with Del(17p) had a median of 4 (range, 1–12) prior therapies. The updated ORR (by independent review) was 78.0% for all-treated pts (83.9% TN-, 76.2% R/R and 55.9% for those R/R with del(17p)). Additionally, 5 R/R pts, 2 with del(17p), had a best response of PR with lymphocytosis. Median DOR was not reached for all-treated pts, and was 25.0 months (range, 4.8–34.3) in pts with del(17p). Median time on study was 29.4 months (range, 0.7–38.1) for all-treated pts, and 27.3 months (range, 0.9–37.5) for R/R pts with del(17p). More pts receiving prior therapy experienced serious or ≥ Grade 3 adverse events that decreased after 1 year on treatment. No new safety signals were observed in long-term follow-up; 64% of pts remain on treatment with ibrutinib. **Conclusions:** Single-agent ibrutinib showed durable responses in pts with TN or R/R CLL/SLL including those with del(17p), as independently confirmed with 3 years of follow-up.

**7015 Poster Highlights Session (Board #7), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**ABT-199 (GDC-0199) in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL): High complete-response rate and durable disease control.** *Presenting Author: John Francis Seymour, Peter MacCallum Cancer Center, Melbourne, Australia*

**Background:** Overexpression of Bcl-2 in relapsed CLL/SLL is associated with dysregulated apoptosis and chemoresistance. ABT-199 is an orally bioavailable, selective Bcl-2 inhibitor that triggers apoptosis of CLL cells in vitro and in vivo, making it a promising agent for the treatment of patients (pts) with CLL/SLL. **Methods:** The primary objectives of this phase I study were to evaluate the safety and pharmacokinetics (PK) and to determine the maximum tolerated dose and a recommended phase 2 dose (RPTD) of ABT-199. A secondary objective was to assess preliminary efficacy. Following early events of tumor lysis syndrome (TLS), a weekly ramp-up period to the final cohort dose (150 – 1200 mg) was implemented. Pts are now being enrolled in the safety expansion (SE) cohort. A ramp-up period with weekly dose increases occurred from 20, 50, 100, 200 mg to the final RPTD of 400 mg. **Results:** As of 12/04/2013, 84 pts (11 in SE) were enrolled with a median time on study of 14.7 (range, 0.5-29.3) months. 23 (27%) pts had del(17p) and 48 (57%) had fludarabine (F)-refractory CLL. Most common AEs were diarrhea (37%), nausea (36%), neutropenia (35%), upper respiratory tract infection (29%), and fatigue (27%). Grade 3/4 AEs (≥3 pts) were neutropenia (32%), anemia (8%), TLS (8% including 1 G5), and febrile neutropenia, thrombocytopenia, hyperglycemia, and hypokalemia (6% each). 28 have discontinued: 18 for progressive disease, 8 for AEs, and 2 for other reasons. The objective response rate (ORR) was 79% (CR/CRi 22%) with a median duration of response (DOR) of 20.5 months [95% CI; 13.8, 20.5] for the 63 pts evaluable for efficacy. At 12 months, 91% of CR and 65% of PR pts remain progression free. The ORR was 78% for del(17p) and 79% for F-refractory CLL. Of the 14 CR/CRi pts, 9 were evaluated in local labs for minimal residual disease (MRD); 5 were negative and 4 of these were F-refractory. **Conclusions:** ABT-199 induces a high rate of response in pts with R/R CLL, including those with del(17p) and F-refractory disease. Responses are durable, especially in the 22% achieving CR/CRi, with several of these high risk pts achieving MRD negativity. Enrollment in the SE cohort is continuing. Clinical trial information: NCT01328626.

**7016 Poster Highlights Session (Board #8), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**BK virus as a predictor of chronic kidney disease in hematopoietic stem cell recipients.** *Presenting Author: Ala Abudayyeh, Section of Nephrology, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Nephropathy from BK virus (BKV) infection is an evolving challenge in hematopoietic stem cell transplantation (HSCT) recipients. In contrast to kidney transplantation, where there are screening protocols for early detection and prevention of symptomatic BKV nephropathy, there is no such guideline in HSCT. We hypothesized that BKV infection is a marker of poor renal outcomes in the HSCT survivor population. **Methods:** We analyzed all engrafted patients undergoing first allogeneic HSCT at MD Anderson Cancer Center between January 2004 and December 2012, with normal kidney function at the time of HSCT. We evaluated the renal outcome and factors impacting poor renal outcome in these patients. BKV positivity was defined as BKV detection in urine by PCR testing. Renal outcome was determined as the time between HSCT to chronic kidney disease (CKD), defined by constant decrease of 25% or more in estimated glomerular filtration rate (eGFR) compare to the baseline at the time of transplant. **Results:** In a total of 2,477 SCT patients, BK viruria was manifested in 25% (n=629) of the patients. Conditioning regimen consisted of a myeloablative in 1,275 (52%), reduce intensity in 697 (28%), and non-myeloablative in 498 patients (20%). The source of stem-cells was peripheral blood in 1,575 (64%), bone marrow in 697 (28%), and cord blood in 205 (8%). In multivariate analysis, with the adjustment of age, gender, acute GVHD, chronic GVHD, preparative conditioning regimen, graft source, and tacrolimus serum level, BKV viruria showed significant association with renal outcome (Hazard Ratio (HR) (95% confidence interval (CI) = 1.706 (1.483, 1.964), P-Value <0 .0001). Additionally, BK viral load showed significant association with CKD (HR (95% CI) = 1.023 (1.017, 1.029) for one-fold increase, P-Value <0 .0001). **Conclusions:** To the best of our knowledge, this is the first study to identify BKV as a strong independent predictor of long-term renal outcome following HSCT. This study shed more light about the differences and similarities of BKV infection in HSCT and kidney transplant survivors and helps to formulate plans for more effective future prevention and treatment.

**7017 Poster Highlights Session (Board #9), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Haploidentical transplantation (HaploSCT) with post-transplant cyclophosphamide (PTCy) and melphalan-based conditioning: A retrospective analysis of the first 100 patients treated at MD Anderson Cancer Center.** *Presenting Author: Piyanuch Kongtim, Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Outcomes of HaploSCT have recently improved with the use of post-transplantation cyclophosphamide (PTCy). Here we report results of the first 100 pts treated at our institution between 9/2009-7/2013. **Methods:** Diseases were: AML/MDS 54 (36 had high-risk cytogenetics), lymphoma/CLL 17 (12 not in remission at transplant), ALL 12 (11 beyond first remission), CML 12 (all progressed to accelerated/blast phase), other 5 pts. The median age was 45 years (range 19-67). The conditioning regimen included melphalan (100-140 mg/m$^2$), fludarabine (160 mg/m$^2$) +/- thiotepa (5-10 mg/kg). GVHD prophylaxis consisted of PTCy 50mg/kg on day +3 and +4, tacrolimus and mycophenolate. All but 4 pts received a bone marrow graft. 23 pts had previous allogeneic (11) or autologous (12) SCT and 42 pts were not in remission at transplant. **Results:** The median follow-up was 18 months (range 2-48). 94 pts had neutrophil engraftment (median 18 days). Three-year PFS of the entire cohort was 43.3% (44.6% for 1$^{st}$ SCT and 32.7% for 2$^{nd}$ SCT). The cumulative incidence (CI) of relapse and treatment-related mortality (TRM) at 3 years were 38.4% and 25.4% for 1$^{st}$ SCT; 61.8% and 10% for 2$^{nd}$ SCT, respectively. CI of aGVHD was 45% (grade 2-4 30%, grade 3-4 10%) and cGVHD was 15% (extensive cGVHD 8%). Transplant outcomes by disease type are summarized in Table1. In multivariate analysis, factors associated with worse outcomes were lack of remission at SCT (HR 1.73, 95%CI 1.02-3.03, p=0.04) and the development of aGVHD grade 3-4 (HR 2.6, 95%CI 1.08-6.26, p=0.033). **Conclusions:** HaploSCT with melphalan-based conditioning and PTCy is well tolerated with low TRM and outcomes comparable with matched transplantation. Prospective studies comparing HaploSCT with matched transplants are needed.

**Transplant outcomes by disease type.**

| Outcomes (%) | Myeloid malignancies in CR (N=40) | Lymphoid malignancies (N=17) | ALL (N=12) |
|---|---|---|---|
| 3-year PFS | 56.5 | 62.3 | 44.4 |
| 1-year TRM | 11.8 | 25.9 | 33.3 |
| 1-year CI of relapse | 30.1 | 24.4 | 33.3 |
| aGVHD grade 2-4 | 25 | 35.3 | 50 |
| aGVHD grade 3-4 | 0 | 11.8 | 41.7 |
| cGVHD | 12.5 | 11.8 | 44.4 |
| cGVHD (extensive) | 10 | 5.9 | 8.3 |

**7018 Poster Highlights Session (Board #10), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Outcomes after second allogeneic hematopoietic stem cell transplantation: A single-center experience.** *Presenting Author: Waseem Touma, Washington University School of Medicine in St. Louis, St. Louis, MO*

**Background**: Relapse and graft failure continue to be major challenges after allogeneic hematopoietic stem cell transplantation (alloHSCT). There is no standard treatment for either condition and a 2$^{nd}$ alloHSCT is often considered. **Methods**: Here we report outcomes of 77 patients who underwent 2$^{nd}$ alloHSCT at Washington University School of Medicine between 1997 and 2012. Univariate survival analyses (Kaplan–Meier log-rank test) were performed to investigate factors affecting disease–free survival (DFS) and overall survival (OS). **Results**: The median age was 44 years (19–70). Acute leukemias (ALL and AML) and myelodysplastic syndromes accounted for 82% of the cases. Indications for 2$^{nd}$ alloHSCT were mostly disease relapse (78%) and graft failure (16%). Median time between the two transplants was 330 days (15–3835). 49% of patients underwent 2$^{nd}$ alloHSCT with active disease and 57% underwent myeloablative conditioning. The grafts were mostly from matched unrelated donors and matched siblings (52% and 38%, respectively). The original donor was used in 38% of the 2$^{nd}$ transplants and 34% of the recipient-donor pairs were gender mismatched. OS at 1 and 5 years were 31% and 14%, respectively [median 162 days (5–5966)]. Factors prolonging OS were: acute graft versus host disease (aGVHD) (p=0.007), chronic GVHD (cGVHD) (p=0.027), disease status not active at the time of transplant (p=0.003) [median survival 316 days vs. 129 days], period between the two transplants more than 2 years (p=0.045), and post transplant STR above 95% (p=0.0004). Choosing the same donor as in the 1$^{st}$ transplant improved the OS if that donor was gender mismatched from the recipient (p=0.021). DFS at 1 and 5 years were 46% and 35%, respectively [median 106 days (5–5966)]. Factors prolonging the DFS were cGVHD (p=0.024) and disease remission at the time of 2$^{nd}$ transplant (p=0.0008). The incidences of aGVHD and cGVHD were 39% and 32%, respectively. **Conclusions**: This single center experience suggests that performing a 2$^{nd}$ alloHSCT on patients with active disease has very poor outcomes. OS is improved when there is long remission following initial alloHSCT. Choosing the same donor can improve OS if the recipient and donor are gender mismatched.

**7019 Poster Highlights Session (Board #11), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Inotuzumab ozogamicin (IO) in combination with low-intensity chemotherapy as front-line therapy for older patients (pts) and as salvage therapy for adult with R/R acute lymphoblastic leukemia (ALL).** *Presenting Author: Elias Jabbour, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Outcome of older pts with ALL and those with R/R disease is poor. Addition of IO to effective low-intensity chemotherapy might improve outcome. IO is a CD22 monoclonal antibody bound to a toxin, calecheamicin, and has shown single-agent activity in R/R ALL. **Methods:** Pts ≥60 years (yrs) with newly-diagnosed ALL and pts ≥18 yrs with R/R disease were eligible. Chemotherapy was low intensity and referred to as mini-hyper-CVD (cyclophosphamide and dexamethasone at 50% dose reduction, no anthracycline, methotrexate at 75% dose reduction, cytarabine at 0.5 g/m$^2$ x 4 doses). Rituximab and IT chemotherapy were given for first 4 courses. IO was given on Day 3 of each of the first 4 courses. The first 6 pts received 1.3 mg/m$^2$ for course 1 and 0.8 mg/m$^2$ for subsequent cycles; pt 7 onwards received 1.8 mg/m$^2$ for course 1 and 1.3 mg/m$^2$ for subsequent cycles. **Results:** 44 pts were treated so far (Table). Grade 3-4 non-hematological toxicity included increased LFTs in 5 (11%): VOD in 1 (2%). 10 pts (23%) were switched early to maintenance due to thrombocytopenia and infectious complications. Of the 20 pts with de novo ALL, 16 (80%) are alive:14 (70%) in CR from 1 to 25 mos, 2 relapsed after 12 and 3 mos; and 4 died, 3 in CR (sepsis in 2, gun shot in 1) and 1 did not achieve CR and died 2 mos later after receiving a salvage regimen. At the last follow-up, 17 of the 24 pts (71%) with R/R ALL are alive:15 (63%) in response from 1 to 10 mos, 2 relapsed after 1 and 2 mos; and 7 died: 4 early death within 3 weeks, and 3 from resistant disease. **Conclusions:** IO + low-intensity mini-hyper-CVD is safe and shows very encouraging results (95% ORR) in the frontline setting in older pts with ALL and as a salvage approach (75% ORR). These results appear to be better than those achieved with a chemotherapy only approach and may become the new standard of care. Clinical trial information: NCT01371630.

| Parameter | Front line (N=20) | Salvage (N=24) | N (%); Median [range] |
|---|---|---|---|
| Follow-up (mos) | 13 [2-26] | 6 [1-11] | |
| Age (yrs) | 69 [60-79] | 35 [17-71] | |
| Salvage 1 | - | 13 (54) | |
| ≥ Salvage 2 | - | 11 (46) | |
| CR | 15 (75) | 11 (46) | |
| CRp | 4 (20) | 6 (25) | |
| Cri | 0 | 1 (4) | |
| Neg MRD | | | |
| at D21 | 12/16 (75) | - | |
| overall | 19/20 (95) | - | |
| Early death | 0 | 4 (17) | |
| ORR | 19 (95) | 18 (75) | |
| PFS % | at 1-yr, 83 | at 6-mos, 87 | |
| OS % | at 1-yr, 84 | at 6-mos, 74 | |

**7020 Poster Highlights Session (Board #12), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Phase I trial of autologous CD19-targeted CAR-modified t cells as consolidation after purine analog-based first-line therapy in patients with previously untreated CLL.** *Presenting Author: Jae Hong Park, Leukemia Service, Memorial Sloan-Kettering Cancer Center, New York, NY*

**Background:** In order to address the previously recognized limitation of autologous T cells modified to express chimeric antigen receptor (CAR) targeting CD19 in patients (pts) with chemotherapy refractory and relapsed CLL (Brentjens RJ et al., Blood 2011), we designed a phase I trial wherein CLL pts with residual disease following the first-line chemotherapy will receive the CD19-targeted CAR$^+$ T cells as a consolidative therapy. **Methods:** Pts with CLL who have achieved either partial (PR) or complete response (CR) with detectable minimal residual disease (MRD) to the first-line therapy consisting of 6 cycles of pentostatin, cyclophosphamide and rituximab (PCR) were enrolled. Autologous T cells were transduced with a retroviral vector encoding the anti-CD19 scFv linked to CD28 co-stimulatory and CD3$\zeta$ signaling domains (19-28z). Pts received cyclophosphamide conditioning therapy followed by 3 escalating doses of CAR$^+$ T cells. Response was assessed at 3 months according to the NCI-WG criteria. **Results:** 7 pts have received the CAR$^+$ T cells in 3 dose cohorts (3x10$^6$ - 3x10$^7$ CAR$^+$ T cells/kg). 6 pts had unmutated IgHV and 2 pts had del11q. All 7 pts achieved PR following the PCR chemotherapy. 4 pts had palpable lymphadenopathy (1 pt with bulky lymph nodes) prior to the T cell infusion. Median follow-up was 11 months (range, 3 – 17 mos). No DLT was observed. Mild and self-limiting cytokine release syndrome (CRS) was observed in 3 pts, and there was a positive correlation between the development of CRS and the CAR$^+$ T cell persistence. 1 pt achieved CR; 2 pts achieved CR in the bone marrow (1 MRD negative CR) but had progressive disease in lymph node only; 3 pts achieved PR; and 1 pt had progressive disease but this pt had rapidly rising ALC at the time of T cell infusion. **Conclusions:** Autologous CD19-targeted CAR$^+$ T cells appear to be safe and have promising anti-tumor efficacy in pts with high-risk CLL undergoing first-line chemoimmunotherapy. Our findings suggest that the CD19-targeted CAR$^+$ T cells are more effective in eradicating disease in the marrow versus lymph nodes, and further studies are being conducted to better understand the mechanism of resistance. Clinical trial information: NCT01416974.

**7021 Poster Highlights Session (Board #13), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Efficacy and safety of imatinib in CML over 10 years.** *Presenting Author: RÃ¼diger Hehlmann, III. Medizinische Universitätsklinik, Medizinische Fakultät Mannheim der Universität Heidelberg, Mannheim, Germany*

**Background:** Tyrosine kinase inhibitors (TKI) have changed the natural course of CML. With the advent of 2nd generation TKI and the now available choice of drugs, safety issues have gained interest. **Methods:** We have used 1,551 patients of the randomized CML-Study IV for a long-term safety and efficacy evaluation of imatinib. Adverse drug reactions (ADR) were reported at each follow-up visit, coded and graded according to the NCI CTC AE list. Molecular analysis for residual BCR-ABL transcripts was adjusted by the international scale. **Results:** 1,501 patients have received imatinib and were evaluable. Median age at diagnosis was 53 years, 88% were EUTOS low risk. At the last evaluation (04/11/2013) 1,003 patients still received imatinib, 164 have died, 275 have been switched to a 2nd generation TKI, 106 have been transplanted (numbers in part overlapping). The longest observation time was 11.5 years, the median observation time 6.5 years. Efficacy: 10-year progression-free and overall survival probabilities were 81% and 84%, respectively. 10-year cumulative response rates reached 89% for MMR, 81% for MR$^4$, 74% for MR$^{4.5}$ and 63% for MR$^5$. Safety: In 1,018 out of 1,375 patients (74%) non-hematologic ADR were reported during imatinib treatment, in 193 grade 3/4 ADR (14%); 8-year probabilities (all grades) were: fluid overload or edema 41 (36–46)%, gastrointestinal 38 (34–43)%, myalgia or arthralgia 25 (21–29)%, rash 20 (17–24)%, musculoskeletal 17 (13–22)%, fatigue 17 (13–20)%, neurological 11 (8–13)%, and flu-like 10 (8–13)%. Probability profiles over time have been generated for each ADR. In 5 patients peripheral arterial occlusive disease grade 2 or 3 was reported, but none could be clearly assigned to imatinib. A definite association between any ADR and death was not found. Most patients had their first ADR during the first three years with decreasing frequency later on. **Conclusions:** Given that no imatinib-related death was recorded and that grade 3/4 ADR could typically be symptomatically improved and tolerated we consider imatinib a safe, comparably well tolerated TKI even after prolonged treatment. After 10 years imatinib continues to be an excellent choice for the treatment of CML in most patients. Clinical trial information: NCT00055874.

**7022^ Poster Highlights Session (Board #14), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**A phase 1b, dose-finding study of ruxolitinib plus panobinostat in patients with myelofibrosis.** *Presenting Author: Florian Heidel, Otto von Guericke University of Magdeburg, Magdeburg, Germany*

**Background:** Myelofibrosis (MF) is a myeloproliferative neoplasm characterized by dysregulation of the Janus kinase (JAK) pathway resulting in bone marrow fibrosis, splenomegaly, and debilitating symptoms. Ruxolitinib (RUX) is a potent JAK1/JAK2 inhibitor that decreased spleen volume, improved symptoms, and prolonged survival in phase 3 studies. Panobinostat (PAN) is a potent pan-deacetylase inhibitor (DACi) that has shown splenomegaly reduction and improvement of marrow fibrosis in phase 1/2 studies. RUX and PAN demonstrated synergistic anti-MF activity in preclinical studies. Here, we present the updated results of a phase 1b study of the combination of RUX and PAN in MF patients (pts). **Methods:** Eligible pts had intermediate-1, -2, or high-risk MF by International Prognostic Scoring System criteria with palpable splenomegaly. Pts received RUX (5-15 mg) twice daily, every day (BID) and PAN (10-25 mg) once daily, 3 times a week (TIW; days 2, 4, and 6), every other week (QOW) in a 28-day cycle. The primary objective was determination of the recommended phase 2 dose (RP2D) and/or maximum tolerated dose (MTD). Dose escalation was guided by a Bayesian logistic regression model with overdose control based on cycle 1 dose-limiting toxicities (DLTs) and other safety results. Additional pts were enrolled and treated at the RP2D in the expansion phase. **Results:** A total of 48 pts were enrolled (38 escalation phase and 10 expansion phase). Preliminary RP2D was identified at RUX 15 mg BID/PAN 25 mg TIW/QOW. Grade 3/4 adverse events (AEs) included anemia (42%), thrombocytopenia (21%), abdominal pain (8%), and diarrhea (8%) in the escalation phase and anemia (20%) and asthenia (10%) in the expansion phase. Preliminary activity in the dose escalation phase was demonstrated by a ≥ 50% decrease in palpable spleen length at any time in 76% of pts and 50% of patients demonstrating a 100% (non-palpable spleen) response. In the expansion phase, all 4 evaluable pts demonstrated a best spleen response of 100% (non-palpable spleen). **Conclusions:** The combination of RUX and PAN has a tolerable safety profile and encouraging efficacy as demonstrated by spleen responses. Additional safety and efficacy data from the expansion phase will be presented. Clinical trial information: NCT01433445.

**7023 Poster Highlights Session (Board #15), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**EPIC: A phase III trial of ponatinib (PON) versus imatinib (IM) in patients (pts) with newly diagnosed CP-CML.** *Presenting Author: Jeffrey Howard Lipton, Princess Margaret Hospital, Toronto, ON, Canada*

**Background:** PON is a potent oral TKI active against native and mutated forms of BCR-ABL, including T315I. The ph 2 PACE study demonstrated that PON is highly active in heavily pretreated Ph+ leukemia pts. **Methods:** EPIC was an international, Ph 3 trial of PON (45 mg QD) vs IM (400 mg QD) in newly diagnosed CP-CML pts, with randomization stratified by Sokal risk score. The primary endpoint was major molecular response (MMR) rate at 1 yr. On 18 Oct 2013,EPIC was terminated due to accumulating vascular events in long-term follow-up of the PACE trial. Data as of 7 Oct 2013 are presented, median follow-up 3 (0.03-12) m. **Results:** At the time of analysis, 306 were randomized. Baseline characteristics were balanced for PON vs IM; median age 55 vs 52 yrs, 17% vs 16% high Sokal risk score, 62% vs 66% received prior hydroxyurea. Data on 267 treated pts were available (133 PON; 134 IM). 77% PON and 84% IM pts were ongoing; 14 PON and 6 IM pts D/C, (D/C due to AE; 9 PON pts [most common: thrombocytopenia and rash] and 1 IM pt). Response rates are in the table (evaluable pts). Most common (≥25%) all grade (G) AEs were PON: rash (36%), abdominal pain (32%), headache (31%), lipase increased (26%), myalgia (26%); IM: nausea (32%), muscle spasms (31%). 11% PON and 2% IM had G 3/4 thrombocytopenia; 3% PON and 8% IM had G 3/4 neutropenia. Serious AEs (SAEs) occurring in ≥3 PON pts were: pancreatitis (5 pts), atrial fibrillation (3), thrombocytopenia (3); no individual SAEs occurred in ≥3 IM pts. 9 (7%) PON and 5 (4%) IM pts experienced vascular occlusive events (SAEs: 6 PON, 1 IM). Updated data will be presented. **Conclusions:** While PON demonstrated early activity in frontline CP-CML, EPIC was terminated as its objectives could not be met with PON dose reductions implemented mid-trial due to safety observations in PACE. Further investigation of PON safety is warranted. PON remains an important treatment option for pretreated CML and Ph+ ALL pts in whom the need and benefit outweigh the risk. Clinical trial information: NCT01650805.

| | At 3 m | | At 6 m | | At 9 m | |
|---|---|---|---|---|---|---|
| | PON | IM | PON | IM | PON | IM |
| MMR | 29% (28/95) | 0% (0/98) | 66% (27/41) | 21% (9/42) | 83% (10/12) | 44% (7/16) |
| MR4.5 | 4% (4/95) | 0% (0/98) | 10% (4/41) | 0% (0/42) | 25% (3/12) | 0% (0/16) |
| ≤10% BCR-ABL transcripts | 94% (89/95) | 68% (67/98) | 100% (41/41) | 83% (35/42) | | |

**7024 Poster Highlights Session (Board #16), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Ten-year follow up of patients with newly diagnosed chronic myeloid leukemia in chronic phase treated with 400 mg or 800 mg of imatinib daily.** *Presenting Author: Koji Sasaki, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** The tyrosine kinase inhibitor imatinib is standard therapy for patients with chronic myeloid leukemia in chronic phase (CML-CP). It has been suggested that higher-dose imatinib (HD-IM) may offer faster and deeper responses. The purpose of this study was to assess long-term follow-up data of patients treated with HD-IM (minimum follow-up 8 years). **Methods:** Patients with newly diagnosed CML-CP received daily imatinib 400 mg (IM400; 70 patients) or 800 mg (IM800; 201 patients) in consecutive clinical trials. Patients were assessed for cytogenetic and molecular response, overall survival (OS), event-free survival (EFS), transformation-free survival (TFS), and failure-free survival (FFS). **Results:** The 271 patients' median follow-up time was 118 months. The median age was 48.3 years (range, 15.1-84.8 years). Sokal risk scores, rates of best response, FFS, TFS, EFS, and OS are given in Table 1. The response rates at 3, 6, and 12 months in IM800 patients were significantly higher than those of the IM400 patients. The overall MMR4.5 and MMR rates of the IM800 patients were significantly higher than those of the IM400 patients. The IM800 patients also had significantly higher 10-y EFS and 10-y TFS, with small, non-significant trends for 10-y OS and 10-y FFS. **Conclusions:** IM800 patients tended to have better response rates than IM400 patients, particularly for MR4.5. This translates into better EFS but not OS.

**Patient characteristics and outcomes.**

| | IM400 [n= 70], % | IM800 [n= 201], % | P value |
|---|---|---|---|
| Sokal risk | | | 0.239 |
| Low | 69 | 63 | |
| Intermediate | 29 | 28 | |
| High | 3 | 9 | |
| Response at 3M | | | |
| CCyR | 30 | 56 | <0.001 |
| MCyR | 71 | 89 | 0.001 |
| Response at 6M | | | |
| CCyR | 39 | 77 | <0.001 |
| MCyR | 79 | 90 | 0.020 |
| Response at 12M | | | |
| CMR | 3 | 11 | 0.033 |
| MR4.5 | 17 | 30 | 0.038 |
| MMR | 36 | 72 | <0.001 |
| CCyR | 60 | 80 | 0.001 |
| Best (cumulative) response | | | |
| CMR | 47 | 57 | 0.166 |
| MR4.5 | 56 | 74 | 0.005 |
| MMR | 74 | 86 | 0.032 |
| CCyR | 84 | 90 | 0.191 |
| 10-y outcome | | | |
| FFS | 50 | 55 | 0.378 |
| TFS | 83 | 91 | 0.051 |
| EFS | 66 | 77 | 0.041 |
| OS | 80 | 84 | 0.590 |

**7025 Poster Highlights Session (Board #17), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Effect of continued imatinib (IM) in pts with detectable BCR-ABL after ≥ 2 years on study on deep molecular responses (MR): 36-month update from ENESTcmr.** *Presenting Author: Nelson Spector, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil*

**Background**: With 24 mo f/u, ENESTcmr demonstrated higher rates of stable, deep MRs with nilotinib (NIL) vs IM in pts on long-term (≥ 2 y) IM with residual disease. Here, we present 36-mo results, including crossover from IM to NIL after 2 y on study. **Methods**: Pts with Philadelphia chromosome–positive CML-CP (N = 207) with complete cytogenetic response but detectable BCR-ABL (by RQ-PCR with a sensitivity of ≥ 4.5 logs) after ≥ 2 y on IM were randomized to NIL 400 mg twice daily (BID; n = 104) or IM 400 or 600 mg once daily (QD; n = 103). Crossover from IM to NIL was allowed for pts with detectable BCR-ABL after 24 mo, treatment failure, or confirmed (≥ 2 consecutive assessments) loss of response at any time. **Results**: Significantly more pts achieved $MR^{4.5}$ by 36 mo with NIL (Table). Median time to $MR^{4.5}$ was 24 mo in the NIL arm and not reached in the IM arm with 36 mo f/u. 46 of 103 (45%) pts randomized to IM crossed over to NIL. When accounting only for responses up to crossover, 47% and 24% of pts on NIL and IM, respectively, achieved $MR^{4.5}$ ($P = .0003$). At 24 mo, 52 pts on NIL and 78 pts on IM had detectable disease; 4/52 who continued NIL, 0/35 who continued IM, and 11/43 who crossed over from IM to NIL achieved undetectable BCR-ABL by 36 mo. The rate of $MR^{4.5}$ appeared higher in pts randomized to NIL (33% by 1 y in pts without $MR^{4.5}$ at baseline [BL]) than in pts who crossed over to NIL (21%) with similar follow-up. Adverse event profile was similar to the 12 mo report. **Conclusions**: By 36 mo, significantly more pts achieved $MR^{4.5}$ by switching to NIL vs remaining on IM and median time to $MR^{4.5}$ was accelerated by more than 1 y in the NIL arm. Pts with detectable disease who crossed over from IM to NIL after 24 mo were able to achieve deep MRs by 36 mo on study, whereas no pts who remained on IM achieved undetectable BCR-ABL. Delaying switching from IM to the more potent BCR-ABL inhibitor NIL does not increase the proportion of pts achieving deep MR. Clinical trial information: CAMN107A2405.

| | NIL 400 mg BID (n = 98) | IM 400 or 600 mg QD (n = 96) | *P* Value |
|---|---|---|---|
| $MR^{4.5}$ in pts without $MR^{4.5}$ at BL (intention to treat analysis) | n (%) | n (%) | |
| By 12 mo | 32 (33) | 13 (14) | 0.0020 |
| By 24 mo | 42 (43) | 20 (21) | 0.0006 |
| By 36 mo | 46 (47) | 32 (33) | 0.0453 |
| By 36 mo, excluding pts who crossed over to NIL | 46 (47) | 23 (24) | 0.0003 |

**7026 Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

**Results of a prospective, randomized, open-label phase 3 study of ruxolitinib (RUX) in polycythemia vera (PV) patients resistant to or intolerant of hydroxyurea (HU): the RESPONSE trial** *Presenting Author: Srdan Verstovsek, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** PV is a myeloproliferative neoplasm characterized by increased erythrocytosis, disease-related symptom burden (eg, pruritus), and risk of vascular events (thrombosis and/or hemorrhage). Maintaining hematocrit (HCT) control is a key therapeutic goal. RESPONSE is the first phase 3 study to evaluate a JAK inhibitor (RUX) in treating PV. **Methods:** Phlebotomy (PBT)-dependent patients (pts) with splenomegaly (> 450 $cm^3$) and HU resistance/intolerance were randomized 1:1 to RUX 10 mg bid or best available therapy (BAT). The primary endpoint was the proportion of pts who achieved both HCT control without PBT from wk 8 to 32 (with ≤ 1 PBT from wk 0 to 8) and a ≥ 35% reduction in spleen volume (SV) from baseline (BL) by MRI at wk 32. Key secondary endpoints included the proportion of pts who maintained the primary response at wk 48 and the proportion of pts who achieved complete hematologic response (CHR) at wk 32. Other endpoints were duration of response, symptom improvement by MPN-SAF diary, and safety. BAT-treated pts could cross over to RUX from wk 32. The primary analysis occurred when all pts reached wk 48 or discontinued. **Results:** 110 and 112 pts were randomized to RUX and BAT, respectively (median exposure: RUX, 81 wk; BAT, 34 wk); 17 (15%) RUX and 108 (96%) BAT pts discontinued randomized treatment (96 crossed over to RUX). The primary endpoint was achieved in 21% of RUX vs 1% of BAT pts ($P < .0001$); 91% of RUX pts maintained their response at wk 48. Overall, 77% of RUX pts met ≥ 1 component of the primary endpoint: 60% of RUX and 20% of BAT pts achieved HCT control without PBT; 38% of RUX and 1% of BAT pts achieved a ≥ 35% SV reduction (median BL SV, 1195 $cm^3$ in RUX and 1322 $cm^3$ in BAT pts). CHR was achieved in 24% and 9% of RUX and BAT pts ($P = .003$); 49% vs 5% had a ≥ 50% improvement in MPN-SAF 14-item total symptom score at wk 32. During the first 32 wk, grade 3/4 anemia or thrombocytopenia occurred in 1.8% and 5.5% of RUX pts, respectively, vs 0% and 3.6% of BAT pts; thromboembolic events occurred in 1 RUX and 6 BAT pts. **Conclusion:** RUX was well tolerated and superior to BAT in controlling HCT without PBT and reducing SV. RUX was also effective in improving PV-associated symptoms. Clinical trial information: NCT01243944.

**7027 Poster Highlights Session (Board #19), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Clinical activity of Crenolanib in patients with D835 mutant FLT3-positive relapsed/refractory acute myeloid leukemia (AML).** *Presenting Author: Robert Collins, The University of Texas Southwestern Medical Center, Dallas, TX*

**Background:** Development of D835 is a common mechanism of resistance to most FLT3 inhibitors. Crenolanib, a type I FLT3 tyrosine kinase inhibitor, has *in vitro* activity against FLT3 ITD and FLT3 D835. Crenolanib trials in relapsed/refractory FLT3 mutant AML (FLT3 ITD, FLT3 D835, FLT3 ITD/D835) are ongoing (NCT01522469, NCT01657682). **Methods:** Clinical data on the first 19 patients (7M, 12F) with a median age of 47 years (21-81) are currently available. 6 patients were refractory and 7 had relapsed within 6 months of induction therapy. 4 had undergone prior allogeneic transplants. 11/19 had progressed after exposure to ≥1 prior FLT3 TKI (8 Sorafenib, 7 AC220, 2 PLX3397, 1 PKC412,). 3 had received 2 or more prior FLT3 TKIs. Initially, crenolanib was given at a fixed dose of 100 mg PO TID but the dose was subsequently individualized to 200 mg/m$^2$/d given in 3 divided doses. **Results:** Crenolanib had a $T_{max}$ of 1.5-2 hours and a $T_{1/2}$ of 8-9 hours. Median day 15 trough levels (from 11 patients) ranged from 136 -785 nM (median 473nM). Commonly observed side effects included nausea and vomiting and transaminase elevations (primarily grade 1, 2). No patient had to go off study due to toxicity. One patient each required crenolanib dose reduction to 80mg TID due to grade 3 nausea or transaminitis, respectively. No QT prolongations on EKG were observed in any patient. 18 patients are currently evaluable for response. 1 patient achieved a rapid molecular and clinical CR with full count recovery. 2 patients achieved a CR with incomplete count recovery (CRi). An additional 4 patients had a partial response. 4 patients were bridged to transplant. **Conclusions:** Crenolanib is a FLT3 TKI that is showing preliminary clinical activity in a heavily pretreated population with both FLT3 D835 and compound FLT3 ITD/D835 mutant AML. Importantly, crenolanib is also the first agent to demonstrate clinical activity in patients refractory to other FLT3 TKIs via the major clinical resistance mechanism. Trials of crenolanib in newly diagnosed as well as first relapsed AML patients, are being initiated. Clinical trial information: NCT 01522469, NCT01657682.

| Patient No. | N=18 |
|---|---|
| CR/CRi | 3 (17%) |
| Partial Response | 4 (22%) |
| Blast Response | 2 (11%) |
| Overall Response | 9 (50%) |
| Patients bridged to transplant | 4 (22%) |

**7028 Poster Highlights Session (Board #20), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**A phase I study of the mitochondrial metabolism inhibitor CPI-613 in combination with high-dose ara-C (HDAC) and mitoxantrone for relapsed or refractory acute myeloid leukemia (AML).** *Presenting Author: Timothy S. Pardee, Comprehensive Cancer Center of Wake Forest University, Winston-Salem, NC*

**Background:** Altered metabolism is an emerging hallmark of cancer and a possible therapeutic target. CPI-613 is a first in class agent that targets mitochondrial metabolism.This trial was designed to determine the maximum tolerated dose, safety, and efficacy of CPI-613 given in combination with HDAC and mitoxantrone in patients with relapsed or refractory AML. **Methods:** CPI-613 was given daily on days 1 through 5 starting at a dose of 500 mg/m$^2$. Beginning on day 3, HDAC at 3,000 mg/m$^2$ (or 1,500 mg/m$^2$ for age ≥60) was given every 12 hours for 5 doses and mitoxantrone at 6 mg/m$^2$ was given daily for 3 doses. The CPI-613 dose was escalated to 2250 mg/m$^2$. If residual disease was present on day 14 re-induction with the same or a three day abbreviated course could be given. Patients who achieved a complete remission (CR) or CR with incomplete count recovery (CRi) could receive additional consolidation cycles. **Results:** A total of 24 patients were enrolled. The median age was 58 (range 21-76). Four patients had refractory disease and six received two or more previous lines of therapy. In patients with relapsed disease the median duration of CR1 was 7.5 months. Cytogenetics were poor risk in 13 patients, intermediate in 8 and good in 3. The response rate was 54% (11CR+2CRi). In patients ≥60 years old the CR/CRi rate was 55% (6/11). In patients with poor risk cytogenetics the CR/CRi rate was 53% (7/13). In a historical cohort of patients treated with HDAC, mitoxantrone and asparaginase, only 25% (4/16) of patients with poor risk cytogenetics achieved a CR/CRi. Five patients (21%) died on or before day 30. Two patients with circulating blasts had blood samples taken before and after CPI-613 infusion. Samples from a patient who cleared her marrow demonstrated robust phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) consistent with depletion of ATP. This phosphorylation was not seen in a patient with persistent disease. **Conclusions:** CPI-613 in combination with HDAC and mitoxantrone is a promising salvage regimen, especially in older patients and those with high risk disease. Induction of AMPK phosphorylation may serve as a predictor of response. Clinical trial information: NCT01768897.

**7029 Poster Highlights Session (Board #21), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Phase I study of Debio1143 (AT406) in combination with daunorubicin (D) and cytarabine (C) in patients with poor-risk acute myeloid leukemia (AML).** *Presenting Author: John F. DiPersio, Washington University School of Medicine in St. Louis, St. Louis, MO*

**Background:** Treatment of AML remains difficult due to the development of treatment resistance. Inhibitors of apoptosis proteins (IAPs) are key negative modulators of apoptosis which represent attractive targets to overcome resistance to chemotherapy. The small molecule Debio 1143 (formerly AT-406) is an orally-active IAP antagonist able to promote apoptosis by restoring caspase activity and modulating the nuclear factor kappa-B signalling in multiple preclinical models, alone and/or in combination with chemotherapy. **Methods:** This multi-center, dose escalation study aimed to evaluate tolerability, pharmacokinetics (PK), pharmacodynamics, and efficacy of Debio 1143 when given along with D and C to poor-risk patients with AML during the induction cycle. Sequential patient cohorts received 100, 200, 300, or 400 mg of oral Debio 1143 on treatment days 1-5. **Results:** Twenty-nine patients were enrolled of whom 23 completed the study. Most common adverse events of any grade deemed related to the treatment were nausea (31% of patients), diarrhoea (14%), and febrile neutropenia (14%). 3 patients had dose-limiting toxicities: a G3/4 reversible ALT/AST elevation at 100mg, a G3 mucositis resulted in electrolyte abnormalities and cardiac arrhythmia at 200 mg, and a neutropenic fever and G4 heart failure at 400 mg. The maximum tolerated dose was not reached. Exposure was highly variable and increase exceeded dose-proportionality but no accumulation over 5 days was observed. $T_{max}$ was reached in about 2h and $T_{1/2}$ was about 6h at day 1. PK of D and C were rather homogeneous among Debio 1143 dose groups. Debio 1143-induced degradation of cIAP-1 was detectable in CD34/CD117+ cells already at the lower dose. A total of 13 (47%) patients achieved complete remission, the majority in the 100 mg dose cohort. Of these, 8 (62%) relapsed still within the study period. Responders more frequently showed plasma increases of tumor necrosis factor alpha and IL-8 after the first dose of Debio 1143. **Conclusions:** Debio 1143 at doses up to 400 mg/day showed good tolerability and can be safely combined with D and C. The efficacy data are inconclusive but warrant further studies in subsets of patients with AML. Clinical trial information: NCT01265199.

**7030 Poster Highlights Session (Board #22), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**First results of a phase 2 study using a 10-day subcutaneous (SC) regimen of the novel hypomethylating agent (HMA) SGI-110 for the treatment of relapsed/refractory acute myeloid leukemia (r/r AML).** *Presenting Author: Elizabeth A. Griffiths, Roswell Park Cancer Institute, Buffalo, NY*

**Background:** SGI-110 is a novel HMA administered as a small volume injection which results in extended decitabine exposure. We previously reported an Overall Complete Remission (OCR=CR+CRi+CRp) rate of 16% in 50 patients with r/r AML using SGI-110 daily x 5 regimen with either 60 or 90 mg/m2/d (Kantarjian et al, 2013). We report here the first results of the daily x 10 Q 28 days regimen using 60 mg/m2/d. **Methods:** Patients with AML who relapsed or progressed following prior treatment were enrolled. There was no limit on the number of prior treatment regimens, total WBC, or blast %. The primary endpoint was OCR using modified IWG 2003 criteria. Secondary efficacy endpoints included duration of response, and Overall Survival. Safety was assessed using the CTCAE Version 4. After 2-4 cycles, investigators were allowed to consolidate with daily x 5 at 60 mg/m2/d regimen until progression. **Results:** The study completed enrolment with 53 patients treated. Patients had a median age of 57 years (range 29-82), 51% were male, 83% had ECOG PS of 0-1, and 17% had ECOG PS 2. Median number of prior regimens was 2 (range 1-7); 13% of patients had prior HMA treatment. The primary efficacy endpoint of OCR was reported in 16 patients (7 CR, 6 CRi, and 3 CRp) or an OCR rate of 30% (95% CI: 18.3%, 44.3%). Seven patients are still on treatment. 30-day and 60-day mortality were 1.9% and 11.3% respectively. Of 162 total number of cycles given at the data cutoff, 149 (92%) were given using the 10-day regimen and 13 (8%) were given using the daily x 5 consolidation. The most common drug-related Grade ≥3 AEs were: anaemia and thrombocytopenia (19% each), neutropenia and febrile neutropenia (5.7% each). **Conclusions:** SGI-110 given as a daily x 10 SC regimen at a dose of 60 mg/m2/d was clinically active in heavily pretreated population of r/r AML with an acceptable safety profile. The results appear to compare favorably with our previously reported complete remission response rate in a similar patient population using the daily x 5 regimen at doses of 60 or 90 mg/m2/d. These results warrant further investigation of this regimen for the treatment of r/r AML. Clinical trial information: NCT01261312.

**7031 Poster Highlights Session (Board #23), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Phase II trial of cladribine and low-dose AraC alternating with decitabine in older patients with AML.** *Presenting Author: Tapan M. Kadia, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Treatment of AML in older patients (pts) is often complicated by poor tolerance to high dose chemotherapy and resistant disease. Lower intensity approaches employing more active combinations are needed. Cladribine works synergistically with araC and has been shown to improve survival when combined with standard-dose araC. **Methods:** We investigated the combination of cladribine and low-dose araC (LDAC) alternating with decitabine in pts aged > 60. Pts with adequate organ function and newly diagnosed AML (except APL) and high risk MDS were eligible. Induction was cladribine 5 mg/m$^2$ IV over 30 min on d 1-5 followed by araC 20mg SQ BID on d 1-10. Consolidation was 2 cycles of cladribine 5 mg/m$^2$ IV over 30 minutes on d 1-3 + araC 20 mg SQ BID on d 1-10 alternating with 2 cycles of decitabine 20 mg/m$^2$on d 1-5, for a max of 18 cycles. **Results:** 59 pts have been enrolled with a median age of 69 yrs (range, 49-85), including 28 pts (47%) ≥ age 70 (Table). 29 pts (49%) had secondary or therapy related AML, 10 pts (17%) had therapy for an antecedent heme disorder, and 4 pts (7%) had a concurrent active 2nd malignancy while on study. Of the 55 pts evaluable for response, there were 32 CR (58%), 3 CRp (5%), and 2 PR (4%) for an overall response rate of 67%. With a median followup of 4+ months, median OS and median CR duration have not been reached. The 1-year OS estimate is 55%. The regimen was very well tolerated, with 0% 4-week mortality. There were no treatment-related grade 3/4 non-heme adverse events (AEs). Most common non-heme AEs were elevated bilirubin, constipation, nausea/vomiting, mucositis, diarrhea and rash. **Conclusions:** The low intensity program of cladribine+LDAC alternating with decitabine is a highly effective, well-tolerated, ambulatory regimen for older pts, including those with unfavorable-risk features. Clinical trial information: NCT01515527.

**Patient characteristics (N=59).**

| Characteristic | N (%) |
|---|---|
| Median age [range] | 69 [49-85] |
| Cytogenetics | |
| Diploid | 19 (32) |
| -5/-7 | 20 (34) |
| Complex without -5/-7 | 6 (10) |
| Misc. other | 10 (17) |
| Insuff | 4 (7) |
| Molecular | |
| NPM1 | 10/54 (19) |
| FLT3-ITD | 6/54 (11) |
| RAS | 13/54 (24) |
| Medians [Range] | |
| BM blast | 30 [8-95] |
| WBC | 2.4 [0.5-51.3] |
| Platelets | 41 [4-447] |
| Peripheral blasts | 5 [0-88] |
| LDH | 597 [301-6498] |
| Creatinine | 0.91 [0.46-1.94] |
| Bilirubin | 0.6 [0.2-1.8] |

**7032 Poster Highlights Session (Board #24), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**A phase 1 dose-escalation study of the oral selective inhibitor of nuclear export (SINE) KPT-330 (selinexor) in patients (pts) with relapsed/refractory acute myeloid leukemia (AML).** *Presenting Author: Karen W. L. Yee, Princess Margaret Cancer Center, Toronto, ON, Canada*

**Background:** KPT-330 (Selinexor) is a slowly reversible XPO1 inhibitor that forces the nuclear retention and activation of >10 tumor suppressor proteins (TSP) including NPM1c, reduces cMYC and BCLx, and induces AML cell death while sparing normal hematopoietic cells. **Methods:** Oral KPT-330 was given at 8-10 doses per 28-day cycle. Elevation in leukocyte XPO1 mRNA following XPO1 inhibition was a pharmacodynamic (PDn) marker for KPT-330 activity. Pharmacokinetic (PK) analyses were performed. Appetite stimulants and anti-emetics were given as part of supportive care. **Results:** 48 pts (24 M / 24 F; median age 68 yrs; ECOG PS 0/1: 11/37; pts were heavily pretreated with median 3 prior regimens (range of 1-7). Pts received KPT-330 across 5 dose levels (16.8 - 55 mg/m$^2$). There have been no DLTs. Cycle 1 grade 3/4 non-DLT adverse events (AEs) in >1 pt included: fatigue (8%), thrombocytopenia (8%), neutropenia (8%), and nausea (4%). The most common Cycle 1 grade 1/2 AEs were diarrhea (35%), anorexia (33%), nausea (29%), and fatigue (25%). Prolonged administration (>4 months) of KPT-330 was feasible and there were no drug-associated deaths. PK and PDn analyses showed dose-dependent increases in $C_{max}$ / $AUC_{0\text{-}inf}$ ($T_{1/2}$ ~6 hrs) and increases in XPO1 mRNA. Higher doses of KPT-330 were associated with greater reductions in blast counts, which were also observed across different AML subtypes. 16 pts did not complete cycle 1 and were therefore not evaluable for response. Responses in 32 evaluable pts were: complete response (CR) with full hematological recovery: 4 pts (12%), marrow CR (CRm): 1 pt (3%), CR without hematological recovery: 1 pt (3%), duration of CR/CRi/CRm 6-13 weeks; Morphological leukemia free state: 1 pt (3%), Partial Response (PR) 2 pts (6%). Twelve (37%) of the remaining pts have experienced stable disease for > 30 days, and 11 (34%) have had progressive disease. **Conclusions:** KPT-330 treatment can be given over months and induce remissions in pts with heavily pretreated AML. A randomized study of KPT-330 vs available agents in chemotherapy-ineligible relapsed AML is being initiated. Clinical trial information: NCT01607892.

**7033 Poster Highlights Session (Board #25), Sat, 1:15 PM-4:15 PM and 4:45 PM-6:00 PM**

**Mobilization and elimination of FLT3-ITD$^+$ acute myelogenous leukemia (AML) stem/progenitor cells by plerixafor, G-CSF, and sorafenib: Phase I trial results in relapsed/refractory AML patients.** *Presenting Author: Michael Andreeff, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** FLT3-ITD mutant AML is associated with poor prognosis. Our group identified sorafenib (S) as potent inhibitor of FLT3-ITD AML. We demonstrated increased preclinical activity of S when combined with the CXCR4 inhibitor plerixafor (P) and G-CSF (G). Here, we report clinical and translational data testing this concept in patients with R/R FLT3-ITD AML, including patients refractory to FLT3-ITD inhibitors. **Methods:** G (10 mg/kg) and P (240 mg/kg) were given s.c. QOD on days 1 through 13, and S (400 to 800 mg) was given on days 1 through 28 (one cycle). Stem cell, adhesion markers, and phospho-proteins were serially assessed by FACS and CyTOF mass cytometry. **Results:** Of 33 patients enrolled, 28 received treatment and 21 were evaluable for toxicity and disease response. Two CRp, four CR and eight PR were achieved, resulting in 62% overall response rate, 28% CR/CRp, and 33% PR. Responses included 3 patients refractory to FLT3inhibitors.Two patients achieved long-lasting molecular remissions. There was no treatment-related mortality. Side effects included hyperleukocytosis, hand foot syndrome, hypertension, diarrhea. Striking mobilization was observed : 30-fold increase in WBC, 40-fold in absolute blasts and increases in circulating LSC : > 100-fold CD34$^+$, CD34$^+$/38$^-$, CD34$^{+/}$38$^-$/123$^+$ (LSC), CXCR4$^+$, VLA-4$^+$, and CD44. Serial FISH analyses demonstrated preferential mobilization of leukemic versus non-leukemic cells and FACS/CyTOF mobilization of primitive LSC, positive for pAKT, pmTOR, pSYK, p4EP1, ERK, and pSTAT5. **Conclusions:** Combination of G-CSF and plerixafor is safe and superior to plerixafor in mobilizing leukemic blasts and LSC in heavily pretreated FLT3-ITD AML patients. Overall response rate was 62%, including 28% CR/CRp. Mobilized LSC displayed increased MAPK/AKT/STAT signaling. This is the first clinical study of G-CSF and plerixafor for the mobilization of leukemic cells, which was aimed at removing these cells from their protective bone marrow microenvironment. The encouraging clinical responses provide proof-of-concept, and can be further improved by more potent FLT3 and CXCR inhibitors.

**7034 General Poster Session (Board #319), Mon, 1:15 PM-5:00 PM**

**The effect of anti-thymocyte globulin on outcomes of reduced intensity conditioning for acute myelogenous leukemia.** *Presenting Author: Patrick Alan Hagen, University of Minnesota, St. Paul, MN*

**Background**: Antithymocyte globulin (ATG) has been administered to patients considered high risk for graft rejection and graft-versus-host disease (GVHD), such as those receiving HLA-mismatched allografts. If the benefits on engraftment and GVHD are offset by increased risk of relapse, delayed T-cell recovery, and increased infections remains controversial. **Methods**: We retrospectively studied the effect of ATG in 144 acute myelogenous leukemia (AML) patients undergoing nonmyeloablative umbilical cord blood transplantation (UCB) or HLA-matched sibling peripheral stem cell transplantation (PBSC). GVHD prophylaxis consisted almost universally of Cyclosporine and Mycophenolate mofetil. ATG was administered to a subgroup of patients who had not received immunosuppressive chemotherapy in the months (UCB = 3 months; PBSC = 6 months) prior to transplantation and considered high risk for graft rejection. **Results**: There were no significant differences between study groups in regards to disease status at treatment, disease risk, cytomegalovirus serostatus, and cytogenetic risk. ATG treated patients had significantly more infections between 46-180 days post-transplantation. The risk of treatment related mortality was 30 vs 20% (p=.45), in particular infection related death at 1 year was 21 vs. 10% (p=.12) for ATG and non-ATG recipients respectively. The cumulative incidences of acute and chronic GVHD were lower, but not statistically significant, in ATG treated patients. The cumulative incidence of relapse at 2 years was also lower (p=.09) in ATG treated patients. Outcomes were not influenced by donor type. **Conclusions**: The lower risk of relapse with ATG likely reflects our indication for ATG, possibly selecting patients with a less aggressive phenotype and longer pre-transplant remission. Regardless, ATG did not adversely influence risk of relapse. The lower, but not statistically significant reduction in the risk of GVHD in the ATG treated patients may reflect the limited number of events in our patients. In summary, we showed that when administering ATG in the non-myeloablative setting according to our institutional criteria in AML patients there was no adverse effect on outcomes.

**7035 General Poster Session (Board #320), Mon, 1:15 PM-5:00 PM**

**Allogeneic stem cell transplantation (SCT) using a CAT-bu conditioning regimen in patients with advanced myelodysplastic/myeloproliferative disorders (MDS-MPDs).** *Presenting Author: Julie Cote, Hôpital Enfant-Jésus, Quebec City, QC, Canada*

**Background:** Many patients with MDS-MPDs are ineligible to allogeneic SCT using a standard myeloablative approach. In this population, we evaluated the efficacy and safety of a novel conditioning regimen called CAT-Bu. **Methods:** The conditioning regimen consisted of CAT (cyclophosphamide IV 300 mg/m2 every 12 hours from day 1 to 3, Cytarabine IV 2000 mg/m2 from day 2 to 6, topotecan 1.25 mg/m2/day by continuous IV perfusion from day 2 to 6) and oral Busulfan adjusted dose from day 14 to 18. Peripheral blood stem cells were infused on day 20. Tacrolimus and mycophenolate were used as graft vs. host disease (GVHD) prophylaxis. All patients received prophylactic trimethoprim/sulfamethoxazole, valacyclovir and posaconazole. Charts from patients who received this regimen between July 2009 and September 2012 were reviewed. **Results:** Sixteen patients received the CAT-Bu regimen. The median age was 60.5 years old. The Hematopoietic Cell Transplant Comorbidity Index was low in 63%. The disorder at diagnosis was MDS in 56% and MPD in 44%. At SCT, active disease was noted in 75% of the population. Nearly half of the patients had transformation to AML (44%). No patient was in complete remission (CR). The majority of donors were fully matched siblings (81%). Median follow up was 729 days for alive patients and 159 days for dead patients. CR was the best response obtained after SCT in 63%. The OS and PFS at 6 months, 1 year and 2 years were respectively: 75%, 56%, 48% and 50%, 44%, 35%. All deaths were related to the hematological neoplasia. Common adverse events were febrile neutropenia (81%), oral mucositis (56%), diarrhea (38%) and hepatic cytolysis (38%). Two grade 4 respiratory distresses were noted. One was probably related to Busulfan's pulmonary toxicity. **Conclusions:** This new sequential approach offers satisfactory efficacy with acceptable toxicity for the studied population, which, for the majority, presented active disease at time of SCT.

| | |
|---|---|
| **Engraftment success** | 15/16 |
| **Median time from SCT to neutrophil recovery (days)** | 18 |
| **Median time from SCT to platelet recovery (days)** | 13 |
| **aGVHD** | 6/16 |
| **aGVHD maximum grade** | 1/6 |
| **1** | 5/6 |
| **2** | |
| **cGVHD** | 10/16 |
| **cGVHD maximum grade** | 6/10 |
| **Limited** | 4/10 |
| **Extensive** | |

**7036 General Poster Session (Board #321), Mon, 1:15 PM-5:00 PM**

**Reduced-intensity cord blood transplantation following a regimen using fludarabine and busulfan in adult patients with advanced hematologic malignancies.** *Presenting Author: Naoko Takei, Department of Hematology, Teikyo University Chiba Medical Center, Chiba, Japan*

**Background:** Cord blood transplantation has grown as an effective alternative therapy for treating patients with advanced or high-risk hematologic malignancies who have no suitable related or unrelated donor. We report the results of reduced-intensity cord blood transplantation (RI-CBT) following a regimen using fludarabine and busulfan in adult patients with advanced hematologic malignancies. **Methods:** 45 patients (median age, 62 years; range, 26-74 years) underwent RI-CBT at Teikyo University Chiba Medical Center and Tsukuba Memorial Hospital between April 2004 and November 2013. Preparative regimens consisted of fludarabine 30 mg/m2 for 6 days and busulfan 0.8 mg/kg x 4 for 2 or 4days. Tacrolimus was used for prophylaxis of graft-vs-host disease (GVHD). The median infused total cell dose was 2.78 x $10^7$/kg (range, 1.94-5.53 x $10^7$/kg). **Results:** 24 patients achieved primary neutrophil engraftment after a median of 22 days(range, 14-47). 12 of 24 patients with engraftment achieved complete donor-type chimerism by day 100. 11 patients developed grade II to IV acute GVHD, and 9 developed chronic GVHD. Transplant-related mortality within 100 days occurred in 11 of 45 patients. 9 patients were alive in remission at median follow up of 27 months (range, 2-117). The estimated 1-year probability of overall survival was 27.2% (95% CI 15.0-41.0). 6 of 45 patients were $\geq$ 70 years old, and all of them died within 100 days. The overall survival probabilities of patients aged 65-69 were found to be similar to younger patients. **Conclusions:** These data suggest that RI-CBT is a feasible option for patients under 70 years of age with advanced hematologic malignancies who lack an HLA-matched donor.

**7037 General Poster Session (Board #322), Mon, 1:15 PM-5:00 PM**

**Inflammation and depression in allogeneic stem cell transplant recipients.** *Presenting Author: Alexandra A. Erdmann, University of Wisconsin, School of Medicine and Public Health, Madison, WI*

**Background:** Depressed mood is a prevalent concern for individuals undergoing allogeneic stem cell transplantation (allo-SCT). Recent research suggests that proinflammatory cytokines can activate central nervous system pathways, eliciting adverse behavioral responses such as depressed mood. We hypothesized that inflammation may contribute to depression in allo-SCT patients. We also examined the extent to which cytokines were associated with neurovegetative (NV) versus cognitive/affective (CA) depression symptoms. **Methods:** Adults with hematologic malignancies undergoing allo-SCT (N = 66) participated in this longitudinal observational study. Participants completed the Inventory of Depression and Anxiety Symptoms pre-transplant and at 1, 3, and 6 months post-transplant. Proinflammatory (IL-6, TNF$\alpha$) and regulatory (IL-10) cytokines were assessed by ELISA in peripheral blood at the same time points. Mixed-effects and subject-level fixed effects regression models were employed to examine relationships between plasma cytokine levels and depression symptoms. **Results:** Participants with elevated IL-6 (z = 3.16, p = .002) and TNF$\alpha$ (z = 2.23, p = .026) reported more severe depressive symptoms compared to those with low/normal levels. Follow-up analyses clarified that these relationships were seen for NV (z = 2.14-3.26, all p values $<$.05) but not for CA symptoms (p values $>$.05). All models adjusted for time since transplant, conditioning regimen, graft-versus-host-disease, and recipient's age. Similarly, within-subjects analyses revealed that among individuals, changes in cytokine levels across the assessments were associated with corresponding changes in depressed mood, with patients reporting greater overall and NV depression symptoms when IL-6 (z = 3.05, p = .003; z = 3.34, p = .001) and TNF$\alpha$ levels were elevated (z = 2.11, p = .037; z = 2.73; p = .007). **Conclusions:** Results provide evidence for a novel biobehavioral pathway by which inflammation from conditioning therapy or transplant-related complications can evoke depressive symptoms among allo-SCT patients, specifically NV symptoms. This potential treatment-related cause of depression could be targeted to improve the quality of life for allo-SCT recipients.

**7038 General Poster Session (Board #323), Mon, 1:15 PM-5:00 PM**

**Effects of acute graft-versus-host-disease on physical and psychological functioning following hematopoietic stem cell transplantation.** *Presenting Author: Mackenzie L Erdmann, University of Wisconsin, School of Medicine and Public Health, Madison, WI*

**Background:** Acute graft-versus-host-disease (aGVHD) is a significant early complication of allogeneic hematopoietic stem cell transplantation (HSCT). Little is known about the effects of aGVHD on quality of life, and no prior studies have examined psychological effects. We compared physical and psychological functioning of HSCT survivors who developed aGVHD to those who did not. **Methods:** Adults with hematologic malignancies were enrolled in this prospective, longitudinal study prior to allogeneic HSCT. Those alive without recurrence at 6 months post-HSCT (N=108) were included in the analyses. Participants completed well-validated self-report measures of physical functioning (fatigue, pain, sleep, physical and functional well-being) and psychological functioning (depression, anxiety, psychological well-being) pre-HSCT and 3 and 6 months post-HSCT. Those diagnosed with mild (grade 1-2) and severe (grade 3-4) aGVHD were compared to those with no aGVHD on all measures after controlling for pre-HSCT measures, age, HSCT regimen, and chronic GVHD. **Results:** 52 participants were diagnosed with mild (n=39) or severe (n=13) aGVHD. By 3 and 6 months post-HSCT, there were no significant differences between those with and without a history of aGVHD on physical functioning measures. There were significant differences in anxiety at 3 and 6 months post-HSCT (F(2, 103)=3.19; p=.049; F(2, 98)=4.99; p=.011). There was also a trend toward a difference in the psychological well-being measure of personal strength at 6 months (F(2, 97)=2.86; p=.070). Follow-up comparisons showed that those with a history of severe aGVHD reported significantly greater anxiety but also a greater sense of personal strength as compared to those with mild or no aGVHD (pvalues$<$.05). **Conclusions:** Findings indicate that HSCT survivors who developed aGVHD, even severe cases, were doing as well as those without aGVHD on all indices of physical functioning and most indices of psychological functioning by 3 and 6 months post-HSCT. However, the experience of severe aGVHD appeared to affect select aspects of psychological functioning, conferring greater anxiety but also an enhanced sense of personal strength.

**7039 General Poster Session (Board #324), Mon, 1:15 PM-5:00 PM**

**Haploidentical stem cell transplantation (Haplo-HSCT) with nonmyeloablative conditioning regimen (NMAC) and postinfusion cyclophosphamide in advanced non-Hodgkin lymphoma (NHL) patients.** *Presenting Author: Sylvain Garciaz, Institut Paoli Calmettes, Marseille, France*

**Background:** In patients lacking HLA identical (HLA-id) donors, haploidentical (Haplo) donors is increasingly considered as a valid alternative stem cell source.The introduction of post-infusion Cyclophosphamide (Cy) as prophylaxis for immunological complications using T-cell replete graft is one of the most usual strategy. However, efficacy is still a matter of debate. Here we reviewed the outcome of 28 consecutives Haplo-HSCT patients with advanced NHL that we compared to an historical control cohort of patients transplanted from HLA-id donors. **Methods:** 28 Haplo-HSCT were performed between 04/06/2010 and 27/09/2013. Diagnoses were aggressive NHL in 22 patients and low-grade NHL in 6. Median age was 48 years (19-67). At transplant, 64% were in complete remission, 29% in partial remission and 7% in stable disease. These 28 patients were fully matched to 61 HLA-id patients. Conditioning regimen varied according to donor source. Haplo-HSCT patients received a NMAC associating of Fludarabine (150mg/m$^2$ total dose over 5 days), pre-infusion Cy (29 mg/kg total dose over two days), Low dose TBI 2 gray and post infusion Cy (100mg/kg total dose over 2 days). The HLA-id cohort reduced intensity conditionning consisted in Fludarabine (150mg/m$^2$ total dose over 5 days), intravenous Busulfan (6.4 mg/kg total dose over 2 days) and antithymocyte globulin (Thymoglobulin; 5 mg/kg total dose over 2 days). **Results:** With a median follow up of 15 months (2-70), the 2-year PFS and OS were 67% and 62% respectively in the Haplo-HSCT group. Incidence of day-100 acute grade 3-4 GVHD was 7%. The 24-months estimated incidence of chronic GVHD (cGVHD) and extensive cGVHD, was 7% and 4%. The 2-year NRM was 18%. The 2-year cumulative incidence of relapse was 20%. There was no statistical difference found when compared to the HLA-id group of patients for all outcomes. **Conclusions:** These results suggest that NMAC HSCT from Haploidentical donors achieves promising anti-tumor effect with an acceptable NRM and a low incidence of GVHD. Haplo-HSCT should represent a valuable alternative for patients with advanced NHL without available HLA-id donors.

**7040 General Poster Session (Board #325), Mon, 1:15 PM-5:00 PM**

**Optimizing donor selection for public cord blood banking in Korea.** *Presenting Author: Junglim Lee, Department of Hematology, Daegu Fatima Hospital, Daegu Fatima Public Cord Blood Bank, Daegu, South Korea*

**Background:** It is well recognized that TNC and CD34 define a superior Cord blood unit (CBU). According to "the Law of Korean CB Banking and Research", only 40% of collected CBUs meet the criteria. To improve a rate of banking, we analyzed the characteristics of CBUs and assessed predictive factors for numbers of TNC and CD34+ in collected CBUs. **Methods:** This study examined 5,065 UCB (2,943 at the Catholic Hematopoietic Stem Cell Bank and 2,122 at the Daegu Fatima Hospital Public Umbilical Cord Bank) collected at two hospitals from Oct 2003 to Jan 2014. The variables were collected from retrospective records at the time of donation. The associations between TNC, CD34+ and variables including maternal age (MA), gestational age (GA), fetal body weight (FBW), time from collection to processing (T) and collecting volume (CV) were analyzed by logistic regression. **Results:** In our study cohort (n=5,064), the median values of TNC, numbers of CD34, MA, GA, FBW, T and CV were $9.02\times10^8$/unit, $2.0\times10^6$/unit, 32.0 years, 277 days, 3,320g, 18 hours and 80.0ml respectively. In univariate analysis, variables that were associated with high TNC (TNC>$9.02\times10^8$/unit) included MA (MA≤32years) [OR 1.32 (95% CI 1.17-1.48 p<0.001)], normal delivery [OR 2.30 (95% CI 1.97-2.66 p<0.001)], GA (GA>277 days) [OR 1.20 (95% CI 1.07-1.34 p=0.002)], female gender [OR 1.27 (95% CI 1.13-1.43 p<0.001)], FBW (FBW>3320) [OR 1.37 (95% CI 1.23-1.53 p<0.001)] and CV (CV>80ml) [OR 2.40 (95% CI 2.15-2.69 p<0.001)]. Variables that were associated with high CD34 (CD34>$2.0\times10^6$/unit) included MA [OR 0.85 (95% CI 0.76-0.95 P=0.005)], normal delivery [OR 1.33 (95% CI 1.15-1.53 p<0.001), GA [OR 1.20 (95% CI 1.07-1.34 P=0.002)], FBW [OR 1.41 (95% CI 1.27-1.58 p<0.001)] and CV [OR 1.42 (95% CI 1.28-1.60 p<0.001)] In multivariate analysis of TNC, CV>80ml [OR 2.84] was the best predictor of followed by normal delivery [OR 2.33], FBW [OR 1.52], female gender [OR 1.36], MA [OR 1.25] and T [OR 1.25]. **Conclusions:** M/D characteristics were associated with normal delivery which is the best predictor for TNC and CD34+ followed by CV for TNC and BW for CD34+ in collected Korean CBUs. These associations could be used to prioritize donations, collections, optimizing and financial modeling in Korean CB banks.

**7041 General Poster Session (Board #326), Mon, 1:15 PM-5:00 PM**

**Myeloablative busulfan with cyclophosphamide (BuCy) versus busulfan with fludarabine (BuFlu) in myeloid neoplasms.** *Presenting Author: Renju V. Raj, University of Iowa, Iowa City, IA*

**Background:** BuCy is considered a standard myeloablative conditioning regimen for allogeneic hematopoietic stem cell transplantation (HSCT). However its use is limited by significant regimen related toxicity. Several reports suggest that the combination of busulfan and fludarabine(BuFlu) in ablative doses may provide effective control of myeloid neoplasms with less toxicity. This study evaluated the effect of replacing BuCy with BuFlu for myeloablative conditioning in myeloid neoplasms. **Methods:** Retrospective analysis of patients (pts) with myeloid neoplasms who underwent allogeneic HSCT after myeloablative conditioning regimen with BuFlu or BuCy between 2006 and 2012 was done. Forty five pts received BuFlu and 38 BuCy. Ten (22.2%) pts in BuFlu and 3 (8%) pts with BuCy had an HLA mismatched transplant. Median age was 58 (range 22-68) in BuFlu group and 53 (range 19-68) in BuCy. Disease risk by CIBMTR classification was advanced in 27 (60%) pts in BuFlu group and 10 (26.3%) in the BuCy. HSCT Comorbidity Index score was high in 24 (53.3%) pts in BuFlu and 17(44.7%) in BuCy. GVHD prophylaxis consisted of tacrolimus and methotrexate in all pts in BuFlu and in 81.6 % pts in BuCy with 7 pts receiving cyclosporine and mycophenolate. Thymoglobulin was administered in unrelated and mismatched donor grafts. Cox proportional hazard models were used to obtain the hazard ratios and 95% confidence intervals. **Results:** All pts engrafted except 1 in the BuCy group. Mortality at day 100 post-transplant was 4.4% in BuFlu and 21% in BuCy (p=0.038). Grade 3 and 4 GVHD was diagnosed in 6.6% in BuFlu and 21% in BuCy group. Risk of relapse or death for pts in the BuCy group was 2.17 times (95% CI 1.08-4.355, p=0.028) higher than for pts in the BuFlu group with a median follow up of 554 days. The trend for overall survival(OS) was better in BuFlu group compared to BuCy (HR 1.97, 95% CI 0.97-3.97, p=0.059). Relapse free survival was also favored in BuFlu pts compared to BuCy (HR 1.550, 95% CI 0.607-3.960, p=0.359) **Conclusions:** In our experience we found that conditioning with BuFlu is better tolerated, has better 100 day mortality, improved time to progression and OS, in spite of the fact that the pts in BuCy group had a higher CIBMTR disease risk score.

**7042 General Poster Session (Board #327), Mon, 1:15 PM-5:00 PM**

**Cyclophosphamide/fludarabine-based nonmyeloablative matched related/unrelated allotransplant for myelodysplasia.** *Presenting Author: Muhammad Rizwan-ul-Haq Khawaja, Indiana University School of Medicine and the IU/Melvin and Bren Simon Cancer Center, Indianapolis, IN*

**Background:** Hematopoietic cell allotransplant (HCT) with reduced intensity conditioning (RIC) offers curative treatment for myelodysplasia (MDS) in patients that are traditionally excluded from myeloablative (MAT) HCT due to age or comorbidities. Concerns regarding disease control with this approach are based on retrospective data pooled from multiple institutions using different RIC regimens. Cyclophosphamide/fludaraine (Cy/Flu) is a minimal intensity RIC regimen which has not been independently compared to MAT. **Methods:** This retrospective study was conducted to compare disease control and survival outcomes of MAT versus Cy/Flu-based nonmyeloablative allotransplant (NMAT), performed at a single institution during 2000-2013. **Results:** Seventy-four patients underwent MAT (n=27) or NMAT (n=47) from a related (n=36) or unrelated (n=38) donor. Patients who received NMAT were older (mean, 57 vs. 44 years; p<0.001), were more likely to have ECOG performance status (PS) greater than zero (17% vs. 0%; p=0.024), to receive mobilized peripheral blood grafts (100% vs. 81%; p=0.005) and cyclosporine-based GVHD prophylaxis (68% vs. 31%; p=0.002) rather than tacrolimus/sirolimus-based prophylaxis. Distribution of related or unrelated donors and IPSS categories were similar in NMAT and MAT groups. Median follow-up was approximately 49 months. Median progression free survival (PFS) was 429 days after NMAT compared to 349 days after MAT (p=0.585); median overall survival (OS) was 488 days and 608 days (p=0.517), respectively. Eighty percent of patients achieved remission following NMAT compared to 71% following MAT (p=0.416). Twenty percent of patients after NMAT experienced progression versus 33% after MAT (p=0.248). After adjusting for age, IPSS categories, PS, donor source, graft source and GVHD prophylaxis, no statistically significant difference in PFS [HR 0.74 (95% CI 0.25-2.17)] or OS [HR 0.73 (95% CI 0.25-2.17)] was found between NMAT and MAT. **Conclusions:** Cy/Flu based NMAT may provide similar disease control and survival in MDS compared to MAT.

**7043 General Poster Session (Board #328), Mon, 1:15 PM-5:00 PM**

**Next-generation sequencing to identify mutations that may predict outcome after allogeneic stem cell transplantation for AML.** *Presenting Author: Marlise Rachael Luskin, Division of Hematology/Oncology, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA*

**Background:** Relapse is the most common reason for failure of allogeneic stem cell transplant (SCT). Identifying patients at increased relapse risk is crucial for improving outcomes. Prognostic somatic mutations have been identified in AML but their prognostic value after SCT is unknown. We hypothesize that next generation sequencing (NGS) can predict SCT outcome in AML. **Methods:** We performed NGS for 33 hematologic malignancy associated genes in 62 adult patients treated with SCT for de novo AML (2003-2013). Relapse free survival (RFS) was compared by Cox regression with adjustment for cytogenetic risk, conditioning intensity, donor type and graft source. **Results:** At least 1 mutation was identified in 56 (90%) patients (median 2, range 0-6) including 35 of 36 (97%) patients with intermediate cytogenetics (median 3, range 0-6). Among patients with intermediate cytogenetics transplanted in CR, poor prognostic mutations were found in 9 of 15 FLT3ITD negative patients (2 DNMT3A; 3 DNMT3A + IDH; 1 DNMT3A + TET2 + IDH2; 1 TET2; 1 TET2 + PHF6; 1 ASXL1); among FLT3ITD positive patients, 4 of 9 were additionally DNMT3A mutant which may confer added risk. Among patients with favorable cytogenetics transplanted in CR2, 2 of 8 patients had kit mutations; there were no mutations in DNMT3A, IDH, ASXL1, TET2, or PHF6. Among patients with unfavorable cytogenetics, 4 of 13 had additional poor prognostic mutations (1 FLT3ITD +TET2, 1 TET2, 2 TP53). In FLT3ITD negative patients with any cytogenetic risk, DNMT3A mutant status significantly worsened RFS (adjusted HR=4.76 [95% CI 1.34-16.9]; p=0.016). **Conclusions:** NGS identifies a high frequency of potentially prognostic mutations in SCT patients. Mutant DNMT3A may negatively impact prognosis in FLT3ITD negative AML post SCT. NGS testing of a larger cohort is warranted and underway. Identifying patients at high risk for relapse by molecular profiling may allow early intervention.

| Gene | Total (VUS) |
|---|---|
| FLT3-ITD | 19 (0) |
| DNMT3A | 17 (1) |
| NPM1 | 19 (0) |
| ATM1 | 10 (7) |
| ASXL1 | 7 (4) |
| TET2 | 8 (2) |
| RUNX1 | 8 (3) |
| IDH1 | 5 (0) |
| IDH2 | 7 (1) |
| KIT | 6 (1) |
| NRAS | 6 (0) |
| WT1 | 4 (0) |
| PHF6 | 1 (0) |
| TP53 | 2 (0) |
| FLT3-TKD | 2 (0) |
| PTPN1 | 5 (0) |

Abbreviations: VUS, variant of uncertain significance.

**7044 General Poster Session (Board #329), Mon, 1:15 PM-5:00 PM**

**Trends in hospitalization outcomes of elderly patients undergoing allogeneic stem cell transplantation for acute myeloid leukemia/myelodysplastic syndrome (AML/MDS).** *Presenting Author: Guru Subramanian Guru Murthy, University of Arkansas for Medical Sciences, Little Rock, AR*

**Background:** Allogeneic stem cell transplant (AlloSCT) is increasingly used for treatment of elderly patients with AML/MDS. This study aims to explore the US national trends in hospital stay, inpatient cost, and outcomes associated with AlloSCT in elderly patients with AML/MDS. **Methods:** Using Nationwide Inpatient Sample database, we identified all hospitalizations for AlloSCT in patients age ≥ 60 years with AML/MDS from 2007 through 2011. ICD 9 codes were used to identify diagnoses and procedure related information. Data on patient demographics, source of stem cell, length of stay (LOS), complications and deaths were obtained. Outcomes were analyzed using Kruskal Wallis test for comparing means and Chi -square test for categorical variables. Multivariate logistic regression method was used to determine factors associated with prolonged hospital stay and death. **Results:** Based on sample weights, an estimated 4242 AlloSCT procedures for AML/MDS in elderly patients were identified nationwide between 2007-2011. Patients had a median age of 64 years (range – 60-78). Inpatient AlloSCT was more common in males (60.1%) and whites (76.7%). There was a significant reduction in the LOS for AlloSCT from 2007 to 2011. Mean LOS in 2007 was 28.70± 0.69 days, and mean LOS in 2011 was 23.69 ± 0.46 days ($p<0.01$). Inpatient cost showed an increase till 2009 followed by a decline (mean cost - USD 257,291 in 2007, USD 344,454 in 2009 and USD 259301 in 2011, $p<0.01$). In-hospital mortality has decreased from 9.4% in 2007 to 5% in 2011 ($p=0.02$). Complications causing prolonged LOS included acute GVHD (4.2%), septicemia (20.0%), acute renal failure (12.9%), parenteral nutrition (12.8%). On multivariate analysis, stem cell source from bone marrow compared to peripheral blood was associated with higher complications, prolonged LOS (OR 1.88, CI 1.55-2.28, $p<0.01$) and higher mortality (OR 2.45, CI 1.87-3.220, $p<0.01$). **Conclusions:** Our study demonstrates an improvement in the hospitalization outcome of elderly AML/MDS patients undergoing AlloSCT in US. Further focus of research in this risk group to reduce complications would improve mortality and cost benefits.

**7045 General Poster Session (Board #330), Mon, 1:15 PM-5:00 PM**

**LINAC-based intensity modulated total marrow irradiation (TMI) in addition to myeloablative fludarabine/IV busulfan conditioning prior to allogeneic stem cell transplant for high-risk hematologic malignancies: A phase I study.** *Presenting Author: Pritesh Rajni Patel, Division of Hematology/Oncology, University of Illinois at Chicago, Chicago, IL*

**Background:** Total body irradiation (TBI) currently has limited use in stem cell transplant due to significant extra-hematologic toxicity. Intensity modulated total marrow irradiation (TMI) represents an innovative technique to selectively irradiate the bone marrow. We combined a fully myeloablative chemotherapy regimen with escalating doses of TMI in a Phase I trial in allogeneic stem cell transplant. (Id: Clinicaltrials.gov NCT00988013). **Methods:** A Phase 1 trial (3+3 design) for adult patients with high risk (HR) hematologic malignancies enrolled 14 patients who were transplanted from related (n=9) or unrelated (n=5) donors and included: HR acute lymphoblastic (ALL) (n=2) or myeloid (AML) (n=9) leukemia, HR multiple myeloma (n=2) and chronic myeloid leukemia (CML) (n=1) resistant to TKI. Median age was 52 years (range 20-65). Patients received fludarabine 160mg/m$^2$, targeted i.v. busulfan (AUC 4800 $\mu$M/min) and IM-TMI (from 3 to 12 Gy). Dose Limiting Toxicity was defined as any grade 3 or 4 toxicity up to day +30 on the Bearman scale. **Results:** Of 14 patients, 3 were enrolled in cohorts 1 (3Gy) and 2 (6Gy), 6 in cohort 3 (9Gy) and 2 in cohort 4 (12Gy). All patients engrafted. Median time for ANC >0.5 and platelets > 20 x 10$^9$/L were 15 and 15.5 days, respectively. No patient experienced grade 3 or 4 toxicity before day +30. Grade 1-2 mucositis was observed in all patients. After a median follow up of 598 days (range 68-1319 days), 7 patients are alive and 6 remain in remission. Cause of death was TRM (after D30) (n=4: pneumonia, liver failure, GVHD and sepsis), all in cohorts 3 and 4 and relapse (n=3). Cohort 4 was terminated after 2 patients experienced significant toxicity and prolonged hospitalization. Lymphocyte reconstitution at 1, 3 and 6 mo was comparable among the groups. **Conclusions:** This is the first study showing that TMI can be safely combined with fully myeloablative chemotherapy. A dose of 9 Gy TMI will be utilized in a Phase II study. Linac based TMI can potentially be replicated in every transplant center and exploited in new autologous or allogeneic stem cell transplantation studies. Clinical trial information: NCT00988013.

**7046 General Poster Session (Board #331), Mon, 1:15 PM-5:00 PM**

**The impact of CD34$^+$ cell dose and comorbidities on engraftment following autologous hematopoietic stem cell transplantation (ASCT).** *Presenting Author: Mark A Fiala, Washington University School of Medicine in St. Louis, St. Louis, MO*

**Background:** The minimum CD34$^+$ cell dose needed to ensure hematopoietic recovery following ASCT is 2x10$^6$cells/kg. Recent studies suggest that 5x10$^6$cells/kg or 8x10$^6$cells/kg is the optimal dose as it results in more rapid and sustained engraftment. To date, little is known about the impact of comorbidities on engraftment. **Methods:** We performed retrospective chart review of 639 consecutive patients with a diagnosis of multiple myeloma (MM), non-Hodgkin's lymphoma (NHL) or Hodgkin's lymphoma (HL) who underwent mobilization and ASCT at the Siteman Cancer Center/Washington University School of Medicine from 2008 to 2011. Independent variables analyzed were: CD34$^+$cell dose, age, gender, diagnosis, coronary artery disease, diabetes mellitus (DM), hyperlipidemia, and hypertension. Kaplan-Meier curves were performed to compare the median time to neutrophil engraftment (TTNE) and the median time to platelet engraftment (TTPE). **Results:** The median age was 58 years (range 18-74); 58% were male; 52% had MM, 39% had NHL, and 9% had HL. The median CD34+ cell dose administered was 4.1x10$^6$cells/kg (range 1.9-42.5). 8 patients received stem cell doses < 2x10$^6$cells/kg and, therefore, were excluded from analysis. Administration of ≥ 5x10$^6$cells/kg was associated with improved TTNE and TTPE (10 and 16 days, respectively, compared to 11 and 18 days; $p< 0.001$) but had no effect on the rates of platelet engraftment failure or 100 day mortality. Cell doses ≥ 8.0 x10$^6$cells/kg had no additional impact on engraftment kinetics or 100 day mortality. TTNE for patients with DM (n=84) was 11 days compared 10 days for patients without ($p = 0.01$). **Conclusions:** Administration of ≥ 5x10$^6$ CD34$^+$cells/kg resulted in only marginal improvement in TTNE and TTPE, and did not improve the platelet engraftment failure or 100 day mortality rates. Therefore, CD34$^+$ cell doses of ≥ 2x10$^6$cells/kg should be considered effective, and additional days of cell collection to achieve a cell dose of ≥ 5x10$^6$cells/kg may not be warranted. DM has been previously reported to increase the length of hospital stay post-ASCT, but its effect on TTNE observed in our cohort is a novel finding.

**7047 General Poster Session (Board #332), Mon, 1:15 PM-5:00 PM**

**Impact of body mass index (BMI) on plerixafor efficacy during hematopoietic progenitor cell (HPC) mobilization.** *Presenting Author: Rebecca M. Gonzalez, WVU Healthcare, Morgantown, WV*

**Background:** Plerixafor in combination with G-CSF is commonly used to mobilize HPC for autologous transplantation. The effect of BMI on plerixafor mobilization efficacy is controversial, with conflicting results from previous studies. **Methods:** One hundred and fourteen patients received G-CSF (10mcg/kg TBW) daily, with plerixafor (0.24mg/kg TBW) added on the evening of day 4 of G-CSF, to mobilize and collect HPCs from 12/2009-12/2013. The first 83 patients before 11/2012 received upfront plerixafor/GCSF mobilization, and the remaining patients received a "just in time" approach, with plerixafor added if peripheral CD34 count was $<10/\mu$L by day 4 of G-CSF. Patients receiving plerixafor were divided into obese (BMI $\geq$30) and non-obese (BMI $<$30) groups, and were compared to evaluate the effect of BMI on plerixafor HPC mobilization outcomes. **Results:** Patient demographics are listed in Table 1. A median of 2 plerixafor doses were given in both the obese (range 1-4) and non-obese (range 1-5) patients. The median peak peripheral CD34+ count was 38/$\mu$L (range 2-389.2) in obese versus 39.5/$\mu$L (range 3-350) in non-obese patients (*P=0.25*). Median CD34+ collection Day 1 was 2.2 (obese) versus 2.3 x $10^6$ cells/kg TBW (non-obese). Total CD34+ cell yield after a median of 2 apheresis sessions was 4.3 x $10^6$ cells/kg TBW in each group (*P=0.51*). Successful collection of $\geq$ 2 and 5 x $10^6$ CD34+ cells/kg TBW occurred in 90% and 40% of obese compared to 87% and 43% of non-obese patients, respectively (*P = 0.77, 0.71*). **Conclusions:** Obesity is not a negative predictive factor for plerixafor HPC mobilization. All collection parameters were similar between both groups.

| | Demographics | | |
|---|---|---|---|
| | Non-Obese (N=54) | Obese (N=60) | P-Value |
| Median age,yrs (range) | 59.5 (22-75) | 61.5 (23-75) | 0.64 |
| Male Gender | 52% | 52% | 0.85 |
| Myeloma | 52% | 53% | 0.85 |
| Lymphoma | 48% | 47% | |
| BM Involvement | 50% | 40% | 0.45 |
| Prior Radiation | 17% | 25% | 0.26 |
| Lines of Prior Therapy, mean/median (range) | 1.8/2 (1-5) | 1.5/2 (1-3) | 0.24 |
| Lenalidomide Therapy | 22% | 20% | 1.0 |
| · # of cycles, mean/median (range) | 4.1/4 (1-6) | 4/4.8 (2-8) | 0.65 |
| KPS, median (range) | 80 (60-100) | 80 (70-90) | 0.27 |
| HCT-CI score, median (range) | 2 (0-7) | 2 (0-9) | 0.88 |
| Pre-Transplant Status | (N=52) | (N=57) | 0.15 |
| · CR | 48% | 61% | |
| · PR | 52% | 37% | |
| · <PR | 0% | 2% | |

**7048 General Poster Session (Board #333), Mon, 1:15 PM-5:00 PM**

**Early rituximab failure (ERF) in relapsed diffuse large b-cell lymphoma (DLBCL) and prediction of futility of autologous hematopoietic cell transplantation (AHCT).** *Presenting Author: Mehdi Hamadani, Medical College of Wisconsin, Milwaukee, WI*

**Background:** The poor prognosis of DLBCL pts relapsing within 1-yr of initial diagnosis after 1$^{st}$line rituximab-based chemotherapies (Gisselbrecht. JCO 2010) has created controversy about the role of AHCT in this setting. **Methods:** Using the CIBMTR database, we compared AHCT outcomes of chemosensitive DLBCL pts who experienced early failure after rituximab-containing 1st line chemotherapies (i.e pts with primary refractory disease or 1$^{st}$ relapse within 1yr of diagnosis; **ERF group**) *against* those who relapsed more than 1yr after diagnosis (Late Rituximab Failure [**LRF**] **cohort**), between 2000-2011.Chemorefractory pts and transformed lymphomas were excluded. Primary outcomes were non relapse mortality (NRM), progression/relapse (P/R), progression-free survival (PFS) and overall survival (OS). **Results:** ERF and LRF cohorts included 201 and 315 pts respectively (Table). On univariate analysis the 3yr NRM, P/R, PFS and OS of ERF vs. LRF cohorts was 12% vs. 7% (p=0.08), 49% vs. 40% (p=0.07), 39% vs. 52% (p=0.005) and 44% vs. 66% (p<0.001), respectively. On multivariate analysis (MVA) ERF was associated with higher NRM (relative risk (RR) 1.73, p=0.04). Within first 9 months post AHCT, ERF had worse R/P (RR 1.85, p<0.001), PFS (RR 2.02, p<0.001) and OS (RR 2.94, p<0.001), but no significant difference for R/P, PFS and OS existed between the two groups, beyond 9 months post AHCT in the MVA. Age $\geq$60yrs was associated with worse NRM (p=0.03), PFS (0.01) and OS (p=0.02) and KPS $<$90 with inferior NRM and OS. **Conclusions:** ERF does not predict futility of AHCT in DLBCL (with 3yr PFS 39% & OS 44%). AHCT remains standard-of-care in chemosensitive DLBCL regardless of the timing of disease relapse.

| | ERF (%) | LRF (%) | P-value |
|---|---|---|---|
| Median age (range) | 60 (19-77) | 60 (20-76) | 0.41 |
| KPS <90 | 73 (36) | 76 (24) | 0.01 |
| Doxorubicin in 1$^{st}$ line | 184 (92) | 297 (95) | 0.18 |
| Stage 3-4 @ diagnosis | 144 (72) | 218 (69) | 0.41 |
| aaIPI | | | |
| Low/low-intermediate | 175 | 272 | 0.007 |
| High/high-intermediate | 16 | 16 | |
| Bulky | 15 (7) | 24 (8) | 0.13 |
| Median lines of chemotherapies | 3 (1-5) | 2 (1-5) | 0.01 |
| +marrow involvement | 35 (17) | 53 (17) | 0.71 |
| Median follow up (mo) | 49 (3-147) | 48 (3-126) | |

**7049 General Poster Session (Board #334), Mon, 1:15 PM-5:00 PM**

**Social connectivity and outcomes for adolescents and young adults (AYAs) with acute lymphoblastic leukemia (ALL).** *Presenting Author: Andrew Fintel, The University of Tennessee/The West Clinic, Memphis, TN*

**Background:** While the outcomes for AYAs with ALL are worse when treated on adult rather than pediatric protocols, one criticism is that this may be due to "emancipation" of young adults. **Methods:** Using case listing session of SEER 18 (1973-2010) we examined outcomes for AYAs with ALL defined similar to CALGB 10403 (age 18-30) predicated on marital and insurance status as surrogates of emancipation (limiting analysis to 2007-2010). Analyses were conducted with SEER*Stat 8.1.2, Microsoft Excel 2007 and GraphPad Prism 6. Comparisons were made using the chi-squared test and log rank test (Mantel-Cox); all p-values were 2-sided. **Results:** While age (24 and younger versus 25 and older) was predictive of median OS (NR v 33; p=0.0029) (3-yr OS 66% v 49%); social factors were not as detailed in the Table; NR = not reached. **Conclusions:** Social connectivity, as defined by insurance status and marriage, did not influence outcomes for AYAs with ALL, arguing that intrinsic differences in disease and disease-specific therapies are more important than social issues.

| | All | Insured | Uninsured | P | Married | Single | p |
|---|---|---|---|---|---|---|---|
| # | 576 | 503 | 73 | | 112 | 464 | |
| Age | 22 | 22 | 23 | | 27 | 21 | |
| Ethnicity (W/B/O%) | 85/6/9 | 85/6/9 | 84/11/5 | | 92/2/6 | 83/7/10 | |
| Gender (M/F%) | 64/36 | 64/36 | 67/33 | | 63/37 | 64/36 | |
| Median year of Dx | 2008 | 2008 | 2008 | | 2008 | 2009 | |
| Subtype (%) | | | | | | | |
| B-cell ALL, NOS | 5 | 4 | 6 | | 7 | 5 | |
| Burkitt cell leukemia | 2 | 2 | 4 | | 2 | 2 | |
| Precursor cell lymphoblastic leukemia | 80 | 80 | 82 | | 81 | 80 | |
| T-cell leukemia/lymphoma | 12 | 13 | 8 | | 10 | 13 | |
| Median OS (m) | NR | NR | 33 | | NR | NR | |
| 3-yr OS % | 57 | 61 | 50 | 0.2334 | 55 | 62 | 0.1084 |

**7050 General Poster Session (Board #335), Mon, 1:15 PM-5:00 PM**

**Cytogenetic and molecular testing in patients with chronic myeloid leukemia (CML) in a prospective observational study (SIMPLICITY).** *Presenting Author: Stuart L. Goldberg, John Theurer Cancer Center, Hackensack, NJ*

**Background:** Few clinical practice data describe response monitoring in patients (pts) with chronic-phase CML (CP-CML) treated with tyrosine kinase inhibitors (TKIs). **Methods:** SIMPLICITY is an ongoing observational study of CP-CML patients receiving first-line imatinib (IM), dasatinib (DAS) or nilotinib (NIL) in the United States (US) and Europe (EU); its primary objective is to understand TKI use and management patterns in clinical practice (NCT01244750). The study includes 3 'prospective' newly-diagnosed cohorts treated with IM, DAS or NIL since 2010 and a 'historical' cohort treated with IM since 2008. Frequency of testing for cytogenetic response (CyR), by FISH or karyotype, and molecular response (MR), by PCR, were analyzed in 6 and 12 month increments from TKI start. **Results:** 949 pts (EU: 34%, US: 66%) were enrolled through 10/03/2013, receiving IM (n=415), DAS (n=275) or NIL (n=259). Mean ($\pm$ SD) follow-up was 19 ($\pm$ 9) months. Demographics were consistent across cohorts (median age: 56 years; 56% male). Of 713 pts with $\geq$12 months' follow-up, 48% were tested for CyR between 0–12 months (excluding diagnostic tests); of these, 40%, 33% and 28% had 1, 2 and $\geq$3 tests, respectively. The proportion of pts tested for CyR in the first 12 months varied by region (EU: 62%; US: 42%). The proportion of pts with $\geq$12 months follow-up that were tested for MR between 0–12 months was 80% across regions (EU: 85%; US: 78%); of these, 28%, 31%, and 41% had 1, 2 and $\geq$3 tests, respectively. Of 1,399 reported MR tests, 72% used the International Scale (IS), 6% did not use the IS and 22% were listed as 'unknown'. The proportion of MR tests that used the IS in EU and US was 86% and 65%, respectively. Of 713 pts, 113 (16%) had neither CyR nor MR testing and 600 (84%) had either a CyR or a MR test in the first 12 months. Comparison of these data with a follow-up independent survey of SIMPLICITY investigators, and monitoring patterns by practice type, will be presented. **Conclusions:** Response monitoring in clinical practice differs from ELN and NCCN recommendations and shows regional variation. More pts are monitored for MR than CyR, with a more pronounced difference between the US and EU in frequency of CyR testing than in MR testing.

**7051 General Poster Session (Board #336), Mon, 1:15 PM-5:00 PM**

**Chronic myelomonocytic leukemia: Next-generation sequencing in 30 treatment-naive cases.** *Presenting Author: Priyanka Priyanka, The University of Texas, School of Public Health, Houston, TX*

**Background:** Chronic myelomonocytic leukemia (CMML) belongs to a subtype of myeloid neoplasms called myelodysplastic / myelproliferative neoplasms. While clonal cytogenetic abnormalities have been identified in CMML, these lack specificity. Recently, next generation sequencing (NGS) data has identified a number of mutations in CMML; however, their significance in pathogenesis and prognosis is not well characterized. **Methods:** We performed NGS in a set of 30 treatment naïve CMML cases presenting at a single institution from 09/2012 to 09/2013 as part of routine clinical work up. Genes analyzed included *CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, JAK3, KIT, KRAS, MPL, NPM1, NRAS, PDGFRA, PTPN11, TP53*. Detection of frequently reported (hotspot) mutations in a total of 53 genes was performed on the DNA extracted from bone marrow aspirate specimens. PCR-based DNA analysis was performed for detection of *FLT3* internal tandem duplications (ITD) and codon 835/836 point mutation; and *CEBPA*. **Results:** Of the 30 cases, median age at diagnosis was 71 years (range 42 - 81); male: female ratio was 1:2. Mean hematologic parameters are as follows: hemoglobin: 10.79 ± 2.4 g/dL, WBC: 21.87 ± 27.3 K/UL; absolute monocyte count 3.70 ± 4.4 K/UL; platelets 134.9 ± 86.05 K/UL. Median LDH (n=23 patients) was 667 IU/L (range 323 - 6075). Eleven (36.67%) patients had one, none (0%) had two, 1 (3.3%) had three, 2 (6.6%) had four mutations detected. No mutation was detected in 16 (53.33%) patients. The most frequently identified mutation was in *NRAS* (n=4; 11.4%) followed by *JAK2* V617F (n=3; 10%). Other mutations observed were in *PTPN11* and *TP53 (n*= 2 each; 6.6%) and *NPM1* and *KRAS (n*=1 case each; 3.3%). With univariate analysis, LDH levels were significantly associated with *JAK2*V617F mutation ($p<0.001$) and deletions involving chromosome 13. **Conclusions:** CMML is a heterogeneous disease entity at a genetic level. The presence of multiple genetic mutations in a subset of cases may indicate evolution of the neoplastic clone. Longitudinal analysis to study progressive additional mutations in cases would help to delineate a model for molecular pathogenesis and could lead to developing improved tools for prognosis and treatment of CMML.

**7052 General Poster Session (Board #337), Mon, 1:15 PM-5:00 PM**

**Is obinutuzumab cost-effective in the first-line treatment of CLL?** *Presenting Author: David Leroy Veenstra, University of Washington, Seattle, WA*

**Background:** Obinutuzumab, also known as GA101 (G), is a novel therapy shown to have improved PFS in combination with chlorambucil (GClb) compared to rituximab + chlorambucil (RClb) in the recent CLL-11 trial for previously untreated CLL. The incremental value of G vs. rituximab (R) has not been studied. **Methods:** Patient outcomes were simulated using a 3-state Markov model that included PFS, progression, and death. The patient population was assumed to be analogous to that studied in the CLL-11 trial. Efficacy parameters were 1) probability of progression, and 2) probability of dying after disease progression. The model parameters were fitted to the observed trial data. Drug utilization and adverse events were incorporated based on trial data, and costs were based on Medicare reimbursements and drug wholesale acquisition costs. Sensitivity analyses were conducted to assess uncertainty in the results. **Results:** Treatment with GClb led to an increase in average life years (+0.61 y) and quality-adjusted life years (QALYs)(+0.56 y) relative to RClb, respectively. The average total costs were similar, with higher drug and adverse event costs for GClb being offset by higher cost of disease progression with RClb. In probabilistic sensitivity analyses, the difference in QALYs ranged from 0.03 to 1.02, and the difference in total cost ranged from approximately -$53,000 to $56,0000. There was an 89% probability that G+Clb was cost-effective at the $100,000 per QALY threshold. **Conclusions:** Based on the results of the CLL-11 trial, our analysis suggests treatment with GClb compared to RClb is likely cost-effective. Further analyses based on indirect comparisons with other treatment options, as well as updated follow-up data, will help inform coverage and reimbursement policy decisions.

| Outcome | GClb | RClb | Difference |
|---|---|---|---|
| **Average life years** | 5.05 | 4.44 | 0.61 |
| **Average QALYs** | 3.36 | 2.80 | 0.56 |
| **Total drug cost** | $37,460 | $34,875 | $2,585 |
| **Drug administration** | $1,134 | $803 | $330 |
| **Supportive care** | $128 | $75 | $52 |
| **Adverse events** | $9,851 | $6,766 | $3,085 |
| **Cost of progression** | $40,004 | $46,075 | -$6,070 |
| **Average total cost** | $88,577 | $88,595 | -$18 |

**7053 General Poster Session (Board #338), Mon, 1:15 PM-5:00 PM**

**Feasibility of BIBF1120 (nintedanib) combined with low-dose cytarabine in elderly patients with AML ineligible for intensive treatment.** *Presenting Author: Utz Krug, University Hospital of Muenster, Muenster, Germany*

**Background:** Elderly unfit patients with AML have a dismal prognosis. The oral multikinase inhibitor BIBF1120 (nintedanib) was reported to exert growth inhibitory and proapoptotic effects in myeloid cells, especially when used in combination with cytarabine (AraC). **Methods:** This phase I study evaluated the combination of AraC (20mg subcutaneously twice daily on days 1-10 every 28 days) with BIBF1120 in 3 predefined dose levels (DL: 100, 150, and 200mg orally twice daily) in elderly patients with AML ineligible for intensive treatment or treatment with 5-Aza in a 3+3 design. Protocol-specific definitions: Therapy-related cytopenias constituted no adverse events (AE). AEs of special interest (AESI) were elevation of AST and/or ALT >3x upper level of normal (ULN) combined with an elevation of bilirubin >2x ULN, and any hollow organ perforation occurring after the first intake of study medication. DLT was defined as non-hematological SAR CTC grade ≥IV with possible or definite relationship to BIBF1120 occurring during or up to 28 days after the first cycle. **Results:** Between April 2012 and October 2013, 13 patients were enrolled into the phase I part of this trial (DL1: 3 patients, DL2: 4 patients, DL3: 6 patients). 1 patient in DL2 did not receive study medication and was replaced. Median age was 73 (range: 62 – 86) years. Disease status was untreated (4 patients), relapsed (5) and refractory (4) AML. Cytogenetic risk was favorable (1 patient), intermediate (5), unfavorable (6) or missing (1). 8 SAEs occurred (DL1: 1, DL2: 3, DL3: 5). All of the 3 SARs were neutropenic fever grade 3 (DL2: 1, DL3: 2). 2 SUSARs were observed, 1 fatal hypercalcemia (DL2) and 1 fatal GI tract infection (DL3). No AESI were observed. The phase II recommended dose (P2RD) was set as DL3 by the DMC. 2 patients with relapsed AML responded (1 CR, 1 CRi). Bone marrow blast reductions without fulfilling the PR criteria were observed in 3 patients. One-year survival from start of therapy was 46% after a median follow-up of 308 days. **Conclusions:** BIBF1120 combined with LD-AraC shows a favorable safety profile. Preliminary survival data are promising. Continuation of this trial with a P2RD of 2 x 200mg in a randomised phase II is planned. Clinical trial information: NCT01488344.

**7054 General Poster Session (Board #339), Mon, 1:15 PM-5:00 PM**

**Tyrosine kinase inhibitors as a first-line treatment in patients with newly diagnosed chronic myeloid leukemia in chronic phase: A mixed-treatment comparison.** *Presenting Author: Belal Firwana, University of Missouri, Columbia, MO*

**Background:** Chronic myeloid leukemia (CML) is a myeloproliferative disorder of blood stem cells. After the introduction of tyrosine kinase inhibitors (TKi), patients with CML have had substantially improved responses compared with previous therapies. We sought to summarize the evidence of TKi efficacy and safety in patients with newly diagnosed CML in chronic phase (CML-CP). **Methods:** We included all randomized clinical trials evaluating first-line treatment with a TKi (imatinib, dasatinib, bosutinib or nilotinib) in adults with CML-CP. Staudies of patients with accelerated- or blast-phase CML as well as those on IFN-$\alpha$ or stem cell transplantation were excluded. Main outcomes are complete cytogenetic response (CCyR) and major molecular response (MMR) at 12-month follow-up period. Safety and tolerability outcomes were pooled. A comprehensive literature search was conducted. Bayesian mixed-treatment method was used to rank TKi in terms of effectiveness. **Results:** Eighteen peer reviewed papers and conference abstracts reporting on seven studies were identified involving 2842 patients with CML-CP who were enrolled for initial treatment. At 12-month follow-up, mixed treatment comparison analysis demonstrated superiority of each TKi treatment family over imatinib, except bosutinib and nilotinib, which were not statistically different for CCyR and MMR respectively. Nilotinib ranked first among other TKi in terms of efficacy for CCyR; dasatinib ranked first in terms of MMR. Among second generation TKi, nilotinib had the superior tolerance and the least discontinuation rate from drug-related toxicity, followed by dasatinib then bosutinib. Hematological adverse events were highest for high dose imatinib followed by dasatinib. **Conclusions:** Second generation TKi are associated with a deeper and faster CCyR and MMR compared to imatinib. At 12-month follow-up period, nilotinib ranked first to achieve CCyR and had the lowest treatment discontinuation rate, while dasatinib ranked first to achieve MMR. Long term follow up is required to determine the impact of difference in the response patterns to the overall survival.

**7055 General Poster Session (Board #340), Mon, 1:15 PM-5:00 PM**

**Association of obesity with cytogenetic risk in adult acute myeloid leukemia (AML).** *Presenting Author: Laura Elizabeth Finn, Mayo Clinic, Jacksonville, FL*

**Background:** Obesity, body mass index (BMI) ≥30 kg/m2, is a risk factor for several malignancies. Prospective studies have reported a positive association between obesity and adult leukemia. The association between obesity and AML cytogenetic risk groups is unknown. We therefore evaluated a cohort of 295 AML patients with confirmed cytogenetics analysis diagnosed and treated at Mayo Clinic Florida and Arizona since 1995. **Methods:** Documented patient characteristics including height and weight, past medical history, medications, cytogenetics, treatments, and outcomes regarding their diagnosis of AML were extracted from a central electronic medical record. Standard cytogenetic risk categories (including intermediate abnormal) were applied. The association of obesity with cytogenetic risk was evaluated on multivariable analysis using logistic regression models. **Results:** The median BMI was 26.9 kg/m2 (range 16.9-59.9). 82 patients (28%) in the evaluated cohort were obese. On multivariable analysis obesity had the most significant association with intermediate-abnormal cytogenetics in comparison to additional patient factors evaluated including patient age, secondary AML (sAML), and therapy related AML (tAML). Obesity did not significantly impact remission after induction chemotherapy or survival after AML diagnosis. **Conclusions:** Obesity is significantly associated with intermediate abnormal risk cytogenetics in AML. This supports a link to leukemogenesis and requires validation in a larger controlled prospective therapeutic study.

| | | Cytogenetic risk (OR; 95% CI) | | |
|---|---|---|---|---|
| **Variable** | **N** | **Poor** | **Intermediate-abnormal** | **Intermediate-normal** |
| **Age >60** | 222 | 0.69 (0.38,1.24) P=0.21 | 1.40 (0.71,2.75) p=0.33 | 1.29 (0.72,2.31) p=0.39 |
| **BMI ≥ 30** | 82 | 0.79 (0.45,1.40) p=0.42 | 1.95 (1.09,3.50) p=0.024 | 0.76 (0.44,1.32) p=0.33 |
| **tAML** | 43 | 1.36 (0.70,2.64) p=0.37 | 1.39 (0.67,2.88) p=0.38 | 0.38 (0.17,0.83) p=0.015 |
| sAML | 119 | 2.13 (1.30,3.49) p=0.003 | 0.85 (0.48,1.49) p=0.57 | 0.73 (0.45,1.19) p=0.21 |

| Complete remission after induction chemotherapy (OR; 95% CI) | | |
|---|---|---|
| **Variable** | **Single variable analysis** | **Multivariable analysis** |
| BMI ≥ 30 | 1.02 (0.53,1.97) p=0.95 | 0.94 (0.47,1.89) p=0.87 |

| Survival after AML diagnosis (RR; 95%CI) | |
|---|---|
| **BMI ≥ 30** | 1.14 (0.85, 1.52) p=0.38 |

**7056 General Poster Session (Board #341), Mon, 1:15 PM-5:00 PM**

**Prospective assessment of chemotherapy-induced peripheral neuropathy (CIPN) in children with standard-risk acute lymphoblastic leukemia (SR ALL): Results of Children's Oncology Group (COG) AALL0932.** *Presenting Author: Nina S. Kadan-Lottick, Yale School of Medicine, Smilow Cancer Center, New Haven, CT*

**Background:** Vincristine is associated with CIPN that can impair daily function. **Methods:** Patients 3.0-9.9 years without neurological disorders, enrolled on ALL0932 at 26 sites, were evaluated ~2 weeks post-induction (vincristine x 4 doses, dexamethasone x 28 days, and pegaspargase) by a physical/occupational therapist for peripheral neuropathy, proximal strength and fitness. Parents reported daily physical function with The Pediatric Outcomes Data Collection Instrument (PODCI). Percentages of measured impairments and limited daily function were calculated and analyzed by multivariable logistic regression. **Results:** The 149 (80% of eligible) subjects were 48% female, 56% white non-Hispanic (26% Hispanic, 18% other) and a mean of 5.1± 1.7 years. The table summarizes the substantial frequency of measured and reported impairments. Impaired peripheral motor function in the upper (OR=4.6; p=0.01) and lower extremities (OR=3.4; p=0.06) and younger age (OR=1.7; p=0.02) were associated with report of limited physical function. **Conclusions:** Our data suggest that induction therapy causes significant motor neuropathy predictive of daily physical function in young children with SR ALL. AALL0932 will assess how this neuropathy evolves throughout ALL therapy. Clinical trial information: NCT01190930.

| | **% Impaired** |
|---|---|
| **Peripheral neuropathy** | 21* |
| **Sensory** | 11 |
| **Light touch** | 57* |
| **Protective sensation** | 47* |
| **Vibration** | 27* |
| **Motor (extremity)** | |
| **Upper** | |
| **Lower** | |
| **Proximal strength** | 32* |
| **Upper body** | 45* |
| **Core** | |
| **Fitness** | 48* |
| **Upper extremity and physical function core scale (PODCI)** | 25* |

* P value from two-sided exact test < 0.001 compared to expected value of 7% for measured impairments and 13.6% for PODCI in healthy norms.

**7057 General Poster Session (Board #342), Mon, 1:15 PM-5:00 PM**

**Covariation of psychological and inflammatory variables in patients with chronic lymphocytic leukemia receiving ibrutinib.** *Presenting Author: Neha Godiwala, The Ohio State University, Columbus, OH*

**Background:** Ibrutinib has been shown to induce durable responses in patients with high risk relapsed/refractory (r/r) chronic lymphocytic leukemia (CLL) (Byrd et al., 2013). Psychological factors, particularly stress, have been shown to covary with immunity and cytokines in solid tumor cancers. This pilot study examines temporal changes and covariation in inflammatory/angiogenic markers and psychological variables among r/r CLL patients receiving Ibrutinib. We hypothesized that these variables would improve during treatment and would covary over time. **Methods:** Patients enrolled in our single-institution phase II trial of Ibrutinib with r/r CLL (N=148) provided blood and psychological data on day 1 (of 28) of cycles 1-3. For this pilot, ELISA assays were performed on a subset (N=24; mean age=65; 50% female) of patients representing a distribution of scores (0-33) on a cancer-specific stress measure. Depressive symptoms, mood disturbance, fatigue, and quality of life (QOL) were also assessed. Assays measured IL-6, TNF-alpha, VEGF, CRP, BAFF, CCL3, and IL-16 levels in the patients' plasma. Hierarchical linear modeling examined change over time for all variables and covariation between psychological and inflammatory/angiogenic markers. **Results:** Improvements were observed in stress, depressive symptoms, fatigue, and QOL (p-values < 0.05). Decreases were observed in IL-16, TNF-alpha, and CCL3 (p-values < 0.05). Controlling for age, chromosome 17p deletion, and gender, covariation between the following variables was found: TNF-alpha with stress, depressive symptoms, mood disturbance, and QOL; IL-6 with mood disturbance, fatigue, and QOL; and VEGF with depressive symptoms (all p-values <0.05). That is, changes in inflammatory/angiogenic markers were correlated with changes in psychological variables. **Conclusions:** These pilot data suggest that in addition to providing clinical benefit, Ibrutinib treatment contributes to improvements in psychological functioning and decreases in inflammation. Clinical trial information: NCT01589302.

**7058 General Poster Session (Board #343), Mon, 1:15 PM-5:00 PM**

**Effect of syk inhibition by TAK659 on proliferative, survival, and migratory signals from the microenvironment in chronic lymphocytic leukemia.** *Presenting Author: Noelia Purroy, Laboratory of Experimental Hematology. University Hospital Vall d'Hebron, Barcelona, Spain*

**Background:** Chronic lymphocytic leukemia (CLL) is characterized by the accumulation and proliferation of monoclonal CD5+ mature B-cells in peripheral blood, lymph nodes (LN), and bone marrow (BM). The microenvironment in BM and LN induces proliferation of CLL cells and protects them from spontaneous and chemotherapy-induced apoptosis. Syk is a tyrosine kinase essential for the BCR signaling pathway that also participates in signaling from chemokine receptors and has been shown to be deregulated in CLL. Therefore Syk has been hypothesized to be a rational candidate for targeted therapy in CLL and its inhibition has been tested with the non-specific Syk inhibitor fostamatinib (R406). Against this background we tested the effectiveness of the highly specific Syk inhibitor TAK-659 in suppressing the induction of survival, proliferation and migration of CLL cells by the microenvironment. **Methods:** To mimic the microenvironment of the proliferative centers ex vivo, we co-cultured primary CLL cells with BM stromal cells (BMSC), CD40L, and CpG ODN along with anti-IgM (BCR stimulation). We evaluated the effects of TAK-659 on BCR signaling, proliferation, apoptosis and chemotaxis. **Results:** The co-culture system with BMSC and different stimuli induced survival and proliferation of primary CLL cells. Moreover, in this system CLL cells became chemoresistant to fludarabine and bendamustine. TAK-659 inhibited the phosphorylation of Syk, Akt, and ERK1/2 after BCR stimulation. TAK-659 induced apoptosis of co-cultured CLL cells at lower doses than R406. In addition, combination of TAK659 and fludarabine showed a synergistic effect in inducing apoptosis. TAK-659 also inhibited co-culture-induced proliferation, as assessed by Ki-67 expression, and significantly decreased chemotaxis of CLL cells toward CXCL12, CXCL13 and BMSCs. **Conclusions:** These findings demonstrate that, in this ex-vivo system, the specific inhibition of Syk by TAK-659 effectively overcomes the microenvironment signals that promote proliferation, survival and chemoresistance of primary CLL cells. Altogether, this study provides a rationale for the clinical development of TAK-659 in CLL.

**7059 General Poster Session (Board #344), Mon, 1:15 PM-5:00 PM**

**Phase 2 trial of GS-9973, a selective syk inhibitor, and idelalisib (idela) in chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL).** *Presenting Author: Paul M. Barr, James P. Wilmot Cancer Center, University of Rochester Medical Center, Rochester, NY*

**Background:** GS-9973 is an orally bioavailable, small-molecule, selective inhibitor of Spleen Tyrosine Kinase (Syk). The Kd of GS-9973 for Syk was 7.6 nM with no other kinase < 100 nM. **Methods:** This Phase 2 trial enrolled subjects (subj) with relapsed/refractory CLL (1 cohort) or NHL (4 cohorts). Subj underwent intra-subj dose escalation from GS-9973 400 mg and Idela 100 mg (400/100) BID up to a maximum of 800/150 BID. Plasma drug levels were obtained concurrently with plasma chemo/cytokine levels and phospho flow analysis of circulating leukemic cells. **Results:** This study initiated in July 2013. When enrollment was suspended, 66 subj with CLL (36) or NHL (30) had been enrolled. Median age was 68 (range 28 - 92), 53% were male. The median number of prior treatment regimens was 3 (range 1-9). Of the subj with investigator response assessments, 14 (70%) and 10 (50%) of 20 CLL subj had a decrease of > 50% and > 75% respectively in their measurable lymph node disease; 7 (35%) of 20 NHL subj achieved a decrease of > 50%. (iNHL 6/14; DLBCL 1/4; MCL 0/2). The study was terminated early due to the development of severe, steroid responsive, pneumonitis in 9 subj that occurred despite dose reduction in 4 after a median of 83 (raange 50-105) days on study. Reversible Grade 3 or 4 ALT elevations occurred in 10 (15%) subj. Treatment emergent adverse events occurring in ≥ 15% of subj were fatigue, nausea, pyrexia, rash, diarreha, headache, constipation and cough and were typically low grade. 5 subj died while on study: 2 from disease progression, 1 from pneumonitis, 1 from pneumonia, 1 from sepsis. **Conclusions:** Despite promising activity in CLL, the combination of GS-9973 and Idela resulted in an unexpectedly high rate of pneumonitis and resulted in stopping dosing of the combination These data need to be considered when designing future investigations combining inhibitors of B cell receptor signaling. Additional studies are needed to understand the underlying mechanism of pneumonitis seen with dual Syk and PI3k inhibition Clinical trial information: NCT01796470.

**7060 General Poster Session (Board #345), Mon, 1:15 PM-5:00 PM**

**Long-term evaluation of vascular toxicity in patients with Ph+ leukemias treated with bosutinib.** *Presenting Author: Jorge E. Cortes, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Vascular toxicities (eg, peripheral arterial occlusive disease [PAOD]) have been associated with BCR-ABL tyrosine kinase inhibitor (TKI) treatment (tx). **Methods:** We evaluated vascular (peripheral, cardiovascular, and cerebrovascular) toxicities based on tx-emergent adverse events (TEAEs) with bosutinib (BOS) in 2 ongoing studies: phase 1/2 study of BOS second/third/fourth-line tx (2L/3L/4L, up to 3 y) in Ph+ leukemia patients (pts) resistant/intolerant to prior TKIs; phase 3 study in chronic phase CML pts of BOS vs imatinib (IM) first-line tx (1L; up to 2 y). **Results:** 12.7% of BOS pts had vascular TEAEs (Table) with no significant differences for BOS vs IM (1L: $P \geq 0.122$). Individual cardiovascular TEAE incidences were low; only angina pectoris (1.2%) and coronary artery disease (CAD 1.2%) occurred in >1% of BOS pts. No individual cerebrovascular TEAE occurred in >3 BOS pts. Individual peripheral vascular TEAEs were rare; only hypertension (6.4%) occurred in >2 BOS pts (1L: 6.0% [BOS] vs 4.4% [IM], $P=0.427$). Only 1 pt had PAOD (BOS 3L; y 1). Newly occurring vascular TEAE rates decreased with longer BOS tx (2L/3L/4L: y1, 40/570 [7.0%]; y 2, 21/273 [7.7%]; y 3, 8/208 [3.8%]; 1L [BOS vs IM]: y 1, 16/248 [6.5%] vs 9/251 [3.6%]; y 2, 5/183 [2.7%] vs 5/209 [2.4%]). Risk factors for vascular TEAEs ($P \leq 0.036$) were age ≥65 y (both studies) and history of vascular disorders (2L/3L/4L). Vascular TEAEs were managed mostly by concomitant medication (61.5% of affected pts); few pts required dose delays (n=15) or reductions (n=1). Discontinuation due to vascular TEAEs occurred in 6 (0.7%) BOS pts (2L/3L/4L: CAD n=2, myocardial infarction n=2, cerebrovascular accident n=1; 1L: cerebral haemorrhage n=1 [vs 0 IM, $P=0.497$]). **Conclusions:** Vascular TEAE incidences with BOS in Ph+ leukemia pts were low individually and overall and not significantly different vs IM (1L). Peripheral vascular TEAEs, except hypertension, are rare with BOS. Clinical trial information: NCT00574873; NCT00261846.

| | Pooled | 2L/3L/4L | 1L | |
|---|---|---|---|---|
| | BOS* (n=818) | BOS* (n=570) | BOS* (n=248) | IM† (n=251) |
| Median (range) tx duration, mo | – | 11.1 (0.03–83.4) | 33.1 (0.03–49.6) | 33.3 (0.5–46.9) |
| Vascular TEAEs, % | 12.7 | 13.5 | 10.9 | 7.6 |
| Cardiovascular | 3.4 | 4.2 | 1.6 | 1.2 |
| Cerebrovascular | 1.8 | 2.3 | 0.8 | 0.4 |
| Peripheral vascular | 8.2 | 8.2 | 8.1 | 4.8 |

*500 or †400 mg/d starting dose.

**7062 General Poster Session (Board #347), Mon, 1:15 PM-5:00 PM**

**Lipid cell membrane composition: A novel therapeutic target in cancer.** *Presenting Author: Ravi Kiran Bobba, Ellis Fischel Cancer Center, University of Missouri-Columbia, Columbia, MO*

**Background:** Cell membrane cholesterol, more specifically, the lipid composition of lipid rafts is associated with regulation of trans-membrane receptors. **Methods:** We tested the hypothesis that altering membrane cholesterols, via mevalonate pathway inhibitors, Ro 48-8071, TAK-475, BIBB-515 and YM-53601, may have differential effects on cancer cells in in-vitro models of Small Lymphocytic Lymphoma/ Chronic Lymphocytic Leukemia (CLL) cell lines and Peripheral blood lymphocytes of CLL patients. **Results:** In addition to chemo-sensitization of the cells, in-vitro results showed a statistically significant upregulation of cell surface proteins, CD20 and CD52. Treatment with cholesterol inhibitors resulted in significant upregulation of CD20 protein and glycosphingolipid-GM1 both by confocal microscopy and flow cytometry. Flow cytometry of MEC-2 and WAC-3 showed an upregulation of CD20 and CD52. Quantification of membrane lipids showed upregulation of glycosphingolipid-GM1. LysoPC (lysophosphatidylcholine) was an average of 0.0405 ± .0016 in controls was reduced to 0.0278 ± 0.0021 with BIBB-515 treatment and 0.0247 ± 0.0022 with YM-53601 treatment. PC (phosphatidylcholine) was upregulated from 1.0029 ± 0.02378 in controls to 1.0904 ± 0.04489 with BIBB-515 treatment and 1.1088 ± 0.02269 with YM-53601 treatment ($P<0.05$). Spingomyelin/Dihydrosphingomyelin (SM/DSM) was an average of 0.5863 ± 0.0113 in controls and was upregulated to 0.5997 ± 0.0294 with BIBB-515 treatment ($P<.05$) and 0.6735 ± 0.0159 in YM-53601 treatment ($P<.001$). Ether-linked Phosphatidylcholine (ePC) was upregulated from 0.2938 ± 0.0044 in controls to 0.3328 ± 0.0152 with BIBB-515 treatment and 0.3370 ± 0.0061 with YM-53601 treatment ($P<.001$). Treatment with BIBB-515 and YM-53601 did not affect membrane cholesterol levels significantly. Lovastatin significantly reduced membrane cholesterol from controls ($P<0.05$). **Conclusions:** Mevalonate pathway inhibitors lead to alterations in drug-resistant cancer cell membrane lipids by altering the cell surface receptor proteins CD 20 and upregulation of glycosphingolipid-GM1. A specific biochemical alteration in cancer cell membrane lipids represents a potential novel therapeutic approach to cancer.

**7063 General Poster Session (Board #348), Mon, 1:15 PM-5:00 PM**

**Preliminary safety and efficacy of the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib (IBR) in patients (pts) with hairy cell leukemia (HCL).** *Presenting Author: Jeffrey Alan Jones, The Ohio State University, Columbus, OH*

**Background**: Effective treatments (tx) for classical (c) HCL pts refractory to or ineligible for nucleoside analogs (NA) are limited, and there is no accepted standard for either tx-naïve or relapsed variant (v) HCL. IBR, an oral small molecule inhibitor of BTK, is active in several indolent B-cell malignancies, but its activity in HCL has not been previously assessed. We report preliminary safety and efficacy data from a CTEP-supported phase 2, multicenter study. **Methods**: Pts with cHCL (relapsed after ≥1 NA or unfit for NA) and vHCL who require tx are eligible if ECOG ≤2, free of infection and end-organ function preserved. Pts receive continuous IBR 420 mg daily in 28-day cycles. Response, including bone marrow biopsy with immunohistochemistry for MRD, is assessed after 8 and 12 cycles. Pts may continue IBR indefinitely absent unacceptable toxicity or progressive disease. **Results:** 8 pts (1 tx-naïve and 1 relapsed vHCL, 6 relapsed cHCL) have been dosed (range 1-8 cycles) and all remain on tx. Common treatment-related adverse events were grade (Gr) 1/2 diarrhea, rash, arthralgia/myalgia, and transient Gr 1-3 elevation of hepatic transaminases. 3 cases of Gr 3 neutropenia and 2 cases of febrile neutropenia have been observed during cycle 1, all responding to tx interruption and/or brief course GCSF. Redistribution lymphocytosis (peaking at day 8) occurred in both vHCL pts and 1 V34.4 subtype cHCL pt with circulating disease at baseline. Soluble IL2 receptor (sIL2R) levels decreased after tx in all pts and correlated with improvements in symptoms and peripheral blood counts. Marrow clearance (>90% pre-, <2% post-tx) was observed in the first pt undergoing response assessment after 8 cycles. Pretreatment imunoblots demonstrated the presence of pBTK in several pts that was substantially reduced after IRB. This did not correlate with loss of pERK, suggesting that ERK phosphorylation ex vivo may not be a reliable indicator of IBR activity. **Conclusions:** IBR appears well tolerated and demonstrates early evidence of activity in both cHCL and vHCL. sIL2R levels may correlate with response. Accrual continues at 5 US sites. Updated safety and efficacy data will be presented. Clinical trial information: NCT01841723.

**7064 General Poster Session (Board #349), Mon, 1:15 PM-5:00 PM**

**Phase II study of combination of hyperCVAD with ponatinib in frontline therapy of patients (pts) with Philadelphia chromosome (Ph) positive acute lymphoblastic leukemia (ALL).** *Presenting Author: Susan Mary O'Brien, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Combination of chemotherapy (CTX) with TKI is effective in the treatment of Ph+ ALL. Ponatinib is a more potent BCR-ABL inhibitor. The combination of CTX + ponatinib may be associated with better outcome. **Methods:** Pts with newly diagnosed Ph+ ALL received 8 cycles of hyperCVAD every 21 days. Ponatinib was given at 45 mg po daily for the first 14 days of cycle 1 then continuously for the subsequent cycles. Pts in CR received maintenance with ponatinib 45 mg po daily with vincristine/prednisone monthly for 2 yrs followed by ponatinib indefinitely. **Results:** 34 pts with untreated Ph+ ALL and 3 previously treated (1 course) have received a median of 6 cycles; 12 pts are receiving maintenance in CR. Median age was 51 yrs. All pts were in CR after cycle 1. CCyR rates were 94% and 100% after 1 and 2 cycles, respectively. To date, 35 pts (95%) achieved MMR and 26 (70%) CMR. MRD is negative in 35/36 (97%) pts, in whom a sample was sent for assessment. 8 pts received ASCT after a median of 4 courses. Grade ≥ 3 toxicity included infections during induction in 18 pts (49%), increased LFT's in 13 (35%), thrombotic events in 3 (8%), myocardial infarction (MI) in 3 (8%, 2 unexplained, 1 in the context of sepsis ), skin rash in 4 (11%), and pancreatitis in 6 (16%). With a median follow up of 13 months, 31 pts are alive and in CR; 1 pt died in CR from an unrelated cardiac event after being taken off therapy and placed on imatinib, 1 from MOF (C2D13), 1 from NSTEMI (C2D41), 1 from potential MI (C4D42), 1 from head injury sustained after a fall (C4D13), and 1 from sepsis post ASCT. At the last follow-up, 7 pts (19%) are alive post ASCT; 15 pts (41%) on ponatinib at 15 mg daily in 14, and 30 mg daily in 1; Of the other 9 alive pts, 7 were switched to dasatinib, 1 was switched to imatinib, and 1 is no longer receiving treatment. The 1-year PFS and OS rates were 100% and 86%, respectively. **Conclusions:** Combination of hyperCVAD + ponatinib is highly effective in pts with Ph+ ALL. Due to the vascular events observed, some pts switched to alternative TKI; in the remaining, ponatinib dose was modified to 30 mg daily during consolidation with subsequent reduction to 15 mg in pts in CMR. Clinical trial information: NCT01424982.

**7065 General Poster Session (Board #350), Mon, 1:15 PM-5:00 PM**

**Phase II study of the hyper-CVAD regimen in combination with ofatumumab as frontline therapy for adults with CD-20 positive ALL.** *Presenting Author: Elias Jabbour, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** The hyperCVAD regimen is an effective frontline program for de novo adult ALL. CD20 expression was identified as an adverse prognostic factor, associated with a higher incidence of relapse and lower 3-year OS rates. Addition of rituximab to the hyperCVAD program in patients with CD20+ ALL improved outcome with 3-year CRD and OS rates by 68% and 65%, respectively. Ofatumumab targets a membrane proximal small-loop epitope on the CD20 molecule and was found to be more potent than rituximab. Combination of the hyperCVAD regimen and ofatumumab may be associated with better responses and higher 3-year PFS and OS rates. **Methods:** Pts with newly diagnosed ALL and pts who received 1 prior course of chemotherapy received 8 courses of hyperCVAD alternating MTX-Ara-C; ofatumumab was given on courses 1 through 4. This treatment is to be followed by POMP maintenance therapy for approximately 30 months, interrupted by intensifications months 6, 7 and 18, 19 with MTX/Pegylated asparaginase and hyperCVAD-ofatumumab. CNS prophylaxis was administered. **Results:** 21 pts with de novo ALL and 2 pts in CR previously treated have received a median of 7 cycles; 7 pts did not receive the full 8 planned courses. 15 pts are receiving maintenance in CR. Median age is 50 years. All but 1 pt (95%) achieved CR after cycle 1; 1 pt died of septic shock at C1D21. 22/23 pts (95%) achieved MRD negativity as assessed by FCI; of whom 14 (64%) after induction. Grade ≥ 3 toxicity included increased LFT's in 7 pts (30%), increased bilirubin in 6 (26%), thrombotic events in 1 (4%) and neuropathy in 1 (4%). Febrile neutropenia episodes during induction and consolidation cycles were reported at rates of 71% and 77%, respectively. With a median follow-up of 12 months, 21 pts are alive; two patients developed sepsis and died at C1D21 and C3D17, respectively. 2 pts have undergone ASCT: due to the lack of MRD negativity achievement in one and a highly complex karyotype at diagnosis in the second; the first relapsed 7 months post ASCT. The 1-year PFS and OS rates were 91% and 91% respectively. **Conclusions**: The combination of hyperCVAD/ofatumumab is safe and highly effective in pts with CD20 + ALL. Clinical trial information: NCT01363128.

**7066 General Poster Session (Board #351), Mon, 1:15 PM-5:00 PM**

**Landmark analysis of overall survival (OS) in patients with chronic (CP) or accelerated (AP) phase chronic myeloid leukemia (CML) treated with omacetaxine mepesuccinate.** *Presenting Author: Meir Wetzler, Roswell Park Cancer Institute, Buffalo, NY*

**Background:** Response milestones are used as prognostic indicators in CML. This analysis compared OS in patients with/without response to omacetaxine. **Methods:** This was a post hoc landmark analysis in a subset of CP and AP patients in 2 phase II trials of single-agent omacetaxine; all had received ≥2 tyrosine kinase inhibitors. Kaplan-Meier analysis was used to estimate OS from time of omacetaxine initiation in patients with/without hematologic response (HR; complete [CHR] in CP and major [MHR] in AP) or cytogenetic response (CyR) at 3, 6, and 12 months (mo); patients unevaluable for response at a timepoint were excluded. **Results:** At 3 months, 53 (70%) CP and 15 (43%) AP patients continued treatment; median OS in these patients was 49.3 mo (95% CI, 27.8-NR) and 21.7 mo (6.8-37.2), respectively (vs 27.2 mo [6.8-37.2] and 8.2 mo [1.9-16.0] in those who discontinued prior to 3 mo). In CP and AP patients evaluable for response at 3 mo, median OS was longer in those with HR vs those without (Table). Median OS was similar in CP patients with/without CyR at 3 and 6 mo. Median OS was not reached in CP patients with CyR at 12 mo (n=12; 11 patients were alive with a median follow-up of 48.7 mo [range, 29.5-57.2]), compared with a median OS of 49.5 mo in those without CyR (n=13). **Conclusions:** HR by 3 mo may be a positive predictor of OS in CML patients treated with omacetaxine. In this heavily pretreated population, presence/absence of CyR by 6 months may not be predictive of OS. These findings are limited by the relatively small number of patients and the noncomparative study design. Clinical trial information: NCT00375219 and NCT00462943.

| | Time pt, mo | Response | N | Deaths, n (%) | Median OS, mo (95% CI) |
|---|---|---|---|---|---|
| CP | 3 | CHR | 47 | 21(45) | 49.5 (31.6-NR) |
| | | No CHR | 6 | 4 (67) | 15.0 (7.8-NR) |
| | | Any CyR | 11 | 4 (36) | 49.3 (9.6-NR) |
| | | No CyR | 42 | 21 (50) | 49.5 (22.9-NR) |
| | | MCyR | 8 | 4 (50) | 49.3 (9.6-49.3) |
| | | No MCyR | 45 | 21 (47) | 49.5 (22.9-NR) |
| | 6 | Any CyR | 14 | 4 (29) | 49.3 (40.3-NR) |
| | | No CyR | 29 | 15 (52) | 49.5 (20.3–NR) |
| | | MCyR | 8 | 4 (50) | 49.3 (14.2-49.3) |
| | | No MCyR | 35 | 15 (43) | 59.4 (27.8-NR) |
| | 12 | Any CyR | 12 | 1 (8) | NR(49.3-NR) |
| | | No CyR | 13 | 8 (62) | 49.5 (17.8-59.4) |
| | | MCyR | 6 | 1 (17) | NR (49.3-NR) |
| | | No MCyR | 19 | 8 (42) | 59.4 (27.8-59.4) |
| AP | 3 | MHR | 3 | 3 (100) | 33.0 (24.6-37.2) |
| | | No MHR | 12 | 9 (75) | 17.3 (6.7-40.3) |

Abbreviations: NR, not reached.

**7067 General Poster Session (Board #352), Mon, 1:15 PM-5:00 PM**

**Correlation of KIT expression with higher FLT3 mutations and impact on clinical outcome in patients newly diagnosed with acute myeloid leukemia (AML).** *Presenting Author: Hassan Alkhateeb, Mayo Clinic, Rochester, MN*

**Background:** KIT (CD 117) is a transmembrane tyrosine kinase protein receptor encoded by the c-kit protooncogene. KIT mutations were described in AML and impart a prognostic impact on patients (pt) with core binding factor. However, its expression effect on clinical phenotype and outcome is unknown. **Methods:** A retrospective, single institution study of cases with AML at Mayo Clinic between 2003 - 2011 was performed. Pts with blasts KIT expression studied by flow cytometry at diagnosis were included. Appropriate IRB approval was obtained in accordance with the Helsinki declaration. Comparison between groups' medians was done using Wilcoxon test, while survival estimates were calculated using Kaplan-Meier curves. **Results:** Out of 154 pts who had KIT analysis, KIT+ (>20% of blasts) was in 134 (87%). Median age is 62 year, with median white blood cell (WBC) 9 $x10^9$, Hemoglobin (Hgb) 9.3 g/dl, platelet (PLT) 56 $x10^9$, peripheral blood (PB) blast 10%, bone marrow (BM) blasts 56%. Cytogenetics (CG) was diploid in 55% pt. NCCN grouping for CG was favorable, intermediate and poor in 8%, 71%, 21%. FLT3 was mutated in 25%, NPM1 in 38% pts. CR was found in 105 (68%) pts; 77 relapsed. Median OS is 577 days. Group 1 (KIT-) had median age 62 year, Hgb 9.3 g/dl, PLT 82 $x10^9$, WBC 18 $x10^9$, PB blasts 34%, BM blasts 71%. CG was favorable, intermediate and poor in 8%, 58%, 33%. NPM1 and FLT3 were mutated in 50%, 0, respectively. CR was obtained in 75% with 55% suffering a relapse. Group 2 (KIT+) had median age 62 year, Hgb 9.4 g/dl, PLT 56 $x10^9$, WBC 9 $x10^9$, PB blasts 19%, BM blasts 55%. CG was favorable, intermediate and poor in 8%, 74%, 18%. NPM1 and FLT3 were mutated in 37% and 29%. CR was found in 67% with 51% relapsing. Upon comparison, mutated FLT3 was more frequent in group 2 vs 1 (p=0.002). Median OS was not statistically different between group 1 vs 2 (447 vs 592 days, p= 0.25). On multivariate analysis, only NCCN grouping (p=0.006) affected mOS but not age, WBC, PB/BM blasts, or KIT. **Conclusions:** KIT expression was prevalent in AML pts. We found for the first time that KIT-AML pts did not have mutated FLT3 (0%) but KIT expression did not impact clinical outcome. Additional prospective studies are needed to confirm our results.

**7068 General Poster Session (Board #353), Mon, 1:15 PM-5:00 PM**

**Predicting prognosis in patients with acute myeloid leukemia: The role of next-generation sequencing and mutational profiling.** *Presenting Author: Caroline E Sloan, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA*

**Background**: Although cytogenetics-based prognostication systems are well described in acute myeloid leukemia (AML), Patel *et al.* (NEJM 2012) recently used data from patients <60 years enrolled in a randomized controlled trial to create a new integrated prognostic (IP) schema using mutations in 9 genes. Our objective was to assess whether the IP schema was relevant in clinical practice. **Methods**: Our study consisted of 2 cohorts of patients with de novo AML, each from single large academic institutions. We included 181 patients from the Hospital of the University of Pennsylvania and 188 patients from Washington University (The Cancer Genome Atlas) for whom clinical, cytogenetic and genetic data were available. We evaluated survival outcomes among 4 mutational profiles defined by Patel *et al.* in the IP schema. **Results**: Clinical characteristics and outcomes were similar in both cohorts (n=369 overall, n=217 age <60), so they were combined for further analysis. Median age was 57 years with 59% <60 years. Patients <60 years with intermediate-risk cytogenetics (n=137) were classified as having favorable, intermediate or unfavorable mutational profiles (see table). In patients >60 years, long-term survival was poor for patients with all 4 mutational profiles and was not further evaluated for this study. **Conclusions**: The IP schema identifies mutational profiles that have differential survival in younger patients with intermediate-risk cytogenetics. Our findings validate Patel *et al.*'s IP schema in patients <60 years for some but not all mutational profiles. Performing next-generation sequencing at diagnosis may inform patient management and be cost-effective if gene panels include validated mutations and their use is tailored to patient age.

**Integrated prognostic (IP) assessment of patients <60 years with intermediate-risk cytogenetics.**

| Mutational profile | Prognosis | n | 3-year overall survival | p-value |
|---|---|---|---|---|
| FLT3-ITD negative with mutant NPM1 and IDH1/2 | Favorable | 13 | 55% | 0.004 |
| FLT3-ITD negative with mutant TET2, MLL-PTD, ASXL1 or PHF6 | Unfavorable | 32 | 45% | 0.994 |
| FLT3-ITD positive with trisomy 8 or mutant TET2, MLL-PTD or DNMT3A | Unfavorable | 30 | 17% | 0.039 |
| All others | Intermediate | 62 | 35% | Reference |

**7069 General Poster Session (Board #354), Mon, 1:15 PM-5:00 PM**

**Impact of circulating members of the insulin-like growth factor receptor (IGF-1R) axis on outcomes in acute myeloid leukemia.** *Presenting Author: Reem Karmali, Rush University Medical Center, Chicago, IL*

**Background:** AML is a disease with conservative response rates to standard therapy in the adult population. Dysregulations in insulin-like growth factor receptor-1 (IGF-1R) signaling is implicated in leukemogenesis and chemoresistant disease, but remains poorly elucidated. We explore associations of circulating levels of the IGF-1R axis, consisting of IGF binding proteins 1-7, IGF-1, and c-peptide as a control, with clinical outcomes of patients with aggressive AML. **Methods:** Peripheral blood samples in newly diagnosed non-M3 AML patients (n=30) were collected prospectively under IRB consent. Relevant clinical parameters (cytogenetics, molecular data, treatment response) were annotated for each patient. Circulating levels of the IGF-1R axis were established using Luminex-based assays and analyzed using independent t-tests, ANOVA, and log-rank in SPSS v15.0 and R statistical software. **Results:** The median age was 56. Using the ELN cytogenetic/molecular risk model, patients were stratified as either adverse risk (47% of patients; FLT-3 positive/NMP negative CN AML, c-kit positive CBF AML, MLL gene rearrangement (11q23), chromosome 5 and/or 7 abnormalities, or complex karyotype), good risk (13% of patients; CBF AML without c-kit positivity and FLT-3 negative/NPM mutated CN AML), or intermediate risk (40%; all others). Increased IGFBP-4 correlated with therapy response ($p < 0.05$) using independent t-tests. Median overall survival (OS) in the cohort was 5.2 months. Differences in progression-free survival (PFS) and OS between groups with "low" and "high" protein expression were determined using optimal discovery threshold with log-rank. Increased expression of IGFBP-1 and -6 correlated with improved PFS ($p < 0.03$ and 0.01, respectively) while increased IGFBP-1, -2, -6 and -7 were associated with improved OS ($p < 0.001$, 0.009, 0.003 and 0.001, respectively). A trend for decreased IGFBP-3 in adverse risk patients was noted. **Conclusions:** The IGF-1R axis appears to be relevant in disease refractory AML. IGFBP signatures are predictive tools in AML with applications in remission surveillance, early detection of relapse and the development of IGFBP-directed biologic therapy.

**7070 General Poster Session (Board #355), Mon, 1:15 PM-5:00 PM**

**ASP2215, a novel FLT3/AXL inhibitor: Preclinical evaluation in acute myeloid leukemia (AML).** *Presenting Author: Masamichi Mori, Astellas Pharma Inc., Ibaraki, Japan*

**Background:** Activating mutations in FLT3 receptor tyrosine kinase, characterized by internal tandem duplication (ITD) and tyrosine kinase domain point mutations near position D835, have been identified in up to 30% of AML patients. These mutations are associated with poor prognosis. ASP2215 is a novel small molecule tyrosine kinase inhibitor, currently under clinical trial evaluation. **Methods:** The kinase inhibition profile was investigated using enzyme assays. Antiproliferative activity was evaluated against several AML cell lines with assessment of the inhibition of pFLT3 and downstream molecules using Western blot and flow cytometry. Antitumor activity was evaluated in nude mice transplanted with MV4-11 AML cells. The pharmacokinetics in xenografted mice was also investigated. **Results:** Of the 78 tyrosine kinases tested, ASP2215 inhibited FLT3, LTK, ALK, and AXL kinases by over 50% at 1 nM with an $IC_{50}$ value of 0.29 nM for FLT3, approximately 800-fold more potent than for c-KIT, the inhibition of which is linked to a potential risk of myelosuppression. ASP2215 inhibited the growth of MV4-11 cells, which harbor FLT3-ITD, with an $IC_{50}$ value of 0.92 nM, accompanied with inhibition of pFLT3, pAKT, pSTAT5, pERK, and pS6. ASP2215 also inhibited the growth of Ba/F3 cells expressing FLT3-ITD and/or FLT3-D835 mutation with similar activity. Colony formation of human granulocyte-macrophage decreased to 58% in response to ASP2215 at 100 nM, more than 100-fold higher than required for MV4-11. In MV4-11 xenografted-mice, the concentration of ASP2215 in tumors was more than 20-fold higher than that in plasma with oral administration of ASP2215 at 10 mg/kg for 4 days. Treatment of ASP2215 for 28 days resulted in dose-dependent inhibition of MV4-11 tumor growth and induced complete tumor regression at more than 6 mg/kg. Further, ASP2215 decreased tumor burden in bone marrow and prolonged the survival of mice intravenously transplanted with MV4-11 cells. **Conclusions:** ASP2215, a FLT3/AXL inhibitor, showed potent antileukemic activity against AML with either or both FLT3-ITD and FLT3-D835 mutations. These findings support the development of ASP2215 for the potential use in treating AML.

**7071 General Poster Session (Board #356), Mon, 1:15 PM-5:00 PM**

**ASP2215, a novel FLT3/AXL inhibitor: Preclinical evaluation in combination with cytarabine and anthracycline in acute myeloid leukemia (AML).** *Presenting Author: Yoko Ueno, Astellas Pharma Inc., Ibaraki, Japan*

**Background:** Patients with AML harboring internal tandem duplication (ITD) of FLT3 have a poor prognosis following the current chemotherapeutic treatment of cytarabine (AraC) and anthracycline (daunorubicin, DNR or idarubicin, IDR). ASP2215 is a novel small molecule FLT3/AXL inhibitor in a clinical trial. **Methods:** Cell cycle distribution and apoptosis induction in MV4-11 AML cells, which harbor FLT3-ITD, treated with ASP2215, AraC, and DNR were evaluated via flow cytometry and Western blot. Antitumor efficacy was evaluated in MV4-11 xenografted mice administered with oral daily ASP2215 starting either a week prior to or concomitantly with, intraperitoneal AraC for 5 days, and intravenous DNR or IDR for 3 days. The pharmacokinetics in xenografted mice were also investigated. **Results:** ASP2215 treatment resulted in an increase in the proportion of MV4-11 cells in the G1 phase of the cell cycle at 24 h, and then the concentration-dependent induction of apoptosis, as determined by the increase in annexin V-positive cells and intracellular PARP cleavage. ASP2215 enhanced AraC- or DNR-induced apoptosis regardless of the treatment schedule. In mice xenografted with MV4-11 cells, the simultaneous administration of ASP2215, AraC, and DNR induced tumor regression, including complete remission. In contrast, combination chemotherapy (AraC and DNR) only induced tumor growth inhibition. Further, treatment of ASP2215 for a week followed by combination with DNR and AraC also induced tumor regression with a final tumor volume similar to that of simultaneous combination therapy. No obvious influence of toxicities on body weight, behavior, or diarrhea was noted for treatment of ASP2215. Concentrations of ASP2215, AraC, and DNR in plasma and tumor were not influenced by their use in combination therapy. ASP2215 also enhanced the antitumor efficacy of AraC plus IDR in the same model. **Conclusions:** ASP2215 in combination with AraC and either DNR or IDR induced superior antitumor efficacy compared to combination chemotherapy, regardless of dosing schedule. These findings support the development of ASP2215 in combination with chemotherapy for the potential treatment of AML.

**7072 General Poster Session (Board #357), Mon, 1:15 PM-5:00 PM**

**One-year and longer-term molecular responses to nilotinib and dasatinib for newly diagnosed chronic myeloid leukemia: A matching-adjusted indirect comparison.** *Presenting Author: James E. Signorovitch, Analysis Group, Inc., Boston, MA*

**Background:** Nilotinib and dasatinib are BCR-ABL inhibitors that markedly differ in selectivity. In separate randomized trials, nilotinib and dasatinib have shown superior achievement of molecular response (MR) compared to imatinib for the treatment of newly diagnosed chronic myeloid leukemia (CML) in the chronic phase (CP). In the absence of head-to-head trials, health technology assessment authorities rely on indirect comparisons to inform drug policies. This study compares MR between nilotinib 300mg twice daily and dasatinib 100mg once daily by 12 months and through 48 months via indirect comparison. **Methods:** Data were drawn from individual patients in the ENESTnd trial (nilotinib vs. imatinib) and published results from the DASISION trial (dasatinib vs. imatinib). Patients in ENESTnd were re-weighted to match baseline characteristics reported for DASISION (age, sex, ECOG performance status, white cell count, and platelet count) using a propensity score model. After matching, differences in major MR (MMR measured as a 3-log reduction on the International Scale [IS]), $MR^{4.0}$ (4-log reduction on IS) and $MR^{4.5}$(4.5-log reduction on IS) rates between nilotinib and imatinib were compared with those between dasatinib and imatinib. Cumulative MR rates through 48 months were also compared using adjusted hazard ratios (HRs) relative to imatinib. **Results:** After matching, rates of MR by 12 months were higher with nilotinib vs. dasatinib by 11.7% for MMR ($p = 0.045$), 8.2% for $MR^{4.0}$ ($p = 0.029$), and 8.5% for $MR^{4.5}$ ($p < 0.001$). Through 48 months of follow-up, the adjusted HR comparing MMR achievement with nilotinib vs. dasatinib was 1.44 (95% CI: 1.06, 1.94; p=0.018); the corresponding HRs for $MR^{4.0}$ and $MR^{4.5}$were 1.58 (95% CI: 1.10, 2.26; p=0.013) and 1.30 (95% CI: 0.86, 1.99; p=0.218), respectively. **Conclusions:** This indirect comparison suggested that nilotinib 300mg twice daily was associated with higher rates of achieving MMR, $MR^{4.0}$, and $MR^{4.5}$ by 12 months compared to dasatinib 100mg once daily for the treatment of newly diagnosed CML-CP. Higher rates of MR achievement with nilotinib were also maintained through 48 months of follow-up.

**7073 General Poster Session (Board #358), Mon, 1:15 PM-5:00 PM**

**ENESTnd 5-year (y) update: Long-term outcomes of patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP) treated with frontline nilotinib (NIL) versus imatinib (IM).** *Presenting Author: Richard A. Larson, University of Chicago, Chicago, IL*

**Background:** In ENESTnd, NIL has shown superior efficacy vs IM. Here, we report data based on a minimum follow-up of 5 calendar y. **Methods:** Pts with newly diagnosed CML-CP were randomized to NIL 300 mg twice-daily (BID; n = 282), NIL 400 mg BID (n = 281), or IM 400 mg once-daily (QD; n = 283). *P* values for secondary efficacy endpoints were not adjusted for multiple comparisons and are provided for descriptive purposes only. **Results:** At the data cutoff, 60%, 62%, and 50% of pts in the NIL 300 mg BID, NIL 400 mg BID, and IM arms, respectively, remained on core treatment. Over half of pts in the NIL arms achieved $MR^{4.5}$ ($BCR\text{-}ABL^{IS} \leq 0.0032\%$) by 5 y, and $MR^{4.5}$ rates were significantly higher on NIL vs IM overall and within each Sokal risk group (Table). Rates of major molecular response (MMR; $BCR\text{-}ABL^{IS} \leq 0.1\%$), freedom from progression to accelerated phase/blast crisis (AP/BC), and overall survival (OS) were higher on NIL vs IM. Fewer pts treated with NIL vs IM died from advanced CML. The safety profiles of NIL and IM were as expected. The rates of cardiovascular events (CVEs) of interest remained highest on NIL 400 mg BID and lowest on IM. **Conclusions:** NIL continues to result in superior efficacy vs IM in pts with CML-CP. NIL was generally well tolerated; however, CVEs of interest were more common on NIL vs IM. Clinical trial information: CAMN107A2303.

| | NIL 300 mg BID n = 282 | NIL 400 mg BID n = 281 | IM 400 mg QD n = 283 |
|---|---|---|---|
| $MR^{4.5}$ by 5 y, % (*P* vs IM) | 54 (< .0001) | 52 (< .0001) | 31 |
| Low Sokal risk | 53 (.0148) | 62 (.0002) | 37 |
| Intermediate Sokal risk | 60 (< .0001) | 50 (.0126) | 33 |
| High Sokal risk | 45 (.0041) | 42 (.0105) | 23 |
| MMR by 5 y, % (*P* vs IM) | 77 (< .0001) | 77 (< .0001) | 60 |
| 5-y freedom from progression to AP/BC, % (*P* vs IM)[a] | 96 (.0403) | 98 (.0028) | 92 |
| 5-y OS, % (*P* vs IM)[a] | 94 (.4881) | 96 (.0266) | 92 |
| Deaths from advanced CML, n (*P* vs IM)[b] | 6 (.0292) | 4 (.0057) | 16 |
| Safety population | n = 279 | n = 277 | n = 280 |
| 5-y CVE rates, n (%) | | | |
| Ischemic heart disease | 11 (4) | 24 (9) | 5 (2) |
| Ischemic cerebrovascular events | 4 (1) | 9 (3) | 1 (< 1) |
| Peripheral artery disease | 7 (3) | 7 (3) | 0 |

[a]Kaplan-Meier estimate, including events after discontinuation. [b]Pts for whom the principal cause of death (during treatment or follow-up) was "study indication" or "unknown" or not reported but subsequent to a documented progression to AP/BC.

**7074 General Poster Session (Board #359), Mon, 1:15 PM-5:00 PM**

**ASCO 2014: High prevalence of FLT-3 ITD mutations in patients (pts) with AML who present with CNS relapse.** *Presenting Author: Simon Abi Aad, MD Anderson Cancer Center, Houston, TX*

**Background:** Despite CR rates of 70% with modern chemotherapeutic regimens, most pts with AML relapse. CNS relapses have become uncommon with the use of high-dose cytarabine based regimens. The features associated with a higher risk of CNS relapse are not defined. **Methods:** We analyzed adults who presented with AML and CNS relapses from 2000 until 2014. CNS leukemia was diagnosed by the presence of blasts in a cytocentrifuge preparation of CSF. Pts with blasts in the CSF together with high numbers of red blood cells (> 5) were not considered to have CNS disease if the blasts were high in the PB. **Results:** Of the 1312 pts with AML treated at our institution, 71 (5%) had CNS disease. Median age was 57 years. CNS involvement was detected after a median of 8 months from the initial diagnosis. 4 pts (6%) had isolated CNS relapse that was followed by systemic relapse after a median of 2 weeks. CNS involvement was detected in the setting of refractory AML in 31 pts (44%). 64 pts (90%) received previous high-dose cytarabine. 54 pts (76%) had neurologic symptoms at time of CNS relapse. CNS imaging was performed in 67 pts (94%): 41 (61%) had abnormal findings by MRI suggestive of CNS disease. 4 pts had zero cells with blasts detected on cytocentrifuge preparation only. None of the 4 pts had circulating blasts and all had abnormal findings on brain MRI suggestive of CNS relapse. 18 pts (25%) were FLT3-ITD mutated. CNS involvement was more commonly observed in young pts with increased WBC, BM blasts, and LDH, with M4/M5 phenotype, and FLT3/ITD mutated (12% versus 5%, p=0.003). Treatment for CNS disease consisted of IT chemotherapy in all pts, whole brain radiation therapy in 14, and spinal radiation in 8. Therapy was successful in clearing all signs of CNS disease in 29 (41%). 19 of the 29 pts (65%) subsequently had additional CNS relapses after a median of 3 months. The 2-year survival rate after CNS relapse was 13%. There was no difference in overall survival among patients with or without CNS disease. **Conclusions:** CNS relapse is a rare occurrence in AML (5%) and is associated with a poor prognosis. A high prevalence of FLT3-ITD mutations was observed in these pts. FLT3 mutational status and LDH level may identify patients with AML who may benefit from CNS prophylaxis.

**7075 General Poster Session (Board #360), Mon, 1:15 PM-5:00 PM**

**Outcomes among patients with isolated myeloid sarcoma: A SEER database analysis.** *Presenting Author: Maryam Movassaghian, Massachusetts General Hospital/Harvard Medical School, Boston, MA*

**Background:** Myeloid sarcoma (MS) is a rare extramedullary presentation of acute myeloid leukemia (AML), which can involve a number of primary locations. MS can exist concurrently with marrow involvement or as an isolated phenomenon. Little is known about outcomes in isolated MS due to its rarity. We performed an analysis of isolated MS using the Survival, Epidemiology, and End Results (SEER) database. **Methods:** Using the SEER database, we identified 339 patients, aged ≥ 15 diagnosed with isolated MS between 1973-2010. Overall survival (OS) was calculated as the time from diagnosis to death or censored at last visit or study cutoff (12/31/2010). OS was compared between non-MS-AML and MS using the log-rank test, and estimated by site of presentation using the Kaplan and Meier method. Involved sites were categorized as: head/neck, gastrointestinal (GI) mucosa, chest/abdomen, pelvis/genitourinary (GU), lymphatics/spleen, soft tissue, skin, bones, nervous system, eyes/gonads. **Results:** Median age at diagnosis was 64 for patients with MS and 67 for patients with AML. The 30-day mortality rate was lower for patients with MS compared to AML (0.11 vs. 0.23, p<0.0001). OS was significantly higher for MS than for AML (3-year: 0.319 vs. 0.172, p<0.0001). OS varied by the site of involvement. Data for primary sites of disease in the Pelvis/GU, GI mucosa, and eyes/gonads suggest better survival at 6 months compared to involvement of the nervous system, lymphatics/spleen, or soft tissue (Table). **Conclusions:** Population-based survival for patients with isolated MS appears to be superior to AML. MS outcomes vary depending on site of involvement; patients with disease in the pelvis/GU, GI mucosa, and in the eyes/gonads, may have relatively better survival.

| | Number | Median Age | Male (%) | OS at 6 Months |
|---|---|---|---|---|
| Overall | | | | |
| Non MS AML | 49,039 | 67 | 54 | 0.441 [0.437-0.446] |
| MS | 339 | 64 | 55 | 0.57 [0.51-0.62] |
| Disease Site | | | | |
| Head/Neck | 40 | 64 | 53 | 0.64 [0.47-0.77] |
| GI Mucosa | 31 | 50 | 65 | 0.74 [0.55-0.86] |
| Chest/Abdomen | 29 | 58 | 52 | 0.62 [0.42-0.77] |
| Pelvis/GU | 21 | 55 | 24 | 0.95 [0.71-0.99] |
| Lymphatics/Spleen | 45 | 65 | 56 | 0.40 [0.26-0.54] |
| Soft Tissue | 93 | 66 | 53 | 0.45 [0.34-0.55] |
| Skin | 32 | 74 | 66 | 0.61 [0.41-0.76] |
| Bone | 17 | 56 | 47 | 0.53 [0.28-0.73] |
| Nervous System | 11 | 69 | 45 | 0.24 [0.04-0.53] |
| Eyes/Gonads | 20 | 56 | 85 | 0.80 [0.56-0.92] |

**7076 General Poster Session (Board #361), Mon, 1:15 PM-5:00 PM**

**Role of wnt/ß-catenin pathway in myeloid neoplasms with 5q deletion: A new therapeutic target.** *Presenting Author: Nupur Mittal, University of Illinois at Chicago, Chicago, IL*

**Background:** 5q deletion (del 5q) is a recurring cytogenetic abnormality present in around 10% of de-novo and 40% of therapy related myelodysplastic syndrome (MDS)/ Acute myeloid leukemia( AML). These patients often are relatively resistant to conventional therapies and have unfavourable outcome. Del 5q is associated with haplo-insufficiency of APC gene in hematopoietic stem cells (HSCs) which leads to MDS like disease in mice (Blood 2010). APC regulates the function of HSCs largely through $\beta$-catenin dependent mechanisms ( Blood 2013). We have shown previously that Indomethacin induced $\beta$-catenin inhibition leads to growth suppression in human myeloid leukemia cells with del 5q (UoCM1) but has non-specific targets in addition to $\beta$-catenin. **Methods:** Our objective is to show effects of blocking Wnt/$\beta$-catenin pathway by specific $\beta$-catenin inhibition in del 5q myeloid leukemia. Lentiviral particles expressing a control empty backbone or $\beta$-catenin targeting inhibitory shRNA were transduced into UoCM1 and REH (Leukemia cell line with no del 5q) achieving specific $\beta$-catenin knockdown. Growth , proliferation and apoptosis of the transduced cells was assessed by flow cytometry and In vitro colony forming assay. **Results:** Western Blot confirms higher $\beta$-catenin expression in UoCM1 vs REH line. UoCM1 cells transduced with $\beta$-catenin shRNA showed 60% growth inhibition compared to control vector. In contrast, REH demonstrated comparable growth in control and $\beta$-catenin shRNA transduced cells. There was significant decrease in the fractions of cells in S and G2/M phase and increase in apoptosis ($p < 0.05$) in UoCM1 cells with $\beta$-catenin inhibition compared to control. REH showed no difference in distribution in cell cycle and similar frequency of apoptosis in $\beta$-catenin inhibited and control cells. Decrease in colony formation was observed in UoCM1 cells with $\beta$-catenin inhibition. **Conclusions:** 5q del in myeloid leukemia cell line leads to up-regulation of $\beta$-catenin. Blockade of Wnt pathway by specific $\beta$-catenin inhibition suppresses cell growth and induces apoptosis in a human myeloid leukemia cell line with 5q del. This discovery paves the way for new therapeutic strategies targeting $\beta$-catenin and improving survival in 5q del AML/MDS.

**7077 General Poster Session (Board #362), Mon, 1:15 PM-5:00 PM**

**Correlation between peripheral blood and bone marrow regarding FLT3 ITD and NPM1 mutational status in patients with AML.** *Presenting Author: Weigang Tong, Department of Medicine/Division of Hematology, University of Washington, Seattle, WA*

**Background:** Internal tandem duplications (ITD) of the FLT3 gene and mutations in the NPM1 gene are among the most common genetic aberrations in AML. Patients with these abnormalities frequently present with high circulating blast counts. Hence we hypothesized that the diagnosis of FLT3 ITD, or NPM1, positive AML can be made using peripheral blood (PB) without need for a bone marrow (BM), as has been shown to generally be the case with routine cytogenetic studies (Weinkauff et al Am J Clin Pathol 1999;111:733-740). Here we examined whether the same is true for NPM and FLT3. **Methods:** We reviewed 1016 AML ($\geq$ 20% blasts) patients that were treated at SCCA/FHCRC from January 2008 to December 2013. We identified 30 patients in whom FLT3 ITD and 18 patients in whom NPM1 mutation status was performed in both PB and BM within 3 days of each other. We compared the clinical characteristics of these patients, as well as the correlation for FLT3 ITD allelic ratio in both PB and BM using Spearman correlation analysis. **Results:** For the patients with FLT3 ITD data, the median WBC count was 13,090 (range 170-117,470) and median absolute blood blasts were 1,535 (range 0-113,060) while these values were 21,000 (range 1,190-97,000) and 5,200 (range 230-62,000) respectively for the patients with NPM data. Eight of the 30 FLT 3 patients were positive in both PB and BM, 21 were negative in both, only one patient (WBC 19,800) was negative in PB and positive in marrow (low level, $< 0.01$). There were two patients with very low WBC counts (0.4 and 0.17) and no circulating blasts, but FLT3 ITD was detected in both PB and BM. Allelic ratios were highly correlated in PB and BM correlation coefficient 0.92 (95% CI 0.82 to 0.96; $p < 0.0001$). While there was complete concordance between PB and BM with respect to NPM1 mutational status, only 4 of 18 patients were positive for NPM1 mutation as detected in both PB and BM. **Conclusions:** Within the limits of our patient numbers, these data suggest that in patients with AML, peripheral blood can often serve as a substitute for bone marrow in evaluating FLT3 ITD and NPM1 mutational status, perhaps even in patients with lower white cell counts and blast percentage.

**7078 General Poster Session (Board #363), Mon, 1:15 PM-5:00 PM**

**Longer-term follow up of a phase 1 study of ponatinib in patients (pts) with Philadelphia chromosome-positive (Ph+) leukemias.** *Presenting Author: Moshe Talpaz, Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI*

**Background:** Ponatinib is a potent oral pan–BCR-ABL TKI that is active against native and mutated forms of BCR-ABL. The safety and anti-leukemic activity of ponatinib in pts with chronic myeloid leukemia (CML) or Ph+ acute lymphoblastic leukemia were evaluated in a phase I clinical trial. **Methods:** Pts (N=81) with resistant/refractory hematologic malignancies were enrolled in this ongoing, open-label, dose escalation, phase I study. Ponatinib was dosed once daily (2–60 mg). 65 pts had Ph+ leukemia and are included in this analysis (data as of 15 Oct 2013). Median follow-up was 33 (0.5–57) mos. NCT00660920. **Results:** The median age of pts was 55 yrs; median time since diagnosis was 6.5 yrs. Pts were heavily pretreated (94% had received $\geq$2 prior TKIs, 62% $\geq$3). 65% had baseline BCR-ABL mutations (29% with T315I). 38% (58% chronic phase [CP] CML) of pts remained on study. Adverse events (AEs) and progression were the most common reasons for discontinuation in Ph+ pts (20% and 17%, respectively. The most common treatment-emergent AEs were rash (52%), fatigue (52%), abdominal pain (51%), headache (48%), arthralgia (46%). Treatment-emergent vascular occlusive events were observed in 23% (serious events) and 37% (all events) of pts, including cardiovascular, peripheral vascular, cerebrovascular, and venous thrombotic events [serious (all)] in 15% (23%), 5% (9%), 5% (8%), and 0% (5%). Significant anti-leukemic activity was observed; among CP-CML pts, major cytogenetic response (MCyR), complete cytogenetic response (CCyR), and major molecular response (MMR) rates were 72%, 65%, and 51%, respectively; 75% of pts with MCyR, 69% with CCyR, and 53% with MMR are estimated (Kaplan-Meier [KM]) to maintain response for at least 3 yrs (4 yr KM estimates: 75% MCyR, 53% MMR). Of 28 CP-CML pts with CCyR, 23 remained on study (17 with continuous CCyR); of 22 pts with MMR, 20 remained on study (12 with continuous MMR). **Conclusions:** Substantial and durable responses were observed with ponatinib in heavily pretreated CP-CML pts. Vascular occlusive events were observed. Risk and benefit considerations should be evaluated when utilizing ponatinib in this pt population. Clinical trial information: NCT00660920.

**7079 General Poster Session (Board #364), Mon, 1:15 PM-5:00 PM**

**Comparison of angiopoietin-1 and -2 and VEGF expression in bone marrow and peripheral blood leukemic cells of patients with acute promyelocytic leukemia.** *Presenting Author: Mariana Scaranti, Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil*

**Background:** Angiogenesis is a well-known hallmark of solid cancer, but its relevance in acute leukemia genesis is controversial. Kini et al. (2001) reported that VEGF is secreted by acute promyelocytic leukemia (APL) cells, which also express VEGF receptor 2 (VEGFR2, or KDR). Moreover, arsenic trioxide, which is the most effective agent in the treatment of refractory APL, was shown to have anti-angiogenesis effect in vitro and to reduce microvascular density in bone marrow cells of APL-treated patients (Alimoghaddam et al., 2006). Considering that VEGF has paracrine and autocrine effects and the microenvironment has an important role in VEGF signaling, we decided to determine whether circulating and bone marrow APL cells differ regarding pro-angiogenic factors expression. **Methods:** We assessed VEGF, angiopoietin-1 (ANG1) and angiopoietin-2 (ANG2) gene expression through quantitative PCR (RT-qPCR) in peripheral blood (PB; n=14) and bone marrow (BM; n=24) cells of PML-RAR$\alpha$ positive APL patients. BM (n=7) and PB (n=3) samples from healthy donors were used as controls. Statistical analysis was performed using STATA 12. The Student t-test was used to compare means between two groups and the Kruskal-Wallis test followed by Dunn's post-test to compare three or more groups. **Results:** ANG1 presented lower expression in BM when compared to PB samples of APL patients (BM = 10.6 $\pm$ 0.97, PB = 7.3 $\pm$ 1.06, p=0.03). ANG2 expression was not detected in all samples. VEGF expression was not differentially expressed between PB and BM of control and APL samples. VEGF and ANG1 gene expression did not show any differences when we compared PB and BM of APL patients and healthy donors. **Conclusions:** ANG1 has a lower expression in BM of APL patients when compared to PB.This could be of importance for leukemia spread from BM to PB, since ANG1 is described as a regulator of endothelial monolayer integrity.

**7080 General Poster Session (Board #365), Mon, 1:15 PM-5:00 PM**

**Central nervous system relapse in adults with acute lymphoblastic leukemia.** *Presenting Author: Muhamed Baljevic, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Recurrence of acute lymphoblastic leukemia (ALL) in the central nervous system (CNS) in adults is associated with poor outcome. Few reports have analyzed the impact of contemporary ALL regimens on outcome of patients (pts) with CNS recurrence. This report provides single institution experience in adults with ALL and CNS relapse. **Methods:** The records of 555 (89%) consecutive pts with newly diagnosed ALL with no CNS disease treated at MDACC between 2001 and 2013 were reviewed. Pts were treated with HCVAD ± tyrosine kinase inhibitors (TKIs) and/or Rituximab (R) or with augmented BFM (AUG-BFM). Among 519 (94%) pts who achieved complete remission (CR), 33 (22%) had a CNS relapse: 8 were treated with HCVAD+R, 11 with HCVAD+TKI, 2 with HCVAD+R+TKI, 1 with HCVAD+Nelarabine, 2 with HCVAD and 9 with AUG-BFM. **Results:** Three groups of pts were identified: (A) with isolated CNS relapse (n=17), (B) with CNS relapse after bone marrow (BM) relapse (n=7), and (C) with simultaneous CNS and BM relapse (n=9). The median age (range) at diagnosis was 39 (15-75) yrs. Only LDH 1463 (335-33811) was significantly different compared to pts without CNS recurrence (p=0.05). The median CR duration prior to CNS recurrence was 15.8 months (mo) (2.5–92.6). Intrathecal chemotherapy was effective in achieving CNS CR in 26 (79%) pts. The median overall survival (OS) was statistically different among the 3 groups: median for group A 55.9 mo, 100% alive at 1-year and 30% at 4-years; group B median 25.6 mo, 78% alive at 1-year and 28% at 4-years; and group C median 16.6 mo, 86% alive at 1-year and 0% at 4-years (p=0.01). Entire cohort OS was 41.3 mo; 91% alive at 1-year and 38% at 4-years. Outcome has improved substantially compared to period before yr 2000, when median OS was 6 mo, with 38% alive at 1-year and 6% at 4-years (Surapaneni et al. Cancer 2002). **Conclusions:** Adults with CNS ALL recurrence have a poor prognosis despite effective treatment, particularly those with combined systemic and CNS relapses. However, outcome of these pts has improved significantly in the last decade. Still, effective CNS prophylaxis remains the single best approach for treating patients with CNS leukemia.

**7081 General Poster Session (Board #366), Mon, 1:15 PM-5:00 PM**

**Ponatinib (PON) in patients (pts) with Philadelphia chromosome-positive (Ph+) leukemias resistant or intolerant to dasatinib or nilotinib, or with the T315I mutation: Longer-term follow up of the PACE trial.** *Presenting Author: Hagop M. Kantarjian, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** PON is a potent, oral, pan-BCR-ABL inhibitor with activity against native and mutant forms of BCR-ABL, including the resistant T315I mutant. The efficacy and safety of PON (45 mg QD) were evaluated in the phase 2 PACE trial. **Methods:** 449 pts resistant or intolerant (R/I) to dasatinib or nilotinib or with the T315I mutation were enrolled. Data are as of 3 Sept 2013; median follow-up 24 (0.1-35) mo. NCT01207440. **Results:** Pts were heavily pretreated: 58% received ≥3 TKIs. 42% remained on study (55% CP-CML). The most common reasons for discontinuation: PD (21%) and AEs (14%, most common was thrombocytopenia, 4%). Table shows response rates at any time. In CP-CML, 89% pts maintained MCyR for at least 2 yr; progression-free survival (PFS) and overall survival (OS) at 2 yr were 67% and 86%. For AP-CML, BP-CML, and Ph+ ALL, OS at 2 yr was 72%, 18%, and 21%, respectively. Most common treatment-emergent AEs (≥30%) were thrombocytopenia (43%), rash (40%), abdominal pain (40%), headache (36%), constipation (36%), dry skin (36%). Pancreatitis and pneumonia were the most common serious AEs (SAEs; both 6%). Vascular occlusive AEs [SAEs] were reported as follows: overall 20% [14%], including cardiovascular 9% [6%], cerebrovascular 6% [4%], peripheral vascular 6% [4%] (collectively arterial thrombotic events, ATEs), venous thromboembolic 5% [3%]. Higher dose intensity, older age, and CV risk factors were associated with a higher likelihood of an ATE; pts with and without CV risk factors experienced these events. OS at 2 years was not reduced in pts with an ATE (73%) vs those without (69%); MCyR in CP-CML pts with vs without ATE was 70% vs 51%. **Conclusions:** PON has substantial clinical activity in heavily pretreated pts with Ph+ leukemias. PON is an important treatment option for pts in whom the need and benefit outweigh the risk. Clinical trial information: NCT01207440.

| | R/I, n (%) | T315I, n (%) | Total, n (%) |
|---|---|---|---|
| **CP-CML** | N=203 | N=64 | N=267 |
| **MCyR** | 113 (56) | 46 (72) | 159 (60) |
| **CCyR** | 98 (48) | 45 (70) | 143 (54) |
| **MMR** | 63 (31) | 37 (58) | 100 (38) |
| **AP-CML** | N=65 | N=18 | N=83 |
| **MaHR** | 40 (62) | 11 (61) | 51 (61) |
| **BP-CML** | N=38 | N=24 | N=62 |
| **MaHR** | 12 (32) | 7 (29) | 19 (31) |
| **Ph+ ALL** | N=10 | N=22 | N=32 |
| **MaHR** | 5 (50) | 8 (36) | 13 (41) |

**7082 General Poster Session (Board #367), Mon, 1:15 PM-5:00 PM**

**Phase 1 study of the angiopoietin 1/2 neutralizing peptibody, trebananib, in acute myeloid leukemia.** *Presenting Author: Eunice S. Wang, Roswell Park Cancer Institute, Buffalo, NY*

**Background:** Angiopoietins (Ang-1/2), pro-angiogenic factors binding to the Tie2 receptor on endothelial cells, have been implicated in the pathogenesis of acute myeloid leukemia (AML). Trebananib is a first-in-class neutralizing peptibody that potently inhibits Ang-1/2 by sequestering these factors and preventing their interaction with Tie2. **Methods:** We performed a phase 1b trial evaluating the safety, tolerability, pharmacokinetics (PK) and biologic effects of trebananib in AML patients (pts). Drug was administered at 2 doses (15 and 30 mg/kg) via weekly IV infusion over 1 hour alone (arm A) or in combination with low dose cytarabine (arm B). PK samples were collected at end of infusion (EOI), and 1-3, 4-6, 72, and 168 hrs after EOI on days 1 and 22. Plasma angiogenic factors were assessed by multiplex flow cytometry prior to first dose, on cycle 1 day 29, and at the end of study. **Results:** Twenty-four pts were enrolled. Median age was 74 years (range 29-84). Sixteen (67%) were male. Six had de novo, 13 had refractory, and 5 had relapsed AML. Three pts had undergone prior transplantation. Drug was generally well tolerated. Dose-limiting toxicities included mucositis (1, arm A, 15 mg/kg) and ataxia (1, arm B, 30 mg/kg). The most common AEs were fatigue, dyspnea, nausea, asthenia, anorexia, and edema. Serious AEs included thrombocytopenia (2), nephrolithiasis (1), and ataxia (1). Using a population PK approach, a 3-compartment model adequately characterized trebananib PK, with a mean clearance (CL) and plasma volume (V) estimated to be 0.09 L/hr and 2.74 L/kg, respectively. A trend existed between body surface area (BSA) and CL and V, suggesting that BSA in part explains the inter-patient variability in pts. No neutralizing antibodies were found. Seven pts had elevated plasma Ang-2 levels of unknown significance. Other factors (VEGF-A/C/D, IL-8, G-CSF, HGF, FGF-1/2, PlGF) were not altered. One pt (15 mg/kg) had a partial response, and 4 pts had stable disease over >1 cycle (2 on each arm, 3 receiving 30 mg/kg). **Conclusions:** Trebananib was well tolerated in AML pts alone and in combination with low dose cytarabine. Drug PK was similar to solid tumor pts. Limited clinical efficacy was seen, supporting novel combination strategies. Clinical trial information: NCT01555268, NCI-2011-02979.

**7083 General Poster Session (Board #368), Mon, 1:15 PM-5:00 PM**

**Obinutuzumab (GA101) 1,000 mg versus 2,000 mg in patients with chronic lymphocytic leukemia (CLL): Results of the phase II GAGE (GAO4768g) trial.** *Presenting Author: Joseph M. Flynn, The Ohio State University, Columbus, OH*

**Background:** Early phase 1/2 trials with GA101 in CLL demonstrated single-agent activity with suggestion of a dose response. GAGE (NCT01414205) is a multicenter, randomized study that evaluated GA101 at 2 doses in patients (pts) with symptomatic, untreated CLL. **Methods:** Randomization of 80 pts with intact organ function and ECOG PS <3 were stratified based on Rai stage (1–2 vs 3–4) and tumor mass (single lesion by CT scan, <5 cm vs ≥5 cm): GA101 1,000 mg (100 mg IV d1, 900 mg d2, 1000 mg d8, d15 of cycle 1; 1000 mg d1 of cycles 2–8) or 2000 mg (100 mg IV d1, 900 mg d2, 1,000 mg d3, 2,000 mg d8, d15 of cycle 1; 2,000 mg d1 of cycles 2–8). Each cycle was 21 days. ORR was assessed at 2 months post-therapy according to the International Workshop on CLL (iwCLL) criteria. Pts had similar pre-treatment demographics in the 2 arms. Median age was 67 (34–91) years, 36% women, 41% Rai stage 3-4, 29% with tumor masses ≥5 cm, 54% unmutated IGHV, and 10% del(17p13). Median follow-up was 11 months. **Results:** Key efficacy and safety results are shown in table below. Most frequent adverse event (AE) was infusion-related reactions (IRRs). No Grade (Gr) 3/4 IRRs occurred after cycle 1. A death (myocardial infarction) occurred after cycle 5, judged by site investigator as unrelated to GA101. **Conclusions:** These results demonstrated single-agent efficacy of GA101 at 1,000- and 2,000-mg doses, with a difference in ORR between the 2 arms (*P* = .08). No new safety signals were observed. Incidences of Gr 3/4 AEs were similar in each arm, except for IRRs. Further study is warranted to determine durability of response and long-term side effects of GA101. Clinical trial information: NCT01414205.

| **Total N = 80** | **1,000 mg (n = 41)** | | **2,000 mg (n = 39)** |
|---|---|---|---|
| **ORR[a], n (%)** | 20 (49) | | 26 (67) |
| ***P* value** | | .08[b] | |
| **CR/CRi, n (%)** | 2 (5) | | 8 (21) |
| **SD, n (%)** | 11 (27) | | 9 (23) |
| **PD, n (%)** | 3 (7) | | 0 (0) |
| **Unable to evaluate/missing[c], n (%)** | 7 (17) | | 4 (10) |
| **Gr 3-4 AE, %** | | | |
| **IRR** | 23 | | 11 |
| **Neutropenia** | 33 | | 34 |
| **Infections** | 3 | | 5 |

[a]ORR based on investigator-reported end-of-treatment response, which includes CT scan performed 51+ days from last GA101 dose [b]*P* value is 2-sided, based on stratified Cochran-Mantel-Haenszel test on ORR [c]Pts classified as missing if no post-baseline response assessments were available or all post-baseline response assessment were performed <51 days from last GA101 dose.

**7084 General Poster Session (Board #369), Mon, 1:15 PM-5:00 PM**

**Clinical impact of dose modification and dose intensity on response to ponatinib (PON) in patients (pts) with Philadelphia chromosome-positive (Ph+) leukemias.** *Presenting Author: Andreas Hochhaus, Universitätsklinikum Jena, Jena, Germany*

**Background:** PON is a potent oral pan–BCR-ABL tyrosine kinase inhibitor with clinical activity in pretreated pts with Ph+ leukemias. Dose modification of PON may be used to avoid or manage adverse events (AEs). This post hoc analysis assessed the clinical impact of dose modification and dose intensity on outcomes of pts in the phase 2 PACE trial. **Methods:** PON starting dose was 45 mg QD. Dose reduction: any reduction below 45 mg/d; dose interruption: treatment held for ≥3 consecutive days. Efficacy analyses were performed on CP-CML pts (N=267). Analysis of arterial thrombotic events (ATEs) included all pts (CP/BP/AP-CML, Ph+ ALL; N=449). Data are as of 3 Sept 2013; median follow-up was 24 (0.1-35) mo for all pts. **Results:** 78% of CP-CML pts had dose modification within the first 12 mo (82% at any time). Responses in pts with/without modification were comparable (Table). Of 149 responders, 87 (58%) achieved MCyR at 45 mg/d, 46 (31%) at 30 mg/d, 16 (11%) at 15 mg/d. Most pts who had a dose reduction after achieving a response maintained that response: MCyR (97%), complete cytogenetic response (CCyR; 96%), major molecular response (MMR; 92%). Among pts with a dose reduction lasting ≥6 mo after achieving response at a higher dose, 100% maintained MCyR (96%, CCyR; 93%, MMR). While dose intensity was the most significant predictor of MCyR by 12 mo (multivariate analysis [MVA]), substantial responses occurred at lower doses; estimated response rates were ~75% at 45 mg, ~60% at 30 mg, and ~30% at 15 mg. ATEs occurred in 17% of pts; each 15 mg/d reduction in avg daily dose is predicted to lead to ~40% reduction in risk of ATE (MVA). 2 yr overall survival was similar for CP-CML pts who had dose modifications (86%) v those who did not (86%) and for pts who had ATE (85%) v those who did not (87%). Of pts with ATEs, 46% had dose modifications. **Conclusions:** Pts on PON who undergo dose modification may still respond to treatment and dose modification may be an effective management tool. Careful consideration of the potential benefits and risks of PON should guide treatment decisions. Clinical trial information: NCT01207440.

| CP-CML | n | MCyR[b] % | CCyR[b] % | MMR[a] % |
|---|---|---|---|---|
| Dose modification[a] | 218 | 58 | 47 | 38 |
| No dose modification | 49 | 47 | 45 | 35 |

a, anytime; b, by 12 mo.

**7085 General Poster Session (Board #370), Mon, 1:15 PM-5:00 PM**

**Trends in first-line TKI prescribing preferences (PPrefs) among U.S.-based hematology-oncology physicians (HOPs) for patients with chronic phase chronic myelogenous leukemia (CP-CML).** *Presenting Author: Neil P. Shah, University of California, San Francisco, San Francisco, CA*

**Background:** Imatinib (12/2002), nilotinib (6/2010) and dasatinib (10/2010) are all indicated for first-line treatment of patients (pts) with CP-CML. PPrefs may be influenced by multiple considerations such as assessment of the risk profile of an individual patient's disease, randomized efficacy data, cross trial comparisons of efficacy and toxicity, associated co-morbid conditions, ease of access to and administration/management of specific agents, cumulative pt out of pocket costs, and physician familiarity with available agents. **Methods:** Since 2011 we have used a live, extensively validated research tool to assess PPrefs of U.S.-based HOPs related to first-line TKI selection across several risk-based scenarios in pts with a new diagnosis of CP-CML. Lower risk scenario: 2011/2012 - 59 year old male, spleen palpable 7 cm below the left costal margin (LCM); white blood cell count (WBC) 75,000 with 82% mature polys; 3% basophils, no blasts; Hemoglobin (Hgb) 12.0 gms; Platelets (Plts) 430K. 2013: Identical scenario and labs except age of 63 and spleen palpable 5 cm below LCM. Higher-risk scenarios: 2012: Male, age 59, spleen 11 cm below LCM; WBC 96,000 with 3% blasts, 5% basophils; Hgb 11.1 gms; Plts 935K. 2013: Identical scenario except age of 63, basophils 9% and platelets 965K. **Results:** TKI PPrefs by year and scenario shown in Table. **Conclusions:** PPrefs among US-based HOPs for pts presenting with a new diagnosis of CP-CML appear to be progressively shifting toward use of FDA indicated second generation TKIs as initial therapy. Blood counts and spleen size at presentation appear to impact HOP PPrefs. In 2013, the majority of PPrefs for the higher risk scenario are for second generation agents and there is an equal split in the lower risk population. Among respondents indicating a PPref for a second generation agent as initial therapy, a trend over several years toward increasing PPref for dasatinib is evident.

| | Lower-risk scenario | | | Higher-risk scenario | |
|---|---|---|---|---|---|
| First-line preference | 2011 N=259 | 2012* N=358 | 2013* N=366 | 2012 N=366 | 2013 N=368 |
| Imatinib | 57% | 53% | 48% | 37% | 31% |
| Dasatinib | 17% | 23% | 30% | 31% | 40% |
| Nilotinib | 26% | 23% | 19% | 32% | 26% |
| Other | 0% | 2% | 2% | 0% | 3% |

*May not equal 100% due to rounding.

**7086 General Poster Session (Board #371), Mon, 1:15 PM-5:00 PM**

**Standardized costs and outcome in children treated with gemtuzumab on the AAML0531 trial: A report from the Children's Oncology Group.** *Presenting Author: Richard Aplenc, The Children's Hospital of Philadelphia, Philadelphia, PA*

**Background:** NCI-funded cooperative group oncology group trials report clinical outcomes but do not report cost estimates. The Children's Oncology Group trial AAML0531 randomized 1,022 de novo AML patients to standard chemotherapy ± gemtuzumab (GMTZ). As previously reported, GMTZ improved event-free survival but did not improve overall survival. The Pediatric Health Information Systems (PHIS) database contains standardized inpatient cost data (SC) on children treated at 43 freestanding pediatric hospitals in the United States. We hypothesized that SC would be similar for both treatment arms during on-protocol therapy but lower in the GMTZ arm during all follow up time (defined as time from on-protocol to last COG follow-up). **Methods:** Data from AAML0531 and PHIS were probabilistically merged. PHIS SC were defined by hospital costs multiplied by the ratio of cost to charges and adjusted by consumer price index and geographical region. All available SC were extracted for all merged patients and compared with bivariate statistics. **Results:** Merged patients (n = 373) were representative of the overall trial population. Follow-up time was marginally longer in the GMTZ arm, 223 days vs 238 days, p = 0.1. The overall median SC was $309,785 ($1,943/day) on-protocol and $467,767 ($1,707/day) for all follow-up time. The per day SC did not differ by study arm on-protocol but per day SC were significantly higher in the non-GTMZ arm, $1,877/day vs $1,648/day over all follow-up time, p = 0.03. Table 1 summarizes departmental SC; Room and Board (RB) comprises approximately 50-60% of all SC. **Conclusions:** Merging of PHIS data with COG data enables estimation of regimen specific SC. GMTZ does not increase SC during protocol therapy but is associated with lower per day SC over all follow-up time. Further work is needed to increase the number of patients with SC data, to examine SC variability, and define drivers of SC. Clinical trial information: NCT00372593.

| Department | Median on protocol | Percent* | Median overall | Percent* |
|---|---|---|---|---|
| Pharmacy | 60,866 | 19.6% | 99,881 | 21% |
| Supplies | 3,419 | 1.1% | 5,101 | 1.1% |
| Laboratory | 34,460 | 11.1% | 54,786 | 11.7% |
| Radiology | 4,523 | 1.5% | 7,146 | 1.5% |
| Clinical | 8,282 | 2.7% | 19,142 | 4% |
| RB | 181,774 | 58.7% | 241,794 | 52% |

*Percentage of overall median SC.

**7087 General Poster Session (Board #372), Mon, 1:15 PM-5:00 PM**

**Distinct biomarkers as prognostic in chronic lymphocytic leukemia patients treated with alvocidib and lenalidomide as single agents or combination regimens thereof.** *Presenting Author: William E. Pierceall, Eutropics Pharmaceuticals, Cambridge, MA*

**Background:** Chronic lymphocytic leukemia (CLL) patient outcomes may benefit from targeting therapies alone or in combination to individuals with favorable molecular profiles. Whether such personalized medicine approaches are best tailored to patients treated with single agent therapies or regimens using those agents in combination is an underexplored question. Here, we assessed mitochondrial apoptosis signaling in CLL patients treated with lenalidomide, alvocidib, or lenalidomide + alvocidib. **Methods:** Pretreatment blood mononuclear cell (PBMC) specimens were assessed measuring mitochondrial outer membrane permeabilization following incubation with BH3 peptides as a surrogate for Bcl-2 family proteins function. The study comprised 106 patients: 62 alvocidib-treated patients, 20 lenalidomide-treated patients, and 24 patients treated with combinational lenalidomide + alvocidib. **Results:** In alvocidib-treated patients assessment of biomarker and clinical response association, Bim AUC=.73 (p=.0004) and Hrk (indicating Bcl-xL-dependence) AUC=.73 (p=.0002). Hrk benefitted from trisomy12 inclusion (AUC=.83; p<.0001). In single agent lenalidomide-treated patients, no biomarkers were associated with response, however, priming of Mcl-1, determined by response to the Noxa peptide, was associated with progression-free survival (p=.032). In lenalidomide + alvocidib-treated patients, the prognostic significance was different from either of the two agents independently as Puma (pan-antiapoptoic modulator of Mcl-1, Bcl-xL, and Bcl-2) was associated with clinical response (AUC=.73; P=.027) that improved with addition of bulky adenopathy (AUC=0.84 p=.0063). **Conclusions:** Alvocidib (cyclin-dependent kinase inhibition) and lenalidomide (immunomodulation) have distinct mechanisms of action and offer separate molecular profiles associated with clinical outcomes. Although the importance of Bcl-2 family regulated apoptosis is consistent, biomarker associated outcomes in combination regimen patients differ from those associated with single agent therapies.

**7088 General Poster Session (Board #373), Mon, 1:15 PM-5:00 PM**

**Hyperdiploidy in AML: Outcomes of acute myelogenous leukemia (AML) patients (pts) with a hyperdiploid karyotype.** *Presenting Author: Aditya Shetty, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Hyperdiploidy with greater than 49 chromosomes is an infrequent phenomenon in AML, with a reported incidence of less than 2%. While autosomal loss is known to have poor prognosis, the outcome of patients with hyperdiploid karyotype (HK) is unclear. **Methods:** We reviewed data of 1313 pts with AML treated at our institution between 2003 and 2013. **Results:** Hyperdiploidy was identified in 41 pts (3%). Baseline characteristics in pts with HK at initial diagnosis included: a median age of 68 years (range, 18-81) and a median white blood cell count of 2.1 (range, 0.4-22.4). Median chromosome number in the HK group was 55 (range, 49-104). The most common chromosomes gained included trisomy 8 in 22 pts (54%), trisomy 22 in 16 pts (40%) and trisomy 21 in 13 pts (33%). A monosomal karyotype (MK) was noted in 23 pts (56%) in the HK group. Structural abnormalities defined as intermediate risk by European LeukemiaNet classification were noted in 11 pts (27%). Hyperdiploidy as the only chromosomal aberrations was noted in 6 pts (15%). Thirteen pts (32%) received high-dose ara-C-based induction and 9 pts (22%) received a clofarabine- based induction. 20 pts (49%) achieved a complete remission. The median CR duration was 5 months (range, 0-81 months). 35 pts (85%) had died, with a median overall survival of 7 months (range, 1-84 months) compared with 10 months (range, 0-120 months) for a control group of all AML pts (non-M3, non-cbf) (p=0.16), 6 months (range, 0-115 months) for AML pts with complex, non-hyperdiploid cytogenetics (p=.100) and 15 months (range, 0-120 months) for AML pts with diploid cytogenetics (p=.001). In subgroup analysis limited by small pt numbers, pts with hyperdiploidy alone had median overall survival of 12 months (range, 1-43 months), compared with 6 months (range, 1-51 months) and 9 months (range, 1-84 months) in the structural abnormalities subgroup and the monosomal subgroup, respectively (p=.237). **Conclusions:** Hyperdiploidy is a rare abnormality in AML with trisomy 8, 22 and 21 being the most commonly gained chromosomes. HK pts had a significantly worse outcome compared to a diploid cohort and a minor trend towards better outcomes compared to AML pts with complex cytogenetics.

**7089 General Poster Session (Board #374), Mon, 1:15 PM-5:00 PM**

**European leukemia net (ELN) 2013 response categories: Impact on clinical outcomes across four frontline tyrosine kinase inhibitor (TKI) modalities in chronic phase CML.** *Presenting Author: Preetesh Jain, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** In 2013 ELN proposed new response categories applicable to TKI frontline therapy for CML. We analyzed the outcome by ELN category of patients (pts) on different TKI as frontline therapy for CML-CP. **Methods:** 487 pts treated by TKI from 2000-2013 were analyzed. Pts received imatinib 400 mg/d (IM400; n=70), imatinib 800 mg/d (IM800; n=201), dasatinib (n=107) or nilotinib (n=109) in consecutive or parallel trials. Median follow-up was 99 months (mo). Pts were followed uniformly with cytogenetics and PCR every 3 mo for the first 12 mo, then every 6 mo. **Results:** Median follow-up was 144 mo for IM400, 119 mo for IM800, 54 mo for dasatinib and 49 mo for nilotinib. Cumulative CCyR rates were 85%, 90%, 98% and 93%, and MMR rates were 84%, 88%, 91%, and 94%, respectively. ITT analysis indicated the proportion of pts falling into optimal, warning and failure categories were 89%, 6%, 6% at 3 mo, 78%, 17% and 6% at 6 mo, and at 12 mo 75%, 13% and 13%, respectively. Rates of optimal response at 3 mo were 75% for IM400, 90% for IM800, 89% for dasatinib and 97% for nilotinib; 41%, 80%, 86% and 89% at 6 mo; and 47%, 77%, 76% and 87% at 12 mo, respectively. Pts with optimal response had longer EFS, FFS, TFS and OS compared to those with warning and failure at all-time points. Within each response category, type of TKI did not affect long-term outcome. (Table) **Conclusions:** Imatinib 400 induces optimal response in fewer pts at all times. Optimal responses predict for better outcomes irrespective of the TKI modality.

**Event-free and overall survival probabilities with different TKI modalities stratified by ELN response.**

| % 5-year EFS | | IM400 | IM800 | Dasatinib | Nilotinib | Overall |
|---|---|---|---|---|---|---|
| Response category | | N=70 | N=201 | N=107 | N=109 | N=487 |
| 3 mo | Optimal | 81 | 89 | 95 | 84 | 88 |
| | Warning | 37 | 64 | 100 | 100 | 53 |
| | Failure | 57 | 19 | 83 | 67 | 49 |
| 6 mo | Optimal | 96 | 91 | 97 | 90 | 93 |
| | Warning | 67 | 79 | 61 | 57 | 70 |
| | Failure | 36 | 19 | 100 | 50 | 36 |
| 12 mo | Optimal | 91 | 94 | 96 | 90 | 93 |
| | Warning | 100 | 81 | 86 | 80 | 85 |
| | Failure | 50 | 52 | 60 | 100 | 54 |
| % 5-year OS | | | | | | |
| Response category | | IM400 | IM800 | Dasatinib | Nilotinib | Overall |
| 3 mo | Optimal | 92 | 94 | 99 | 90 | 94 |
| | Warning | 90 | 100 | 100 | 100 | 96 |
| | Failure | 71 | 71 | 83 | 67 | 72 |
| 6 mo | Optimal | 92 | 97 | 97 | 93 | 96 |
| | Warning | 100 | 90 | 100 | 67 | 94 |
| | Failure | 64 | 75 | 100 | 75 | 71 |
| 12 mo | Optimal | 100 | 98 | 100 | 95 | 98 |
| | Warning | 100 | 94 | 92 | 80 | 93 |
| | Failure | 85 | 83 | 100 | 100 | 85 |

**7090 General Poster Session (Board #375), Mon, 1:15 PM-5:00 PM**

**CD96 antibody TH-111 for detection of AML leukemic stem cells, and purging of autografts for stem cell transplantation.** *Presenting Author: Matthias Staudinger, Division of Stem Cell Transplantation and Immunotherapy, 2nd Department of Medicine, University Hospital Schleswig-Holstein and University of Kiel, Kiel, Germany*

**Background:** High relapse rates observed in AML patients after autologous stem cell transplantation may be due to residual leukemic stem cells (LSC) in the graft. Therefore, elimination of LSC by targeted therapy represents a promising therapeutic option. Here, strategies are described addressing CD96 - a marker antigen recently identified on AML LSC - for engineering autologous stem cell grafts by magnetic cell sorting (MACS). Moreover, attempts to improve antibody-dependent killing (ADCC) of LSC may allow therapeutic use in other situations. **Methods:** Biotinylated CD96 antibody TH111 raised in our laboratory was used for MACS separation of AML-LSC. Healthy hematopoietic progenitor cells (HPC) viability, their differentiation properties and the efficiency of depletion were analyzed by colony forming assays and flow cytometry. Chimeric ADCC-optimized CD96 antibodies were analyzed for purity by SDS page and specific binding by flow cytometry. Antibody-mediated effector functions were measured in $^{51}$Cr-release assays. **Results:** To determine the efficiency of antibody mediated LSC purging, stem cell containing grafts were spiked with AML cells. Using biotinylated CD96 antibody up to a 1000-fold depletion of targeted cells was achieved. Viability of healthy HPC as well as their potential to proliferate and differentiate were not affected. To recruit NK cells for lysis of CD96$^+$ AML-LSC by ADCC, chimeric antibodies containing wild type or affinity maturated variable regions in combination with an ADCC optimized human $IgG_1Fc$ were generated. Due to a higher antigen binding affinity of the maturated antibody (EC50 of 0.6 $\mu$g/ml vs. 2 $\mu$g/ml), the NK cell mediated lytic properties against CD96-positive target cells were elevated (EC50: 0.02 $\mu$g/ml vs. 0.15 $\mu$g/ml; E:T ratio 2.5:1). **Conclusions:** The efficient elimination of AML-LSC by MACS may be beneficial for the development of graft-engineering strategies to avoid transplantation of AML-LSC and revitalize autologous stem cell transplantation in this indication. The in vivo application may possibly open additional therapeutic avenues in eliminating residual disease in autologous as well as allogeneic situations.

**7091 General Poster Session (Board #376), Mon, 1:15 PM-5:00 PM**

**Economic burden of tyrosine kinase inhibitor (TKI) treatment failure in patients with chronic myeloid leukemia (CML).** *Presenting Author: Yaozhu J Chen, IMS Health, Alexandria, VA*

**Background:** Treatment failure due to TKI resistance or intolerance is a significant challenge in managing CML; however, there are limited data quantifying the associated real-world health care utilization and cost burden. **Methods:** Treatment episodes for adult patients with a CML diagnosis (ICD-9-CM 205.1x) initiating a TKI of interest (index TKI) during 6/2008-12/2011 were identified from the IMS PharMetrics Plus Health Plan Claims Database. Inclusion required 120-days pre- and 360-days post-index continuous enrollment and no clinical trial participation. A patient could contribute ≥1 episode. Treatment failure was defined as switch to a non-index TKI or discontinuation of index TKI (gap of ≥60 days) observed over 1 year post index. Episodes with failure were matched to those without, based on propensity scores generated by logistic regression including baseline demographic and clinical characteristics, index TKI, and therapy line. Mean all-cause 1-year post-index health care utilization and costs (in 2012 USD) per episode were compared between matched episodes. **Results:** Of 1,774 eligible episodes from 1,624 CML patients (mean age=52.9, 47.8% female), 547 Failure episodes (Fs) were matched to 547 Non-Failure episodes (NFs). As expected, compared to Fs, NFs had more TKI fills (F: 7.1; NF: 11.2; p<.05) over the 1 year post index. However, Fs had significantly higher % hospitalized (28.9% v 13.9%), more inpatient days (22.2 v. 8.5), more outpatient visits (24.1 v. 17.8) and more non-TKI prescription fills (34.0 v. 28.7) (all p<.05). Overall, Fs incurred lower pharmacy costs ($51,238 v. $72,450), but higher medical costs ($52,618 v. $18,180, including $31,305 v. $5,287 for hospitalization), and higher total costs ($103,857 v. $90,630) than NFs (all p<.05). A sensitivity analysis excluding 18 episodes (17 Fs, 1NF) with bone marrow or stem cell transplant yielded qualitatively similar results. **Conclusions:** Although TKI failures have lower pharmacy burden, their overall economic burden is higher, primarily due to increased inpatient days. These findings suggest that minimizing TKI failure through more efficacious treatment may decrease the overall health care burden and costs of managing CML.

**7092 General Poster Session (Board #377), Mon, 1:15 PM-5:00 PM**

**Association of epidemiologic exposures with complete remission after therapy in acute myeloid leukemia (AML).** *Presenting Author: Laura Elizabeth Finn, Mayo Clinic, Jacksonville, FL*

**Background:** Complete remission (CR) after induction chemotherapy is a vital prognosticator in AML. Age and comorbidities impact response and tolerance to AML induction chemotherapy however the influence of epidemiologic exposures is unknown. We therefore evaluated relevant exposures in a cohort of 295 consecutive AML patients with confirmed central cytogenetics analysis diagnosed and treated at Mayo Clinic Florida and Arizona since 1995. **Methods:** Documented patient exposures extracted systematically from a centralized EMR included prior chemotherapy/radiation (therapy AML, tAML) or hematologic malignancy (secondary AML), medications, and prior solid organ transplantation. Patients receiving induction chemotherapy and responses to therapy were identified. The association of epidemiologic exposures with CR after induction chemotherapy was evaluated by multivariable analysis using logistic regression models. **Results:** 188 patients received induction chemotherapy. Age was not an independent predictor of CR. tAML after breast cancer was independently and significantly associated with achieving CR after therapy, as was statin use. In contrast prior solid organ transplant, farm habitat, tobacco use, and poor risk cytogenetics were associated with decreased CR. **Conclusions:** Some epidemiologic exposures impact CR after AML induction chemotherapy in AML. This supports a link between exposures and outcome after therapy with curative intent. This requires validation in a prospective therapeutic clinical trial.

**CR after induction chemotherapy (OR, CI 95%).**

| Variable | N | Single Variable | P | Multivariable | P |
|---|---|---|---|---|---|
| **Age > 60** | 121 | 1.00 (0.54; 1.84) | 1.00 | 0.71 (0.37; 1.37) | 0.31 |
| **Statins** | 38 | 2.87 (1.23; 6.67) | 0.014 | 2.89 (1.22; 6.85) | 0.016 |
| **Farm habitat** | 9 | 0.30 (0.07; 1.24) | 0.095 | 0.23 (0.05; 1.07) | 0.062 |
| **Solid organ Tx** | 7 | 0.10 (0.01; 0.83) | 0.033 | 0.10 (0.01; 0.84) | 0.035 |
| **Tobacco** | 104 | 0.66 (0.36; 1.19) | 0.17 | 0.57 (0.31; 1.07) | 0.079 |
| **Poor cytogenetics** | 63 | 0.31 (0.08; 1.22) | 0.13 | 0.28 (0.07; 1.10) | 0.085 |
| **tAML** | 31 | 1.01 (0.46; 2.22) | 0.99 | 1.00 (0.44; 2.27) | 1.00 |
| **Breast cancer tAML** | 14 | 4.14 (0.90; 19.04) | 0.070 | 3.91 (0.84; 18.26) | 0.083 |
| **NHL tAML** | 9 | 0.30 (0.07; 1.24) | 1.10 | 0.29 (0.07; 1.23) | 0.094 |
| **Secondary AML** | 64 | 0.99 (0.53; 1.83) | 0.96 | 0.90 (0.47; 1.71) | 0.74 |

**7093^ General Poster Session (Board #378), Mon, 1:15 PM-5:00 PM**

**The benefit of treatment with quizartinib and subsequent bridging to HSCT for FLT3-ITD(+) patients with AML.** *Presenting Author: Mark J. Levis, Department of Oncology, Division of Hematologic Malignancies, The Johns Hopkins University School of Medicine, Baltimore, MD*

**Background:** For FLT3-ITD(+) AML patients (pts) who are relapsed or refractory to chemotherapy, allogeneic HSCT offers the best prospect for long-term survival. Pts are unlikely to undergo HSCT unless their blast count can be reduced to an acceptable minimum, ideally below 5% blasts, which defines composite complete response (CRc: CR + CRp + CRi). Quizartinib is an orally active inhibitor of the FLT3 receptor tyrosine kinase being developed for the treatment of AML pts. We present a new analysis from FLT3-ITD(+) pts who were relapsed or refractory to salvage therapy or HSCT treated with quizartinib across two Phase 2 studies in a total of 212 subjects. **Methods:** In Study A, pts received 90-200 mg/day quizartinib; in Study B, pts were randomized to either 30 mg/day or 60 mg/day quizartinib given orally during continuous 28 day cycles. **Results:** Median baseline blast count in Study A was 81% and 67% in Study B. Median age in Study A was 50yrs and 55yrs in Study B. In Study A, 47 of 136 (35%) proceeded to HSCT; of these 26/47 (55%) had achieved a CRc and 18/47 (38%) a PR prior to HSCT. In Study B 28/76 (37%) pts proceeded to HSCT and of these 23/28 (82%) had achieved a CRc and 4/28 (14%) achieved a PR prior to HSCT. In Study A, pts proceeding to HSCT had a median overall survival (OS) of 34.1 weeks and a 1 yr survival rate of 36% compared to an OS of 18.4 weeks and 1 yr survival of 12% for pts not undergoing HSCT. In Study B, pts randomized to 30 mg/day quizartinib and who underwent HSCT had an OS of 31 weeks compared to 19 weeks for pts without HSCT; pts treated with 60 mg/day and who underwent HSCT had an OS of 28.1 weeks compared to 16.3 weeks for pts without HSCT. **Conclusions:** Pts able to receive a HSCT after response to quizartinib have an improved outcome compared to those who did not have a HSCT. The ability of quizartinib to lower the blast count in a high percentage of pts (46% achieved a CRc) and bridge these pts to a potentially curative HSCT, with an acceptable safety profile, represents an important clinical benefit from quizartinib. Clinical trial information: NCT00989261 and NCT01565668.

**7094 General Poster Session (Board #379), Mon, 1:15 PM-5:00 PM**

**Clinical significance of MYC expression in acute myeloid leukemia.** *Presenting Author: Maro Ohanian, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** MYC, a transcription factor controlling DNA replication, is overexpressed in many cancers, yet rarely investigated in myeloid neoplasms, where its clinical significance is unknown. Objectives:Assess MYC expression by immunohistochemistry (IHC) in bone marrow (BM) of patients (pts) with acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and acute promyelocytic leukemia (APL). **Methods**: MYC expression by IHC was assessed in BM of pts with AML, MDS, APL, and normal BM. MYC expression showed a distinct nuclear pattern. Cases were considered positive if > 5% blasts were stained. **Results:** We evaluated BM MYC expression in 220 pts during 2006-2013 (97 mo) with newly diagnosed AML (n=162), previously treated AML (induction failure or relapse) (n=30), MDS (n=19), and newly diagnosed APL (n=11). Median age was 60 yrs (13-88); 56% male. Normal BM (negative controls) showed negligible MYC expression (<5%, n=11). Varying degrees of MYC expression were observed in AML pts with median MYC expression of 20% (range 2-90%) and 50% (range 19-75%) in APL. Median MYC expression across diseases was 20%. MYC expression of >5% was observed in 134 (84%) newly diagnosed AML pts, 22 (73%) previously treated AML, all (n=11) APL, but in only 7 (40%) MDS (p= 0.0001 for difference across groups). High MYC expression correlated with high LDH (rs = 0.390, p<0.0001), WBC (rs = 0.205, p=0.006) and BM blasts (rs 0.341, p=0.0001). MYC levels were similar across karyotypes: trisomy 8 (where *MYC* resides), complex, and core binding factor. In newly diagnosed AML pts, 105 were screened for *NPM1* and 81 for *FLT-3 ITD* mutations. MYC expression was higher in 21 *NPM1* mutated pts (P = 0.04) and in 22 *FLT3-ITD* mutated pts (P = 0.01). MYC expression strongly predicted survival in newly diagnosed AML. Normal MYC expression (n=26) had a median OS of 28 mo (CI 19-37); those with increased MYC expression had a median OS of 14 mo (CI 10-18) (Log-rank p=0.023). Among normal karyotype (NK) pts median OS was 40 mo (CI 16-63) if MYC <5% vs. 16 mo (CI 9-23) if MYC >5%. The OS advantage was similar with or without mutated FLT3-ITD. Among NK cases of varying MYC levels, MYC rearrangement was not detected by FISH. **Conclusions:** MYC expression is a strong predictor of survival, particularly in newly diagnosed NK AML.

**7095 General Poster Session (Board #380), Mon, 1:15 PM-5:00 PM**

**Expression and function of TIM-3, a potential therapeutic target in acute myeloid leukemia.** *Presenting Author: Catherine Joy Lee, University of Pittsburgh Cancer Institute, Pittsburgh, PA*

**Background:** Transmembrane immunoglobulin mucin-3 (TIM-3) is a cell-surface protein that has been identified as a novel acute myeloid leukemia stem cell (AML-LSC) surface marker and a potential candidate for targeted therapy with monoclonal antibodies. However, the function of TIM-3 on LSCs and blasts, and in the pathogenesis of AML, is currently unclear. We have shown in T cells that TIM-3 regulates the growth and survival of normal and transformed cells by activation of kinase Akt (pAkt) and phosphorylation of ribosomal S6 protein (pS6). We hypothesize that TIM-3 may similarly contribute to the survival of AML through activation of pAkt and pS6 in LSCs and leukemic blasts. **Methods:** Established human AML cell lines NB4, U-937, and HL-60 were assessed for surface TIM-3 expression by flow cytometry and western blot when at rest and when stimulated with phorbol 12-myristate 13- acetate (PMA; 5 ng/ml, 10 ng/ml, 50 ng/ml) for 24-72 hrs. Cell surface CD11b was used as a marker for PMA-induced monocytic differentiation. Primary human AML peripheral blood samples were analyzed for TIM-3 and intracellular pS6 expression in the $CD34^+$population by flow cytometry. **Results:** 1) Basal levels of TIM-3 expression were minimal in NB4, U-937, and HL-60 cells; however, TIM-3 expression was up-regulated at least two-fold in all cell lines during PMA-induced differentiation along the monocytic/macrophage lineage by 24 hrs. 2) In a 24-hour kinetics assay, TIM-3 up-regulation occurred at 6 hrs versus 10 hrs for CD11b in NB4 cells. 3) Four primary human AML samples were obtained thus far. We identified a $TIM\text{-}3^+CD34^+pS6^+$population from at least two of these patients. **Conclusions:** We have evaluated the expression and possible function of TIM-3 in AML cell lines and primary human AML samples. In NB4 cells, TIM-3 may be involved in the differentiation pathway of AML cells by PMA as up-regulation of TIM-3 preceded that of CD11b. We have also identified human AML samples that express TIM-3 and pS6 in the $CD34^+$ population. Ongoing studies include the use of TIM-3 modulating antibodies on AML cell lines and on $CD34^+CD38^-TIM3^+$ primary AML samples to determine the role of TIM-3 on downstream signaling activation, and on viability, proliferation, and differentiation.

**7096 General Poster Session (Board #381), Mon, 1:15 PM-5:00 PM**

**A next-generation sequencing approach to capturing CEBPA: A hematologic malignancy sequencing panel capturing clinically useful targets.** *Presenting Author: Jennifer J. Morrissette, Department of Pathology and Laboratory Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA*

**Background:** The use of next generation sequencing (NGS) for clinical diagnosis of cancer promises to improve diagnosis and lead to more precise cancer care. However, this methodology does not cover all regions of the genome uniformly, with some regions not sequenced with sufficient depth for accurate mutation detection. Here we describe the validation of a 34 gene hematological NGS panel, including one gene, CEBPA, which performed poorly and required an alternative NGS method due to GC–rich regions. **Methods:** Fifty five AML patient samples were obtained from the Stem Cell and Xenograft Core at the University of Pennsylvania and analyzed using an Illumina TrueSeq Custom Amplicon panel with subsequent sequencing on the Miseq. To capture CEBPA we developed a separate method using target amplification by a long range PCR followed by library preparation using the Nextera XT kit (Illumina Inc). **Results:** We found NGS of commonly mutated genes in hematologic malignancies is technically feasible and reliable in a clinical diagnostic laboratory, with >99% sensitivity and specificity on variant detection achieved when allele frequency of a given variant was 5% or higher over regions that met our sequencing QC threshold of 250x. The middle of the coding region for CEBPA demonstrated inefficient capture using amplicon or bead based approaches. Using a long range PCR approach followed by Nextera library preparation, 100% coverage of CEBPA was achieved. Given the high GC content a lower limit of detection for CEBPA, at a 10% allele frequency, allowed for 100% sensitivity and specificity in the samples analyzed. **Conclusions:** We have developed a clinical grade multi-gene test for hematologic malignancies using next generation sequencing technology that can reliably detect somatic mutations including single nucleotide variants, insertions and deletions. For most genes on the panel, a minimal allele frequency of 5% was detectable for indels and SNVs. With CEBPA, there was robust mutation detection at an allele frequency of 10% or greater. This combined approach allows for comprehensive mutation screening of the genes relevant to the prognosis of AML, including CEBPA, with a single approach, NGS.

**7097 General Poster Session (Board #382), Mon, 1:15 PM-5:00 PM**

**Propensity score matched comparison of intermediate-intensity chemotherapy induction versus intensive chemotherapy induction in elderly patients (age ≥ 60) with acute myeloid leukemia (AML).** *Presenting Author: Koichi Takahashi, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** A majority of patients (pts) with AML age ≥ 60 are unable to tolerate intensive chemotherapy (IC) induction. Front-line therapy with clofarabine plus low dose cytarabine (CLDA) has been used for this subset of pts. We hypothesized that CLDA provides equivalent outcome on elderly pts with AML compared to conventional IC induction with less toxicity. **Methods:** Previously untreated pts with AML, age ≥ 60, who received front-line therapy between 2002 and 2012 by one of the following regimens were matched by the propensity score to adjust confounding factors: 1) clofarabine plus low-dose cytarabine (CLDA group: N = 142) or 2) idarubicin plus high-dose cytarabine (IA group: N = 104). **Results:** Propensity matching resulted in 66 pts from each group to be matched for their pre-treatment characteristics including age, performance status (PS), organ function and cytogenetics. Response rate (achieving complete remission [CR] within 2 courses of induction) was similar between 2 groups (CLDA vs. IA, 59% vs. 53%, P = 0.48). Mortality at 4 and 8 weeks were similar between 2 groups (CLDA vs. IA, 5% vs. 11% at 4 weeks and 14% vs. 15% at 8 weeks, P = 0.32 and 0.80, respectively). The median hospital stay during induction was similar between 2 groups (CLDA vs. IA, 27 vs. 26 days, P = 0.15). Comparable proportion of pts were bridged to stem cell transplant during 1st CR (CLDA vs. IA, 6% vs. 5%, P = 1.00). The median overall survival (OS) was similar between 2 groups (CLDA vs. IA, 11.4 months [95% CI: 7.0-15.8] vs. 10.4 months [95% CI: 4.9-15.9], P = 0.60). In an analysis sub-grouped by clinical characteristics, no difference in OS was observed between 2 groups in any of the subgroups. Multivariate analysis for OS showed that adverse risk cytogenetics, age ≥ 70, bone marrow blast > 30%, and PS > 2 adversely affected OS but induction regimen did not affect OS. **Conclusions:** Induction therapy with CLDA showed equivalent response rate and OS in pts with AML age ≥ 60 compared to conventional IC induction. Intensity of induction in elderly AML pts may be attenuated without compromising outcome. Prospective randomized trial to confirm these findings is warranted.

**7098 General Poster Session (Board #383), Mon, 1:15 PM-5:00 PM**

**Phase I/II study of vosaroxin and decitabine in older patients (pts) with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS).** *Presenting Author: Naval Guastad Daver, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Vosaroxin is a first-in-class anticancer quinolone derivative (AQD) that intercalates DNA and inhibits topoisomerase II and has previously demonstrated activity in AML. We conducted this study to examine the efficacy and toxicity of the combination of vosaroxin and decitabine. **Methods:** Pts were eligible if they had AML or high-risk MDS (≥ 10% blasts in the bone marrow), were ≥ 60 years, had ECOG PS ≤ 2 and adequate organ function. Pts < 60 years who were unsuitable for standard chemotherapy were also eligible. The treatment regimen included vosaroxin 90 mg/m$^2$ daily on days 1 and 4 with decitabine 20 mg/m$^2$ daily for 5 days. Vosaroxin was reduced to 70 mg/m$^2$ in consolidation cycles, for a total of up to 7 cycles. The primary endpoint is overall response rate (ORR) rate [ORR=CR + CRp + CRi]. **Results:** To date, 23 pts (21 AML, 2 high-risk MDS) with a median (med) age of 71 years (range, 41-78) have been enrolled. They included 11 (48%) with diploid cytogenetics, 7 (30%) with complex cytogenetics including chromosome 5 and/or 7 abnormalities, and 5 (22%) with other. 9 (39%) had antecedent hematological disorders (AHD). 5 pts with AHD had received prior therapy including azacitidine (n=1), ruxolitinib + azacitidine (n=1), lenalidomide (n=1) and hydroxyuea (n=2). Frequently identified mutations included: *IDH1/2* in 8 (35%), *RAS* mutations in 6 (26%), *TP53* in 6 (26%), and *NPM1* in 4 (17%). Med bone marrow blast %, white blood cell, hemoglobin, & platelet counts were 36% (11-97), 4.6 x 10$^9$/L (1.0-25.1), 9.5 g/dL (6.8-11.5), and 42 x 10$^9$/L (7-333), respectively. 16 pts were evaluable for response; 9 (56%) achieved CR, 2 (13%) CRp, and 2 (13%) CRi, for an ORR of 81% with no evidence of minimal-residual disease in 11 of 13 responders (85%). 7 are too early for response assessment. Pts have received a med of 2 cycles (range, 1-5) with med number of cycles to response being 1 (range, 1-4). No pts have relapsed. 1 pt has proceeded to HSCT. Two pts died during induction. Additionally, 1 pt died on day 47 from sepsis and acute myocardial infarction. The main grade ≥ 3 toxicity was mucositis in 2 pts. **Conclusions:** Combination of vosaroxin and decitabine is effective and well tolerated. Enrollment is ongoing. Clinical trial information: NCT01893320.

**7099 General Poster Session (Board #384), Mon, 1:15 PM-5:00 PM**

**Health-related quality of life (HRQL) impact of idelalisib (IDELA) in patients (pts) with relapsed chronic lymphocytic leukemia (CLL): Phase 3 results.** *Presenting Author: Paolo Ghia, Università Vita e Salute; San Raffaele Scientific Institute, Milano, Italy*

**Background:** Pt-reported outcomes (PROs) evaluated HRQL among CLL pts randomized to IDELA + rituximab (R) (n=110) vs double-blind placebo + R (n=110). **Methods:** The 44-item Functional Assessment of Cancer Therapy–Leukemia (FACT-Leu) scale measured Physical (PWB), Functional (FWB), Social (SWB) and Emotional (EWB) Well-being and leukemia-specific concerns (LeuS). The FACT-Leu Total score is the sum of subscales; Trial Outcome Index (TOI) is the sum of PWB, FWB and LeuS. Higher scores reflect better HRQL. Repeated measures mixed-effects models assessed change from baseline within and between-arms. **Results:** IDELA + R was superior for OS: HR=0.28 (0.09, 0.86), p=0.018. In the mixed-effects model analysis, PWB (p=0.015), FWB (p= 0.014), LeuS (p=0.001), TOI (p=0.002), and FACT-Leu Total (p=0.006) scores were significantly higher for IDELA + R. EWB/SWB scores did not change significantly over time. Repeated measure mixed-effects model results are shown in the table. **Conclusions:** In this frail CLL population, IDELA + R had superior efficacy, clinically significant improvements in HRQL, and superior symptom control occurring by 8 weeks compared to R + placebo. Clinical trial information: NCT01539512.

| Week | PWB | FWB | LeuS | TOI | FACT-Leu total |
|---|---|---|---|---|---|
| **2** | -0.1 (0.65) | 0.6 (0.80) | 0.4 (1.31) | 1.3 (2.38) | 1.1 (2.96) |
| **4** | 0.8 (0.66) | 1.0 (0.81) | 2.5 (1.33) | 4.0 (2.41) | 4.0 (3.01) |
| **6** | 0.1 (0.68) | 1.0 (0.84) | 2.2 (1.37) | 2.9 (2.48) | 3.9 (3.09) |
| **8** | 0.6 (0.71) | 0.7 (0.87) | 3.5 (1.43)* | 4.6 (2.57) | 5.2 (3.2) |
| **12** | 1.1 (0.75) | 1.5 (0.92) | 4.7 (1.51 ** | 7.0 (2.72)** | 6.5 (3.39) |
| **16** | 1.9 (0.83)* | 1.3 (1.01) | 5.3 (1.66)** | 8.4 (2.99)** | 9.2 (3.72)** |
| **20** | 1.6 (0.91) | 1.4 (1.13) | 5.4 (1.85)** | 9.0 (3.33)** | 9.0 (4.14)** |
| **24** | 1.8 (1.02) | 1.9 (1.26) | 5.0 (2.06)** | 9.1 (3.69)** | 10.0 (4.58)** |
| **30** | 2.1 (1.14) | 2.6 (1.41) | 3.0 (2.32) | 7.7 (4.13) | 9.6 (5.13) |
| **36** | 1.5 (1.26) | 2.8 (1.56) | 5.1 (2.54)** | 8.2 (4.59) | 9.1 (5.69) |
| **42** | 2.1 (1.57) | 2.8 (1.93) | 3.9 (3.16) | 8.1 (5.57) | 9.1 (6.92) |
| **48** | 3.6 (1.79)** | 3.6 (2.20) | 5.5 (3.60) | 12.4 (6.32)** | 13.1 (7.85) |

* p< 0.05; ** p<0.05 and exceeded established minimally important difference (MID) change scores of 2, 4, 5 and 6 points for PWB, LeuS, TOI and FACT-Leu total, respectively, between arms.

**7100 General Poster Session (Board #385), Mon, 1:15 PM-5:00 PM**

**Final results of a randomized phase 2 study showing the clinical benefit of quizartinib (AC220) in patients with FLT3-ITD positive relapsed or refractory acute myeloid leukemia.** *Presenting Author: Gary J. Schiller, University of California, Los Angeles School of Medicine, Los Angeles, CA*

**Background:** The presence of FLT3-internal tandem duplication (ITD) in patients (pts) with acute myeloid leukemia (AML) is associated with early relapse and poor survival. Quizartinib (AC220) is an orally active inhibitor of the FLT3 receptor tyrosine kinase being developed for the treatment of pts with FLT3-ITD(+) AML. This randomized, open-label, study was conducted to assess the effect of two different dosages of quizartinib in FLT3-ITD+ pts, aged 18 years or older, with relapsed or refractory AML after either one-second line therapy or HSCT. **Methods:** Pts were randomized to quizartinib 30 mg/day (Group A) or 60 mg/day (Group B) given orally during 28-day continuous treatment cycles, until relapse, intolerance or proceeding to HSCT. Primary endpoint was the rate of CRc (CR+CRp+CRi). **Results:** Seventy six pts were randomized equally to the two arms. Demographics and baseline characteristics were balanced between the two arms except for age over 60 years (42% Group A, 26% Group B) and the percentage with secondary AML (8% Group A, 18% Group B). The analysis included a minimum of 8 weeks of follow-up. The median duration of treatment in Group A was 10.9 weeks (range 2.1 to 24.9+ weeks) and 11.0 weeks (range 2.6 to 26 weeks) in Group B. The CRc rate in both groups was 47% and the overall response rate (CRc + partial response (PR)) was 61% in Group A and 71% in Group B. 32% of pts in Group A and 42% in Group B were able to receive a HSCT, mostly after achieving CRc or PR. The median overall survival was 20.7 weeks in Group A; and 25.4 weeks in Group B with 35 of the 76 patients alive at last follow-up (range: 7.4 – 40.4+ weeks). Grade 2 or greater QTcF prolongation occurred in 11% Group A pts and in 17% Group B pts. The most common treatment related adverse events occurring in 15% or more pts were diarrhea (18%), febrile neutropenia (16%), and QT prolongation (15%). **Conclusions:** Quizartinib in second salvage or post HSCT FLT3-ITD+ AML demonstrated a high degree of efficacy (CRc 47%) with an acceptable safety profile, specifically decreased QTcF prolongation rates compared to higher doses used previously. Further analysis with additional follow-up will be available for presentation. Clinical trial information: NCT01565668.

**7101 General Poster Session (Board #386), Mon, 1:15 PM-5:00 PM**

**A decision-analytic model of idelalisib and rituximab combination therapy versus rituximab monotherapy in relapsed, unfit chronic lymphocytic leukemia.** *Presenting Author: Alexander Xenakis, CBPartners, New York, NY*

**Background:** There are few treatment options for relapsed, unfit CLL patients. Idelalisib (IDELA) is a first-in-class inhibitor of PI3Kδ with significant clinical efficacy in relapsed, unfit CLL patients. A recent phase III clinical trial (Study 116) reported that in comparison with rituximab monotherapy (R-MONO), IDELA plus rituximab therapy (IDELA+R) resulted in improved progression-free survival (PFS, HR=0.15) and overall survival (OS, HR=0.28) in relapsed, unfit CLL patients. **Methods:** A decision-analytic model simulated a cohort of relapsed, unfit CLL patients receiving treatment over a 1 to 5 year horizon. Patients received IDELA+R or R-MONO either until death or until transitioning to a progressive-disease (PD) state where they received salvage therapy until death. Survival data for IDELA+R and R-MONO was fit and extrapolated from Study 116. A claims analysis of a large dataset provided disease- and treatment-related adverse events (AEs) and medical resource utilization rates for the PD state. Utility was based on literature review. All outcomes were discounted at 3% per year. **Results:** Treatment with IDELA+R over R-MONO resulted in better health outcomes, increasing life-years (LYs) by 1.0 to 9.7 mos, increasing progression-free life-years (PFLYs) by 4.6 to 11.6 mos, and improving quality-adjusted life-years (QALYs) by 0.1 to 0.7, while decreasing AEs by 46% to 2% and reducing hospitalizations by 48% to 5% over a 1 to 5 year time horizon. **Conclusions:** IDELA+R was projected to yield better health outcomes in relapsed, unfit CLL patients compared to R-MONO, largely driven by and improved PFS and OS; reductions in AEs were specifically related to a delayed progression to the PD state.

| Health outcomes (per patient) | Time horizon (years) | IDELA+R | R-MONO | Δ(IDELA+R-R-MONO) |
|---|---|---|---|---|
| LYs (months) | 1 | 11.2 | 10.2 | +1.0 |
| | 3 | 29.9 | 24.2 | +5.7 |
| | 5 | 40.4 | 30.6 | +9.7 |
| PFLYs (months) | 1 | 10.3 | 5.7 | +4.6 |
| | 3 | 17.4 | 6.0 | +11.4 |
| | 5 | 17.5 | 6.0 | +11.6 |
| QALYs | 1 | 0.7 | 0.6 | +0.1 |
| | 3 | 1.8 | 1.3 | +0.5 |
| | 5 | 2.3 | 1.7 | +0.7 |

| Health outcomes (1,000 patient cohort) | Time horizon (years) | IDELA+R | R-MONO | Δ(IDELA+R-R-MONO) |
|---|---|---|---|---|
| No. AEs incurred | 1 | 99 | 182 | -83 |
| | 3 | 378 | 470 | -92 |
| | 5 | 592 | 602 | -10 |
| No. hospitalizations incurred | 1 | 114 | 218 | -104 |
| | 3 | 366 | 571 | -206 |
| | 5 | 728 | 766 | -37 |

**7102 General Poster Session (Board #387), Mon, 1:15 PM-5:00 PM**

**Feasibility of geriatric assessment for older adults with acute myeloid leukemia (AML) receiving intensive chemotherapy on a cooperative group trial: CALGB 361006 (Alliance).** *Presenting Author: Heidi D. Klepin, Wake Forest University, School of Medicine, Winston-Salem, NC*

**Background:** Geriatric assessment (GA) may improve characterization of fitness for intensive AML therapy and identify vulnerabilities to target for improved treatment tolerance. Feasibility of performing GA prior to intensive induction has not been demonstrated in a multi-site cooperative group trial. **Methods:** CALGB 361006 was a companion study offered to patients (pts) enrolled on CALGB 11001, a phase 2 trial of adults ≥60 years of age with newly diagnosed FLT3 mutated AML testing the efficacy of adding sorafenib to intensive therapy. On CALGB 361006, a GA was administered prior to induction therapy and prior to post-remission therapy. The GA is divided into items completed by a health care professional (HCP) (comorbidity index, performance status, Timed up and go test, cognition screen, nutrition screen) and a self-administered pt questionnaire (physical function, health, falls, comorbidity, medications, mood, social activities/support). Prior to enrollment, phone training on GA procedures was conducted with site research teams. Feasibility outcomes include recruitment, implementation (time to completion, difficulty with administration, percent of pts requiring assistance) and satisfaction with the assessment. **Results:** Among 54 eligible pts, 43 (80%) enrolled on the GA companion (median age 67.6 years, 44% female). Of these, the HCP assessment and pt questionnaire were completed and available for 86% and 88% at baseline respectively. Median time to complete the entire GA was 30 minutes (range 5-65); median time for each component was 10 and 21 minutes for HCPs and pts respectively. Among HCPs, 100% reported no difficulty completing the baseline assessment. Among pts, 84% reported no difficulty understanding any question; 78% required no assistance with completion; 95% reported no upsetting questions. The majority of pts (82%) were satisfied with assessment length. **Conclusions:** Recruitment to and implementation of a primarily self-administered GA is feasible prior to intensive induction for older adults with AML in the multi-site cooperative group setting. Next steps will explore the predictive utility of GA on toxicity.

**7103 General Poster Session (Board #388), Mon, 1:15 PM-5:00 PM**

**Comprehensive genetic characterization of 12 AML cell lines using a novel AML targeted sequencing strategy.** *Presenting Author: Andrew R. Carson, Genection, Inc, San Diego, CA*

**Background:** Next generation sequencing (NGS) has revealed much of the common genomic architecture of Acute Myeloid Leukemia (AML). However, the high cost of NGS and its interpretation limits specificity and coverage in most sequencing strategies. This prevents broad clinical adoption of NGS for characterizing AML samples and cell lines. Instead, investigators use limited diagnostic assays that fail to fully characterize complex variants such as internal tandem duplications in *FLT3*. Full characterization of variants in AML cell lines is essential, as these cells may be used to model cancer pathogenesis, develop therapeutics, and standardize diagnostic performance. Furthermore, discerning clonal architecture may prove crucial for personalized therapies. To illustrate the increased capacity and resolution of NGS for the comprehensive characterization of AML samples, we sequenced the "AMLome" (the complement of genes known or predicted to be involved in AML pathogenesis) of 12 AML cell lines using a novel AML specific targeted strategy. **Methods:** To examine the AMLome, we targeted coding regions of 171 genes and potential genomic breakpoints in 34 genes within known somatic gene fusions using the MyAML gene panel. We sequenced target loci to an average depth of coverage >350x on the Illumina MiSeq platform. Using a custom bioinformatics pipeline, we performed mutation detection analyses to identify single nucleotide variants (SNVs), indels, inversions and translocations. In addition, we calculated allelic frequencies to investigate potential aneuploidy and clonality. **Results:** Targeted sequencing of 12 AML cell lines identified previously unreported genomic variants with the potential to significantly impact experiments using these cell lines. These mutations include potential activating missense SNVs in oncogenes, damaging missense SNVs and frameshift indels in tumor suppressors, and translocations creating possible fusion genes. **Conclusions:** We demonstrate that by targeting the AMLome using the MyAML gene panel, we comprehensively characterize mutations within AML cell lines. Our results also suggest that this strategy can be extended to the characterization of AML patient samples.

**7104 General Poster Session (Board #389), Mon, 1:15 PM-5:00 PM**

**A DNA methylation signature for stemness in acute myeloid leukemia.** *Presenting Author: Timothy J Triche, University of Southern California, Los Angeles, CA*

**Background:** In an effort to assign immunophenotypes to AML samples where no immunohistochemistry had been recorded, we trained a DNA methylation classifier using Illumina HumanMethylation450 beadarray data from normal and malignant cells with known immunophenotype. Remarks from clinical malignant hematologists led us to investigate whether a resulting CD34-associated signature was also prognostic. **Methods:** Data from flow-sorted cells and from blasts with immunohistochemistry results were used to identify differentially methylated regions, which we then ranked and fit via logistic regression as predictors of CD34, CD33, CD14, and myeloperoxidase status. A strong DNA methylation signature was associated with CD34 immunophenotype in normal hematopoeitic stem/progenitor cells (HSPCs), cultured peripheral blood HSPCs from other groups, and CD34-positive TCGA AML samples. In cross-validation, a panel of 20 differentially methylated regions correctly predicted immunophenotype for 96% of AML, normal CD34+ cells, normal CD14+ cells, and normal neutrophil granulocytes when true labels were masked. When we plotted percent methylation across each region in unsorted TCGA AML blast samples and our own, a gradient appeared, with normal CD34+ cells at one extreme, normal CD14+ cells near the other, and AML blasts in between. We thus fit reduced signatures, as well as the normalized rank for each AML, as predictors of overall and relapse-free survival in the TCGA AML cohort (N=191 samples with usable data) using the 'glmnet' package in R. **Results:** The DNA methylation "stemness" score was a significant ($p < 0.02$) predictor of poorer overall and event-free survival in TCGA AML cases. The individual differentially methylated regions comprising the signature overlapped numerous intronic and intergenic enhancer elements, microRNAs, Piwi RNAs, and noncoding transcripts known to play roles in specification of hematopoeitic cell fates. Many of the associated transcripts are expressed at low but detectable levels in normal CD34+ HSPCs but not in progeny, or vice versa. **Conclusions:** Epigenetic plasticity, as reflected by HSPC-like DNA methylation, is a negative prognostic factor for overall and event-free survival in AML.

**7105 General Poster Session (Board #390), Mon, 1:15 PM-5:00 PM**

**Treatment patterns, mortality, and costs of care in unfit patients (pts) with relapsed chronic lymphocytic leukemia (CLL).** *Presenting Author: Helen Varker, Truven Health Analytics, Inc., Cambridge, MA*

**Background:** CLL pts who are ineligible for treatment due to age or with major comorbidities and pts who relapse after initial therapy represent significant unmet needs for this disease. To better understand these populations, we examined the prevalence, treatments, outcomes, and costs for pts who might be considered unfit for chemotherapy and, among unfit treated pts, those who showed evidence of relapse after initial therapy. **Methods:** The Truven Health MarketScan Database was used to identify pts with newly diagnosed CLL in 2004-2013 using ICD-9-CM diagnosis codes. Pts were defined as unfit for chemotherapy if their age was $\geq 80$ or had evidence of major comorbidity. Unfit and relapsed (U/R) pts were defined as having $\geq 2$ lines of antineoplastic therapy where the 2$^{nd}$line represented a change in therapy. Pts were followed from the index date until end of enrollment or death. Reimbursements were adjusted to 2013 dollars. **Results:** Of a total of 80,096 pts with CLL, 18,776 met the unfit criteria; and 1,109 pts met the U/R criteria. Unfit pts were 57% male, mean age of 69 (SD 18), and had a Charlson comorbidity score (CCI) of 2.4 (SD 2.0). Comorbidities at diagnosis: lipometabolic disorders (37%), hypertension (37%), diabetes mellitus (20%), chronic pulmonary disease (17%), congestive heart failure (7%), renal disease (7%). U/R pts were 63% male, mean age of 63 (SD 20), and had a CCI score of 3.4 (SD 2.2). Mean survival times for unfit and U/R pts were 26.7 (SD 23.8) months and 21.8 (SD 20.2) months, respectively. Among U/R pts, the most common 1st-line regimens were rituximab (R) ± prednisone(P)/ dexamethasone (D) (24.0%), R + bendamustine ± P/D (9.6%), and R + cyclophosphamide + fludarabine ± P/D (7.2%). Among U/R pts, per patient per month total costs by 1st and 2nd lines of therapies were $15,907 (SD $19,893) and $18,506 (SD $36,977) respectively. **Conclusions:** The most commonly used regimens for U/R CLL pts included rituximab. Survival for U/R after therapy is modestly lower than for those who might be considered unfit at diagnosis, suggesting that some who might otherwise be considered unfit can benefit from therapy. Medical costs were substantial for this cohort of pts.

**7106 General Poster Session (Board #391), Mon, 1:15 PM-5:00 PM**

**Activity of the Wee1 inhibitor MK1775 plus cytarabine in AML through interference with DNA repair capacity at the DNA level.** *Presenting Author: Raoul Tibes, Mayo Clinic, Scottsdale, Scottsdale, AZ*

**Background:** Cytarabine (AraC) resistance is a fundamental characteristic of refractory/relapsed AML. In previous RNAi screens we identified WEE1 kinase as top candidate target whose inhibition sensitized to AraC in AML. The WEE1 inhibitor MK1775 potently synergized with AraC ex vivo and in vitro and clinical trials are in preparation. However, a mechanistic understanding has remained elusive. **Methods:** In siRNA rescue screens of 44 genes involved in WEE1 and DNA damage repair (DDR) pathway regulation were conducted and below described experiments conducted. **Results:** Several RNAi hits converged on DDR repair genes with a focus on the MRN (MRE11, Rad51, NBS1) complex. Interfering with MRN complex members significantly altered the response of AML cells to combined AraC+MK1775 vs. single agent MK1775 or AraC. Unexpectedly the ATM-CHEK1 pathway was not activated, and Homologous recombination (HR)-mediated repair was compromised as shown by a DR-GFP expression vector. Consistently other HR markers decreased as well. The cell cycle was globally dysregulated by slower S-phase kinetics (progression), an expected abrogated G2/M checkpoint as well as de-regulated DNA replication origin formation and firing as evidenced by Cdt1 and Mus81. As a consequence high-single and double strand breaks (H2AX) occurred with early mitotic entry (increased phospho-histone H3) induced by AraC + MK1775 vs. single agents. Changes were followed by massive induction of apoptosis, with specific anti-apoptotic members decreasing and pro-apoptotic BH3 members increasing. Finally, AraC+MK1775 dramatically reduced colony formation vs. single agent MK1775 or even high-dose AraC incubations indicating a stem cell targeting combination, which was p53 independent. **Conclusions:** Herein we propose combined AraC+MK1775 as a potent AML regimens by directly interfering with DDR via compromising the MRN complex with subsequent reduced HR, early abortive mitotic entry subsequent massive ÒdefaultÓ apoptosis, in a p53 independent manner. These data provides a rationale to clinically evaluate AraC+MK1775 in patients with AML, points towards a mechanistic understanding as well as offers suggestions for biomarkers.

**7107 General Poster Session (Board #392), Mon, 1:15 PM-5:00 PM**

**Cellular level of Abelson interactor-1 as a marker predicting chemoresistance.** *Presenting Author: Anna Chorzalska, Brown University, Providence, RI*

**Background:** In hematological malignancies, quiescent leukemic stem cells are responsible for persistence of minimal residual disease and relapse. Emerging evidence points to the involvement of the bone marrow microenvironment in survival and systemic retention of leukemic stem cells. Integrins, particularly $\alpha4\beta1$, which controls hematopoietic stem cell trafficking, were shown to be required for leukemic stem cells lodging in the bone marrow niche, and were shown to be crucial for the persistence of minimal residual disease. We have just recently obtained evidence that $\alpha4$ integrin interacts directly with Abelson interactor-1 (Abi-1) and this signaling cross-talk is involved in acquired drug resistance in Bcr-Abl positive leukemic cells. **Methods:** Gene expression analyses were performed on human Bcr-Abl positive CD34+ leukemic progenitor cells isolated at first diagnosis or at relapse. Imatinib mesylate resistant cell lines were used to confirm gene profiling data and determine the effect of deregulated $\alpha4$-Abi-1 cross-talk on adhesion and cell cycle. Immunodeficient NOD.Cg-Prkdc$^{scid}$ Il2rg$^{tm1Wjl}$/SzJ (NSG) mice were used in xenotransplant experiments to confirm critical role of Abi-1 in lodging of Bcr-Abl positive cells to the bone marrow. **Results:** We present evidence that signaling crosstalk between $\alpha4$ integrin and Abi-1 is involved in acquisition of an anchorage-dependent phenotype and drug resistance in Bcr-Abl positive leukemia cells. Comparison of Abi-1 (ABI-1) and $\alpha4$ integrin (ITGA4) gene expression in relapsing Bcr-Abl positive CD34+ progenitor cells demonstrated a reduction in Abi-1 and an increase in $\alpha4$ integrin mRNA in the absence of Bcr-Abl mutations. This inverse correlation between Abi-1 and $\alpha4$ integrin expression, as well as linkage to elevated phospho-Akt and phospho-Erk signaling, was confirmed in imatinib mesylate (IM) resistant leukemic cells. **Conclusions:** Obtained results indicate that the $\alpha4$-Abi-1 signaling pathway may mediate acquisition of the drug resistant phenotype of leukemic cells and ABI-1/ITGA4 gene levels may be used as a markers predicting chemoresistance.

**7108 General Poster Session (Board #393), Mon, 1:15 PM-5:00 PM**

**The clinical characteristics and therapeutic outcomes of elderly patients with chronic myeloid leukemia: A retrospective multicenter study.** *Presenting Author: Serdal Korkmaz, Cumhuriyet University, Department of Hematology, Sivas, Turkey*

**Background:** We aimed to investigate if older age leads to limitations in starting dose of imatinib in daily practice of chronic myeloid leukemia (CML) and the compliance with tyrosine kinase inhibitors (TKIs) therapy in elderly patients. **Methods:** To analyze the clinical characteristics and therapeutic outcomes of elderly patients with CML aged >65 years, data were collected from 13 institutions in Turkey, retrospectively. **Results:** A total of 69 cases were evaluated retrospectively. Of the patients, 42 (60.9%) were females. The median age was 71 years (range; 66-85). Ninety-six percent (66/69) of the patients were in chronic phase when diagnosed. Of the patients, 3 (4.3%) were in accelerated phase. The sokal risk at diagnosis was low in 3 patients, intermediate in 29 patients, and high in 37 patients. RT-PCR was the most used method to diagnose patients. Sixty-three (91.3%) patients were under imatinib tharapy as first line. The initial dose of imatinib was 400 mg/day in 59 (93.6%) patients, 100 mg/day in 2 (3.2%) patients, 300 mg/day in one (1.6%) patient, and 600 mg/day in one (1.6%) patient. Imatinib treatment induced 57 (90.5%) complete hematologic responses (CHR) at 3 months and 29 (46%) complete cytogenetic responses (CCyR) at 6 months, and 49 (77.7%) major molecular responses (MMR) at 12 months. Of the patients, 2 have discontinued imatinib for hematologic and/or non-hematologic toxicities; as a result of resistance in 7 patients, and loss of MMR in 5 patients, nilotinib and dasatinib were used in 14 patients as second-line therapy. Second-line TKIs induced 9 (64.3%) CHR at 3 months and 4 (28.6%) CCyR at 12 months, and 7 (50%) MMR at 18 months. Fifty-six (81.2%) of the patients are still alive and being followed up regularly. The median overall survival and progression free survival rates were 35 months (range; 1-95) and 17 months (range; 0.8-95), respectively. **Conclusions:** No need to reduce starting dose of imatinib and no upper age limit should be applied for the administration of TKIs to elderly patients with CML. Elderly patients should receive TKIs according to the same guidelines that apply to younger patients.

**7109 General Poster Session (Board #394), Mon, 1:15 PM-5:00 PM**

**GATA1 in patients with essential thrombocythemia and anagrelide treatment.** *Presenting Author: Ciro Roberto Rinaldi, University of Lincoln, Lincoln, United Kingdom*

**Background:** GATA1 is the founding member of the GATA transcription factor family and is essential for cell maturation and differentiation within the erythroid and megakaryocytic lineages. Disturbance of its functions causes severe hematopoietic dysfunction and can result in blood disorders, such as thrombocytopenia, anaemia and even leukaemia. Several studies, have suggested a connection between GATA1 and myeloproliferative neoplasia (MPN). We previously reported, high GATA1 transcript levels are found in the bone marrow of patients with ET and PV, independent of the JAK2 V617F mutation, but not in other MPN. Anagrelide (ANA) has been proven to be an effective drug in reducing platelet count in ET. However, the mechanisms by which this drug induces this effect is still unclear. Recently Erusalimsky has reported that ANA results in down-modulation of GATA1 and its co-factor FOG1 in MK during in vitro differentiation. **Methods:** In this study, we analysed by Real Time PCR the expression of GATA1 in peripheral blood (PB) samples from 30 patients with ET and compared the levels of expression before and after treatment with common cytoreductive agents such as hydroxyurea (HU) and ANA. **Results:** We confirmed the data obtained in BM, with a significant up-regulation of GATA1 in ET compared to controls. When we measured the expression of GATA1 before and during treatment with ANA, there was a significant reduction of the GATA1 expression at 3 and 6 months of therapy, concomitantly with a reduction in platelets (PLT) counts. Interestingly, this was not equally observed in patients treated with HU, where despite reduction in PLT counts, the GATA1 levels rose. Furthermore, when we analysed patients on combination treatment ANA + HU, GATA1 expression reduced only when patients were taking ANA. When ANA treatment was stopped and the patient continued only on HU, GATA1 levels rose again. This data suggests a direct effect of ANA on GATA1 expression. **Conclusions:** GATA1 may represent a generic molecular marker in ET and a possible additional diagnostic criteria in thrombocytosis. GATA1 overexpression is independent from JAK2 mutations, and responds specifically to ANA therapy suggesting a role in monitoring therapy response.

**7110 General Poster Session (Board #395), Mon, 1:15 PM-5:00 PM**

**Predictive analysis of microenvironment impact on clinical outcomes to drug agents using simulation of myeloproliferative neoplasms.** *Presenting Author: Peter P. Sayeski, University of Florida, Gainesville, FL*

**Background:** The Jak2-V617F mutation is frequently found in MPN. The bone marrow micro-environment of MPN patients constitutes high levels of TNF$\alpha$, IFN$\gamma$ and IL-6. Since resistance to drug agents is of great clinical relevance, we teased the impact of the individual cytokines on drug efficacy. **Methods:** To predict the response to the JAK2 inhibitor class of agents, we (1) employed predictive simulation to model JAK2 bearing cell lines (2) identified novel synergistic combinations of Bcl-2 and JAK2 inhibitors against this JAK2 driven pathogenesis, (3) simulated the impact of TNF$\alpha$ and IFN$\gamma$ on growth and proliferation and (4) validated the outcomes on Jak2 mutant cells. We used a previously characterized JAK2 small molecule inhibitor, G6, which exhibits significant efficacy in Jak2-V617F-mediated MPN and ABT737 was the selected Bcl-2 agent. The predictive simulation approach from Cellworks provides a representation of disease physiology incorporating signaling and metabolic networks with an integrated phenotype view. We modeled the JAK2-V617F expressing HEL and SET-2 cell lines along with G6 and ABT737. We then screened prospectively these agents, both individually and in combination, and with and without the microenvironment inflammatory cytokines. **Results:** The simulation identified a dose response based synergistic impact of the combination of G6 and ABT737 on cell proliferation and viability.TNF$\alpha$ increased the sensitivity of the single drug agents and their combinations. IFN$\gamma$ sensitized the drug action further beyond a certain dose threshold. IL-6 did not show any impact on the cells due to lack of IL-6 signaling within these cells. Simulation studies though have predicted IL-6 induced resistance to these drug agents and possibly cancelling out the positive impact of TNF$\alpha$ and IFN$\gamma$ clinically. **Conclusions:** Thus, this study validates the impact of the micro-environment on drug response and the use of simulation based technology to predict patient responses to drug agents. By accurately predicting responses of a patient's cells to targeted agents *a priori*, the *in silico* simulation model provides an innovative approach to precision medicine for Jak2-mediated MPN.

**7111 General Poster Session (Board #396), Mon, 1:15 PM-5:00 PM**

**A phase 2 study of IPI-926, an oral hedgehog inhibitor, in patients with myelofibrosis.** *Presenting Author: Koji Sasaki, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Aberrant expression of the Hedgehog (Hh) signaling pathway initiates cancer, promotes tumor survival, and is related to the development of desmoplastic tumor stroma. We conducted a phase 2 study of IPI-926, an oral Hh inhibitor, in patients (pts) with myelofibrosis (MF); NCT01371617. **Methods:** Pts with performance status ≤2, adequate organ function, no active infection, and a life expectancy of at least 3 months, received 160 mg IPI-926 orally daily in continuous 28-day cycles. Response was defined by IWG consensus criteria. Using a Simon 2-Stage method to differentiate a response rate of ≤10% and >30%: ≈12 evaluable pts with MF were to be enrolled; if at least 2 responses occurred, up to 35 pts were to be enrolled. **Results:** 14 pts were treated for a median of 5.1 months (range, 0.7-7.3). Their age was 71 years (range 55-82), with a median of 5.8 years since diagnosis; 4 had palpable spleen of median 10.5 cm (range 6-23), 6 (43%) were transfusion dependent, 8 (57%) had primary MF, and all had ≥ intermediate-2 MF. While several pts had reduction in spleen size by palpation (<50%), no pt had significant improvement in symptoms. One pt had clinical improvement with transfusion independence for 6 months. Two patients progressed to acute leukemia, and 11 were taken off therapy due to no response and/or side effects. Adverse events of any grade (in >30% of patients) included elevated AST or ALT in 11 pts, nausea in 8, increased conjugated bilirubin in 7 (3 with gr 3 toxicity), decreased appetite in 6 (1 with gr 3 toxicity), and constipation or vomiting in 5 pts each. Correlative studies on samples after >3 months on therapy were analyzed: 2/8 pts had reduction in GLI1 mRNA in bone marrow (BM) aspirate cells; 3/10 pts had reductions in GLI1 protein by immunohistochemistry in BM biopsies by 3 months; 4/10 pts had minimal to modest decreases in fiber-length density in BM biopsies at 3 months. Serum cytokine levels measured at baseline and after 4 weeks of treatment were not qualitatively different. **Conclusions:** The safety and clinical activity (ORR ≤ 10%) of IPI-926 did not support continued evaluation as a monotherapy in MF. The preliminary biologic activity suggests Hh pathway inhibitors in combination with other novel agents in MF should be considered. Clinical trial information: NCT01371617.

**7112 General Poster Session (Board #397), Mon, 1:15 PM-5:00 PM**

**Survival outcomes of primary myelodysplastic syndrome in United States.** *Presenting Author: Guru Subramanian Guru Murthy, University of Arkansas for Medical Sciences, Little Rock, AR*

**Background:** Hypomethylating agents were approved for use in treatment of MDS after 2004. This study aims to delineate the discrepancies in survival of MDS at population level before and after approval of these agents. **Methods:** Using Surveillance, Epidemiology and End Results (SEER-17) database, adult patients with primary MDS, diagnosed between 2001 to 2010 were identified. Overall survival analysis was performed using Kaplan-Meier method and compared by log rank. Period of diagnosis for survival was analyzed between 2001-2005 and 2006-2010. Multivariate analysis was performed using Cox Proportional Hazards regression method. **Results:** 22,051 patients with MDS with a median age of 76 years were included. Median overall survival (OS) for different age groups was as follows: age $<$ 60 – 59 months, age 60 to70 – 36 months, age $>$ 70 – 23 months, $p < 0.001$). We found that 5 year OS has improved across all age groups diagnosed from 2006-2010 compared to 2001-2005 (age $<$ 60 – 50.3% vs. 16%, age 60-70 – 37.8% vs. 14 %, age $>$ 70 – 23% vs. 3% $p<0.01$). Females had a better overall survival than males (32 month vs 24 months respectively, $p < 0.001$). Blacks had a higher overall survival than whites or other races (34 months vs 27 months) (p-not significant). On multivariate analysis age $>$ 60 years ( HR-1.38 95% CI 1.30-1.46, $p<0.01$) and male sex ( HR-1.17, 95% CI 1.13-1.21, $p<0.01$) were significantly associated with higher mortality. Diagnosis after the year 2005 was associated with decreased mortality (HR 0.78, 95% CI 0.74-0.82, $P<0.001$). **Conclusions:** Overall survival has continued to improve across all age groups with introduction of hypomethylating agents and better supportive care.

**7113 General Poster Session (Board #398), Mon, 1:15 PM-5:00 PM**

**PKC412 (midostaurin) is safe and highly effective in systemic mastocytosis: Follow up of a single-center Italian compassionate use.** *Presenting Author: Cristina Papayannidis, DIMES, Institute of Hematology, Bologna, Italy*

**Background:** Treatment of SM usually focuses on symptom relief by histamine receptor antagonists and other supportive therapy. However, in aggressive and leukemic variants, cytoreductive and targeted drugs must be applied. **Methods:** From 2008, 22 patients (male/female=11/11) affected by SM have been referred to our Institution. Twelve (55%) was diagnosed with ASM, presenting with systemic symptoms associated with signs of organ involvement (skeletal lesions, ascites, liver function impairment or bon marrow disfunction). Therefore, due to the failure of a first line therapy (IFNalfa, Imatinib and 2CdA in 56%, 11% and 33% of the patients, respectively), a personalized use of PKC412 was asked and obtained for 9 out of 12 ASM patients. Thus, from March 2011, 9 (M/F =3/9) patients with ASM have been treated with PKC412, administered orally, at the dosage of 100 mg twice daily, continuously. The median age was 60 years (range 39-75); the median time from diagnosis was 6 months (range 2-53). Median serum tryptase level was 100 mcg/L(range 19.3-1160). *C-kit* mutation D816V was present in 8 out of 9 patients. Cytogenetic analysis was normal in all the patients. **Results:** Seven out of nine patients were evaluable for response. The median duration of therapy was 517 days (range 327-970+). According to European Criteria, a Major response was observed in one patient, and a partial response in 6 patients. Overall, the drug was well tolerated, and no serious adverse events were observed. All the patients obtained a quick improvement of clinical symptoms, in terms of weight gain, bowel function and skeletal pain. At the bone marrow evaluation, the persistence of the D816V c-kit mutation was observed, despite a significant decrease of mast cell marrow involvement. **Conclusions:** In a small cohort of ASM patients, the prolonged therapy with PKC412 is safe and effective, mainly on symptoms improvement and haematological profile. Nevertheless, the persistence of the D816V c-kit mutation suggests that many other oncogenic factors may be responsible for the pathogenesis of the disease.

**7114 General Poster Session (Board #399), Mon, 1:15 PM-5:00 PM**

**Phase 2 trial of PRM-151, an antifibrotic agent, in patients with myelofibrosis: Stage 1 results.** *Presenting Author: Srdan Verstovsek, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** PRM-151 (PRM) is a recombinant form of Pentraxin-2, an endogenous human protein that acts at sites of tissue damage, inducing macrophage differentiation to prevent and reverse fibrosis. PRM has broad anti-fibrotic activity in multiple preclinical models of established fibrotic disease and no dose limiting toxicities in Phase 1 trials. This study investigates the potential of PRM in myelofibrosis (MF) to reduce bone marrow (BM) fibrosis and to improve key MF-related disease features including abnormal blood counts, splenomegaly, and symptoms. **Methods:** Patients with Intermediate-1, intermediate-2, or high risk MF with grade $>$2 BM fibrosis, either on no current therapy or on a stable dose of ruxolitinib (RUX) for at least 12 weeks were eligible for stage 1 of this open label adaptive trial. Assignment to one of the 4 treatment arms was per investigator and patient choice: PRM IV 1-hour infusion on days 1, 3 and 5, then weekly (QW) or every 4 weeks (Q4W), alone or with continuous oral rux. Primary endpoint is overall response rate by IWG-MRT criteria (spleen by palpation). A decrease in BM fibrosis by $\geq$ 1 grade with otherwise stable disease is also considered a response. BM biopsies are obtained at baseline, 3 and 6 months, read by local pathologists and a blinded central reviewer. **Results:** 27 subjects were enrolled in Stage 1: 7 PRM QW, 7 PRM Q4W, 7 PRM QW + RUX, 6 PRM Q4W + RUX. As of January 13, 2014, 15 and 6 subjects have completed 8 and 12 wks of treatment, respectively (none have yet completed 24 wks). There was no apparent treatment-related myelosuppression, and among all AEs, only herpes labialis and anemia occurred in $>$1 subject. There have been 4 serious adverse events in 3 subjects: 1 with abdominal pain, 1 with hypoxia, and an 85 year old subject who died from gastroenteritis and pneumonia. Improvement in bone marrow fibrosis (Grade 3 to 1; Grade 2 to 0; read by a local pathologist) was observed in 2 of 6 subjects at the 3-month BM mark (1 on PRM Q4W, 1 on PRM Q4W + RUX). **Conclusions:** In stage 1 of this phase 2 trial of MF patients, PRM has shown good tolerability both alone and in combination with RUX. Updated safety and efficacy data on all 27 subjects will be presented at the meeting, including central BM (3 and 6 month) reviews. Clinical trial information: NCT01981850.

**7115 General Poster Session (Board #400), Mon, 1:15 PM-5:00 PM**

**Clinical relevance of genetic mutations on treatment response to the demethylating agents in myelodysplastic syndromes.** *Presenting Author: Hyun Ae Jung, Department of Medicine, Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

**Background:** In the post-epigenetic therapy era, treatment approaches for patients with MDS have improved significantly over the last decade, especifically, in terms of quality of life and leukemic transformation and survival. Unlike, conventional chemotherapy, it often takes several cycles of hypomethylating agent to visualize the effect of the therapy. However, previous study had heterogenous study populations and had low response rate to hypomethylating agent. We investigate the prevalence of recurrent genetic mutations in de novo MDS patients and elucidate the prognostic and predictive role of mutations on the 1st line decitabine treatment in MDS. **Methods:** We investigated genes including spliceosomal machinery genes (SRSF2, USAF1, ZRSR2) and methylating machinery genes (TET3 and DNMT2) and NRAS by Sanger sequencing in patients who were diagnosed with de novo MDS at Samsung medical Center between June 2008 and December 2011 and who were treated with 1$^{st}$line 5-day regimen of decitabine treatment. **Results:** We analyzed clinical data including treatment outcomes in 70 patients (total 290 cycles). The overall response (complete remission, partial remission, marrow complete remission and hematologic improvement) rate was 52.5%. The median time to any response was two (range 1-6). Patients who showed hematologic improvements had significantly longer survival than those who did not (9.8 vs 22.9 months, P-value=0.004). The prevalence of mutations in the methylating machinery genes were 17.1% (N=12). In the baseline characteristic between wild type and mutated genes, there was no significant difference. The overall response rate was significantly higher in the patient who had the mutations in methylating machinery genes (46.6% vs 82.3%, P-value=0.027). **Conclusions:** The current results showed that methylating machinery gene TET2$^{MUT}$, DNMT3A$^{MUT}$ had clinical relevance as preditive biomarker for hypomethylating agents.

**7116 General Poster Session (Board #401), Mon, 1:15 PM-5:00 PM**

**Impact of high-dose radiation exposure on myelodysplastic syndrome patients treated with azacitidine in Nagasaki atomic bomb survivors.** *Presenting Author: Tatsuro Jo, Department of Hematology, Japanese Red Cross Society Nagasaki Genbaku Hospital, Nagasaki, Japan*

**Background:** Myelodysplastic syndromes (MDS) may arise de novo or secondarily after treatment with chemotherapy and/or radiation therapy for other cancers or, rarely, after environmental exposures. High-dose radiation exposure (such as an atomic bomb) increases the risk of developing MDS. Azacitidine (AZA), a hypomethylating agent, is the mainstay of therapy in MDS in Japan. But there have no reports investigating the efficacy of AZA in atomic bomb survivors suffering from MDS. **Methods:** We retrospectively evaluated 33 pts diagnosed MDS between April 2011 and April 2013 at Nagasaki Genbaku Hospital. All patients, included 13 atomic bomb survivors, received AZA. The primary objective was to estimate overall survival rates (OS). **Results:** The Table summarizes baseline characteristics and response rates. There was no clear difference in the background excluding age ($P$=0.0258) between atomic bomb survivors (A) and non-atomic bombed (non-A) pts. ORR (CR/mCR/PR) was no difference ($P$=0.2635), but the median OS at November 2013 was significantly different between two groups (13 months for A vs undefined for non-A, $P$=0.0429). **Conclusions:** These data demonstrated that despite the same ORR, OS of MDS pts in Nagasaki atomic bomb survivors was significantly short compared to non-atomic bombed pts. A certain influence by exposure of the atomic bomb can be considered. Further studies to clarify the cause are warranted.

| | | Atomic bomb survivor (A) n=13 | Non-atomic bomb patients (non-A) n=20 | *P* value |
|---|---|---|---|---|
| **Age (median)** | | 68–84 (74) | 46–87 (67) | |
| **WHO subtype** | RCMD | 7 (54%) | 13 (65%) | 0.00258 |
| | RAEB-1 | 2 (15%) | 5 (25%) | |
| | RAEB-2 | 4 (31%) | 7 (54%) | |
| **IPSS at diagnosis** | Int-1 | 5 (39%) | 8 (40%) | 0.2857 |
| | Int-2 | 6 (46%) | 10 (50%) | |
| | High | 2 (15%) | 2 (10%) | |
| **Cytogenetics** | Good | 7 (54%) | 8 (40%) | 0.3020 |
| | Intermediate | 3 (23%) | 2 (10%) | |
| | Poor | 3 (23%) | 10 (50%) | |
| **Blood transfusion dependence** | + | 10 (77%) | 16 (80%) | 1.0000 |
| | - | 3 (23%) | 4 (20%) | |
| **Overall response rate** | CR | 2 (15%) | 7 (35%) | 0.2635 |
| | marrow CR | 1 (8%) | 1 (5%) | |
| | PR | 2 (15%) | 0 (0%) | |
| | SD | 8 (62%) | 12 (60%) | |
| **AZA cycle (median)** | | 4 (1-19) | 7 (1-21+) | |

**7117 General Poster Session (Board #402), Mon, 1:15 PM-5:00 PM**

**Impact of palifermin use on pediatric patient (PedPts) hematopoietic cell transplant (HCT) outcomes.** *Presenting Author: Wael Saber, Medical College of Wisconsin, Milwaukee, WI*

**Background:** Palifermin (KGF) is an FDA approved prophylactic human keratinocyte growth factor for prevention of severe chemoradiotherapy-related mucositis. Clinical trials that evaluated KGF enrolled few PedPts. Using CIBMTR data, this study evaluates effects of KGF use in a pediatric population. **Methods:** We performed a 1:3 (KGF vs. no KGF) matched cohort analysis (matched on HCT, donor type, disease, disease status and age). Stratified Cox models were built and propensity scores were used to adjust for potential confounders. **Results:** From 2005-2012 816 patients were selected; 60% underwent Allogeneic HCT (AlloHCT), mostly for acute lymphoblastic leukemia (ALL). 40% underwent Autologous HCT (AutoHCT), mostly for solid tumors (Table 1). Two-year survival (OS) and disease-free survival (DFS) in AlloHCT group (58 vs. 66%, p=0.10; 49% vs. 60%, p=0.06) and AutoHCT group (73% vs. 77%, p=0.47; 60% vs. 64%, p=0.63) were not different between KGF and no KGF, respectively. Similarly, in multivariate analysis, there were no differences in outcomes between the two groups. **Conclusions:** Among PedPts undergoing HCT, KGF use is not associated with OS, DFS, neutrophil recovery or graft vs host disease (GVHD) rates. Due to data limitations, rate of mucositis was not assessed in this study.

| | KGF N (%) | No KGF N (%) |
|---|---|---|
| **N** | 210 | 606 |
| **Age, yrs** | 9 (<1 - 18) | 9 (<1 - 18) |
| **Disease** | | |
| **AML** | 27 (13) | 78 (13) |
| **ALL** | 86 (41) | 252 (42) |
| **NHL** | 13 ( 6) | 35 ( 6) |
| **Hodgkin disease** | 15 ( 7) | 42 ( 7) |
| **Solid Tumors** | 69 (33) | 199 (33) |
| **Donor (AlloHCT)** | | |
| **HLA-identical sibling** | 33 (16) | 97 (16) |
| **Other related** | 5 (2) | 15 (2) |
| **Match Unrelated** | 24 (11) | 72 (12) |
| **Mismatch Unrelated** | 29 (14) | 79 (13) |
| **Cord blood** | 29 (14) | 86 (14) |
| **Conditioning regimen*** | | |
| **AutoHCT: BEAM** | 40 (44) | 153 (60) |
| **AlloHCT: TBI+others** | 105 (88) | 298 (85) |
| **Median follow-up of survivors, m** | 31 | 36 |

| | KGF (yes vs. no) RR (95% CI) | P |
|---|---|---|
| **AlloHCT only:** | | |
| **Acute GVHD, II-IV** | 1.19 (0.79-1.80) | 0.40 |
| **Chronic GVHD** | 0.66 (0.39-1.10) | 0.11 |
| **AlloHCT and AutoHCT:** | | |
| **Neutrophil recovery** | 1.20 (0.98-1.48) | 0.08 |
| **DFS** | 1.14 (0.84-1.53) | 0.39 |
| **OS** | 1.20 (0.87-1.66) | 0.27 |

*Largest group provided

**7118 General Poster Session (Board #403), Mon, 1:15 PM-5:00 PM**

**Characteristics of patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN): Male predominance, propensity for extramedullary involvement, and poor outcomes.** *Presenting Author: Naveen Pemmaraju, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive hematologic malignancy. Little is known about characteristics and outcomes of patients (pts) with BPDCN. **Methods:** We performed an updated retrospective review of pts age ≥ 18 years with a pathological diagnosis of BPDCN. **Results:** 26 pts were evaluated at our institution (Oct 1998-Dec 2013). Median age was 58 years (range 20-86). 23 (88%) were male. Bone marrow (BM) was involved in 17 (65%), skin in 13 (50%), lymph nodes in 7 (27%), CSF in 3 (12%) and 1 (4%) pt each had disease involving the brain, uterus/ovary, elbow/soft tissue, and pleural fluid. Tumor immunophenotype: CD4+ (23/23), CD56+ (21/23), TCL-1+ (14/15), CD 123+ (13/14). CD22 was expressed in 2/5 pts. Cytogenetics in 14 pts showed: diploid (8), complex karyotype (5), and del (12p13) (1pt). Median CBC was: WBC 5.6 x $10^9$/L (1.7-76.5), Hb 12.3 g/dL (8.3-14.6), and platelet count 160 x $10^9$/L (44-294). Median BM blasts: 19% (0-94). Therapies given: 16 (62%) first-line therapy with Hyper-CVAD, 4 (15%) CHOP, 2 (8%) bortezomib-based, 1 clinical trial (DT-IL3), 1 daunorubicin+ARAC, 1 oral MTX, 1 interferon-based therapy. Five (19%) pts received radiation (XRT) as part of their therapy. Median follow-up time: 24 months (5-59 mo). Median number of chemotherapy regimens: 2 (1-6). CR was achieved in 14 pts. The median CR1: 18 mo (4-39 mo). Median overall survival (OS) was 29 mo (1-59 mo). 8 pts (31%) received stem cell transplant (SCT) (3 autologous, 3 allogeneic, 2 cord). Median OS for pts receiving SCT was 31 mo (13-40 mo) versus a median OS for non-SCT group (n=18) of 29 mo (1-59), p= 0.98. **Conclusions:** We observed a large male predominance, propensity for extra-medullary disease involvement, and overall poor outcomes despite intensive multi-agent chemotherapy and SCT for pts with BPDCN. A better understanding of the biologic basis of this disease and novel, targeted treatment approaches are urgently needed. Among novel therapies available, targeting cell surface CD123 appears to be most promising (DT-IL3) and investigation is ongoing (5/5 (100%) evaluable patients with major responses; Frankel,AE et al. ASH 2013).

**TPS7119 General Poster Session (Board #404A), Mon, 1:15 PM-5:00 PM**

**An open-label, phase 1b, dose-escalation study (CA180-373) of dasatinib plus nivolumab, an investigational anti-programmed cell death 1 (PD-1) antibody, in patients (pts) with previously treated chronic myeloid leukemia (CML).** *Presenting Author: Kimmo Porkka, University of Helsinki and Helsinki University Central Hospital Cancer Center, Helsinki, Finland*

**Background:** CML has become a chronic disease for many pts treated with BCR-ABL1 tyrosine kinase inhibitors (TKIs). However, new approaches are needed to increase the prevalence of deep responses suitable for treatment discontinuation and to treat resistant/recurrent CML. Immune cell–mediated approaches (eg, stem cell transplantation, interferon-$\alpha$) can be effective. PD-1 ligation provides a negative costimulatory signal governing the balance between T-cell activation and tolerance. The potent second-generation TKI dasatinib may have synergy with nivolumab, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody. Nivolumab has shown encouraging clinical activity against several solid tumors. PD-1 is upregulated on CD8+ T cells in CML pts (Christiansson *PLoS ONE* 2013;8: e55818) and blocking the PD-1/ligand interaction prolonged survival in a murine model (Mumprecht *Blood* 2009;114:1528-36). The study will assess safety, tolerability, and preliminary efficacy of dasatinib + nivolumab in previously treated CML in chronic or accelerated phase (CP/AP). **Methods:** In this open-label, phase 1b dose-escalation study, pts must be aged ≥18 years (y) and have Philadelphia chromosome–positive CML-CP/AP, ECOG performance status ≤1, and no known dasatinib-resistant BCR-ABL1 mutations. Pts must have received ≥2 prior TKIs, be progressing, or have had resistance, intolerance, or suboptimal response to the most recent therapy. Treatment in the dose-escalation phase is dasatinib 100 mg (CP) or 140 mg (AP) once daily with nivolumab 0.3 mg/kg (dose level [DL] –1), 1 mg/kg (DL 1), or 3 mg/kg (DL 2) by intravenous injection every 2 weeks for ≤2 y, followed by ≤1 y of dasatinib only. Treatment in the expansion phase will be dasatinib (same doses) + nivolumab (dose based on safety). The primary objective is to determine safety and tolerability. Secondary endpoints are major molecular response (MMR) and molecular response ($MR^{4.5}$ rates at 6, 12, 24, and 36 months and time to and duration of MMR and $MR^{4.5}$ up to 36 months. Estimated completion: August 2018. Clinical trial information: NCT02011945.

**TPS7120^ General Poster Session (Board #404B), Mon, 1:15 PM-5:00 PM**

**Multicenter, phase III, open-label, randomized study in relapsed/refractory CLL to evaluate the benefit of GDC-0199 (ABT-199) plus rituximab compared with bendamustine plus rituximab.** *Presenting Author: Mehrdad Mobasher, Genentech, Inc., South San Francisco, CA*

**Background:** Response rate to initial treatment of CLL is high, but relapsed/refractory (R/R) CLL may be characterized by resistance to chemotherapy. Bendamustine and rituximab (B+R), commonly used to treat patients with relapsed CLL, has shown an overall response rate (ORR) of 59% and median progression-free survival (PFS) of 15.2 mo. Despite progress, CLL remains incurable, and new treatments are needed to improve outcomes. Universal overexpression of Bcl-2, an anti-apoptotic protein, and dysregulation of the intrinsic apoptotic pathway in CLL likely contributes to chemotherapy resistance. GDC-0199/ABT-199 (199), a selective, potent, orally bioavailable Bcl-2 inhibitor, has shown preliminary anti-tumor activity, including complete remissions, in R/R CLL. This study will compare 199+R vs B+R to determine if 199+R provides a more effective and tolerable treatment strategy for R/R CLL, providing a chemotherapy-free regimen. **Methods:** Approximately 370 patients will be enrolled at approximately 150 sites in North America, Europe and Asia Pacific, and randomized 1:1 to receive 199+R (Arm A) or B+R (Arm B). In both arms, R treatment will consist of infusions on Day 1 of each 28-day cycle for 6 cycles (Cycle 1: 375mg/m$^2$; Cycles 2-6: 500mg/m$^2$). In Arm A, after an initial ramp-up period, patients will receive 400mg of 199 daily. After completion of 199+R, 199 will be continued until disease progression or for a maximum of 2 years. In Arm B, bendamustine will be infused (70mg/m$^2$) on Days 1 and 2 of each 28-day cycle for 6 cycles. Patients in both arms will be followed until disease progression. Key eligibility criteria include a diagnosis of R/R CLL; previously treatment with 1-3 lines of therapy; ECOG PS $\leq$1; and adequate marrow function. The primary outcome is investigator-assessed PFS (time from randomization until disease progression or death from any cause). Secondary outcomes include ORR, adverse events, and patient-reported outcomes. The study opened in Dec 2013; primary estimated completion is Aug 2020. Clinical trial information: NCT02005471.

**TPS7121 General Poster Session (Board #405A), Mon, 1:15 PM-5:00 PM**

**A phase 2 open-label study of the efficacy of ABT-199 (GDC-0199) in patients with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) harboring 17p deletion.** *Presenting Author: William G. Wierda, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Evasion of apoptosis is a hallmark of cancer. Overexpression of the anti-apoptotic Bcl-2 protein is associated with tumorigenesis and resistance to chemotherapy. ABT-199 is a selective, potent, orally bioavailable small molecule Bcl-2 antagonist that works by directly relieving the inhibition of apoptosis, downstream of p53. Preliminary phase 1 data with ABT-199 indicate promising therapeutic activity, with a greater than 80% overall response rate in patients (pts) with heavily pretreated CLL, independent of poor prognostic indicators including 17p deletion [del(17p)]. This Phase 2 multinational study is designed to evaluate ABT-199 monotherapy in patients with R/R CLL harboring del(17p). **Methods:** ABT-199 treatment starts with a lead-in 20mg daily dosing period with weekly dose increases up to 400 mg daily as the study final dose. Treatment continues once daily until progression or discontinuation for toxicity. Study visits are weekly through week 4 or 5, every 4 weeks until week 36, and every 12 weeks thereafter. Key eligibility criteria include relapsed or refractory CLL harboring del(17p) in $\geq$7% of cells, as determined by central diagnostics; clinically measurable disease; and no previous allogeneic hematopoietic cell transplant (alloHCT), evidence of Richter's transformation, or uncontrolled autoimmune cytopenias. The primary objective of this study is to evaluate overall response rate (ORR), using IWCLL 2008 criteria. Secondary objectives are to evaluate the complete remission rate, partial remission rate, duration of response, progression-free survival, time to progression, overall survival, and the percentage of pts who are able to proceed to alloHCT. Minimal residual disease status in the peripheral blood and bone marrow will be assessed as an exploratory objective. Pharmacokinetic data will be evaluated using a population approach. The ORR for ABT-199 will be tested to reject the null hypothesis of a 40% ORR once 70 pts have completed 6 months of treatment or after all enrolled pts have discontinued ABT-199, whichever is earlier. The study began in June, 2013 and is currently enrolling patients. (NCT01889186) Clinical trial information: NCT01889186.

**TPS7122 General Poster Session (Board #405B), Mon, 1:15 PM-5:00 PM**

**DUO: A phase 3 trial of the PI3K-$\delta,\gamma$ inhibitor IPI-145 versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma.** *Presenting Author: Ian Flinn, Sarah Cannon Research Institute, Nashville, TN*

**Background:** Phosphoinositide 3-kinase (PI3K)-$\delta,\gamma$ isoforms are preferentially expressed in leukocytes and are central to the growth and survival of certain B and T cell malignancies. Inhibition of these isoforms by IPI-145, an oral PI3K-$\delta,\gamma$ inhibitor, has unique therapeutic potential in hematologic malignancies. IPI-145 has shown clinical activity and a favorable safety profile in a broad range of hematologic malignancies in an ongoing phase 1 trial (IPI-145-02). Based on these data, the DUO phase 3 trial (IPI-145-07; ClinicalTrials.gov number: NCT02004522) has been initiated to evaluate the efficacy and safety of IPI-145 compared to ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). **Methods:** This open-label, two-arm trial includes adult patients with active CLL/SLL who meet at least one of the International Workshop on CLL (IWCLL) 2008 treatment criteria; have disease progression during or after previous CLL therapy; are not appropriate for purine analog-based therapy; and not refractory to ofatumumab. The trial will enroll approximately 300 patients, randomized 1:1 to IPI-145 or ofatumumab at sites in and outside the US. Patients randomized to IPI-145 will receive 25 mg IPI-145 orally, twice daily in 28-day treatment cycles for up to 18 cycles or until disease progression or unacceptable toxicity. After 18 cycles, patients may receive additional cycles of IPI-145 for up to 3 years, if they have documented evidence of response and disease requiring continued treatment. Patients randomized to ofatumumab will receive treatment consistent with the approved product label. Patients on both arms will be followed for up to 3 years from the first dose of study drug. The primary efficacy endpoint is progression-free survival. Key secondary endpoints include safety, overall survival and pharmacokinetic parameters. Patients with progressive disease during the trial may be eligible to receive the opposite study medication in a separate Infinity-sponsored extension protocol (IPI-145-12). This trial is currently enrolling patients. Clinical trial information: NCT02004522.

**TPS7123 General Poster Session (Board #406A), Mon, 1:15 PM-5:00 PM**

**A phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib in combination with bendamustine and rituximab for previously untreated chronic lymphocytic leukemia.** *Presenting Author: Gilles A. Salles, Lyon Sud University Hospital, Pierre-Bénite, France*

**Background:** PI3K$\delta$ is critical for activation, proliferation and survival of B cells and plays a role in homing and retention in lymphoid tissues. PI3K$\delta$ signaling is hyperactive in many B-cell malignancies. Idelalisib (GS-1101) is a first-in-class, targeted, highly selective, oral inhibitor of PI3K$\delta$ that reduces proliferation, enhances apoptosis, and inhibits homing and retention of malignant B cells in lymphoid tissues (Lannutti et al, 2011). A recent phase 3 trial demonstrated that idelalisib plus rituximab is highly active in pts with relapsed CLL compared to placebo plus rituximab: patients receiving idelalisib had improved rates of overall response (81% vs. 13%) and overall survival at 12 months (92% vs. 80%), with an acceptable safety profile (Furman et al, 2014). The regimen of bendamustine + rituximab has demonstrated efficacy in the treatment of patients with previously untreated CLL. **Methods:** 280 patients with previously untreated CLL and measurable lymphadenopathy will be enrolled in this global phase 3, multicenter, randomized, double-blind, placebo-controlled trial. Pts will be randomized in a 1:1 ratio to Arm A or B of the study. On Arm A, subjects will receive idelalisib (150 mg BID continuously for 96 weeks) plus rituximab (6 infusions of 375 – 500 mg/m$^2$ over 6 months) and bendamustine (12 infusions of 90 mg/m$^2$ over 6 months). In Arm B, subjects will receive placebo instead of idelalisib. Stratification factors include *IGHV* mutational status, del(17p) status, and Rai stage. The primary endpoints of the study are minimal residual disease and PFS. The secondary endpoints are ORR, nodal response rate, CR, and OS. The difference in PFS will be compared between Arm A and Arm B in the ITT analysis set using Kaplan-Meier methods and the stratified log-rank test. The study opened for enrollment in Jan 2014. Clinical trial information: NCT01980888.

**TPS7124 General Poster Session (Board #406B), Mon, 1:15 PM-5:00 PM**

**Treatment-free remission (TFR) following nilotinib (NIL) in patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP): ENESTfreedom, ENESTop, ENESTgoal, and ENESTpath.** *Presenting Author: Francois-Xaxier Mahon, Université Victor Ségalen, Bordeaux, France*

**Background:** Approximately 40% of pts who achieve deep, sustained molecular response (MR) on imatinib (IM) are able to successfully maintain TFR (Mahon FX, et al. *Lancet Oncol.* 2010;11:1029-1035). NIL results in higher rates of deep, sustained MR vs IM and may enable more pts to achieve successful TFR. Four ongoing studies will evaluate the key factors for achieving and sustaining TFR following NIL in pts with CML-CP (Table). **Methods:** Each study includes a NIL consolidation phase, during which pts undergo frequent molecular monitoring, followed by a TFR phase. In ENESTfreedom and ENESTop, pts with $MR^{4.5}$ (BCR-ABL $\leq$ 0.0032% on the international scale [$BCR\text{-}ABL^{IS}$]) on NIL directly enter the 1-y consolidation phase upon enrollment. In ENESTgoal and ENESTpath, pts without deep MR on IM are switched to NIL upon enrollment; after switching to NIL, pts in ENESTgoal who achieve $MR^{4.5}$ and pts in ENESTpath who complete 2 y of NIL therapy and achieve $MR^4$ ($BCR\text{-}ABL^{IS} \leq 0.01\%$) will be randomized to a 1- or 2-y consolidation phase. Each study protocol defines a required MR level that pts must maintain during the consolidation phase to be eligible for the TFR phase. During the TFR phase of each study, pts must re-initiate therapy if their MR rises above a defined threshold (ie, molecular relapse). The rate and duration of successful TFR on NIL will be evaluated in each study. Clinical trial information: NCT01784068.

| | ENESTfreedom NCT01784068 | ENESTop NCT01698905 | ENESTgoal NCT01744665 | ENESTpath NCT01743989 |
|---|---|---|---|---|
| Planned N | 175 | 117 | 300 | 1,058 |
| Treatment prior to enrollment (duration) | Frontline NIL ($\geq$ 2 y) | Second-line NIL ($\geq$ 3 y total; $\geq$ 2 y NIL) | IM ($\geq$ 1 y) | IM ($\geq$ 2 y) |
| Response at enrollment | $MR^{4.5}$ | $MR^{4.5}$ | MMR but not $MR^{4.5}$ | Complete cytogenetic response but not $MR^4$ |
| NIL consolidation phase duration | 1 y | 1 y | 1 y or 2 y | 1 y or 2 y |
| MR required during NIL consolidation phase to be eligible for TFR phase | $MR^{4.5}$ | $MR^{4.5}$ | $MR^{4.5}$ | $MR^4$ |
| Trigger to re-initiate therapy | Loss of MMR | Loss of MMR or confirmed loss of $MR^4$ | Confirmed loss of $MR^4$ | Loss of MMR or confirmed loss of $MR^4$ |

Abbreviations: MMR, major molecular response ($BCR\text{-}ABL^{IS} \leq 0.1\%$).

**TPS7125 General Poster Session (Board #407A), Mon, 1:15 PM-5:00 PM**

**Phase 3 study of oral lenalidomide as maintenance therapy for patients with B-cell chronic lymphocytic leukemia (CLL).** *Presenting Author: Asher Alban Akmal Chanan-Khan, Mayo Clinic, Jacksonville, FL*

**Background:** Despite recent advances in chemo-immunotherapy combinations for the treatment (Tx) of CLL, most patients (pts) relapse and eventually die from the disease. Maintenance therapy has made impact in other B-cell cancers, such as myeloma; its role and the optimal agent in CLL is unknown. Recent trials of rituximab have shown promise as maintenance therapy; however, the clinical use may be limited due to the intravenous formulation. Lenalidomide (LEN) shows encouraging efficacy in CLL pts; this and its positive impact on survival outcome as maintenance Tx in myeloma pts rationalizes its investigation in CLL. Additionally, the oral formulation makes it better suited as a long-term, single-agent Tx regimen. **Methods:** This phase 3, multicenter, randomized, double-blind, placebo controlled, parallel-group study investigates the efficacy and safety of oral LEN as maintenance therapy for CLL pts who showed a partial response (PR) to second-line therapy. Primary objectives are PFS and OS. Secondary objectives include safety, tumor response, response duration and health-related quality of Life. Additionally, the occurrence of secondary primary malignancy is monitored. Eligible pts ($\geq$18 years) have previously received a chlorambucil-, a purine analog-, an anti-CD20-antibody-, or a bendamustine-based regimen in first- and/or second-line therapy, and must have achieved $\geq$PR to second-line therapy. Pts with del(17p) may have previously received an alemtuzumab-containing regimen. 400 pts (260 pts currently enrolled) with $\geq$PR following second-line therapy will be enrolled and randomized (1:1) to either the placebo or the LEN arm. Pts will receive placebo or 2.5 mg LEN per day (QD) on days 1-28 of each 28-day cycle. Subsequent LEN dose escalation to 5 mg QD at cycle 2 and to 10 mg at cycle 6 may occur, if tolerated in the previous cycle. Prior to study commencement, pts are tested for poor prognostic indicators (del(17p), del(11q), unmutated IGVH and high B2M). Exploratory biomarkers include (ZAP-70, immune cell analysis and CD80). This study is conducted in accordance with good clinical practice and all applicable regulatory requirements. Clinical trial information: NCT00774345.

**TPS7126 General Poster Session (Board #407B), Mon, 1:15 PM-5:00 PM**

**Connect MDS and AML: The myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) disease registry.** *Presenting Author: David P. Steensma, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Diagnostic approaches, treatment (tx) patterns, and clinical outcomes for patients (pts) with MDS or AML outside of clinical trials are poorly characterized. The Connect MDS and AML Registry (Clinicaltrials-.gov Identifier NCT01688011) is a prospective, longitudinal, multicenter observational registry for pts newly diagnosed with MDS or AML. It is designed to capture diagnostic evaluation, risk assessment, and tx patterns; objective clinical and pt-reported outcomes (PROs); and biospecimens from pts cared for in community or academic centers. **Methods:** Approximately 1,500 pts from $\approx$ 150 clinical sites across the United States will be enrolled into 4 cohorts: IPSS low/Int-1–risk MDS (n = 700, including $\approx$ 250 del(5q) MDS), Int-2/high-risk MDS (n = 200), unknown-risk MDS due to unsuccessful bone marrow cytogenetics (n = 100), and AML (n = 500). Pts must have confirmed newly diagnosed ($\leq$ 60 days prior to enrollment) MDS or primary or secondary AML, excluding acute promyelocytic leukemia, based on WHO 2008 diagnostic criteria. AML pts must be $\geq$ 55 years of age. First pt was enrolled in December 2013. Pts will be followed for up to 8 years, until withdrawal from the study, death, or study end. There will be 1 initial remote monitoring visit. Appropriate methods for observational data will be utilized. Primary objectives are to describe current and evolving patterns of diagnosis/prognosis, evaluation, tx, clinical monitoring, and outcomes; compare actual clinical practice with existing management guidelines; describe tx sequencing and associated short- and long-term outcomes, including response, safety, disease progression, and survival; and summarize PROs and health economic outcomes and their association with pt characteristics, tx, and clinical outcomes. Additionally, biospecimens will be collected for correlative studies, including assessment of somatic mutations. Registry results may provide new insights into how tx regimens and tx sequencing data combined with baseline prognostic factors relate to clinical outcomes of pts with MDS or AML. Furthermore, PROs and correlative molecular data will help elucidate the association of tx patterns with relevant effectiveness outcomes.

**TPS7127 General Poster Session (Board #408A), Mon, 1:15 PM-5:00 PM**

**A phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with bendamustine and rituximab for previously treated chronic lymphocytic leukemia (CLL).** *Presenting Author: Herbert Aaron Eradat, David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA*

**Background:** PI3K$\delta$ is critical for the activation, proliferation and survival of B cells and plays a role in homing and retention of B cells in lymphoid tissues. PI3K signaling is hyperactive in many B-cell malignancies. Idelalisib is a first-in-class, selective, oral inhibitor of PI3K$\delta$ that reduces proliferation, enhances apoptosis, and alters trafficking of malignant B cells in lymphoid tissues (Lannutti, 2011). Phase 1 trials demonstrated that idelalisib is highly active in heavily pretreated pts with CLL as a single agent or in combination with rituximab (R), bendamustine (B), or BR: pts experienced reductions in disease-associated chemokines, profound and rapid reductions in lymphadenopathy, and durable clinical benefit with an acceptable safety profile (Sharman et al, 2011; Coutre et al, 2012; Furman et al, 2014). **Methods:** Study will enroll 390 pts with previously treated CLL who have measurable lymphadenopathy, have received prior therapy containing a purine analog or B and an anti-CD20 monoclonal antibody, are not refractory to B, have experienced CLL progression within 36 months from the completion of the last prior therapy, and are currently sufficiently fit to receive cytotoxic therapy. Pts will be randomized in a 1:1 ratio to Arm A or B of the study. On Arm A, subjects will receive idelalisib continuously at 150 mg BID + R at 375 mg/m$^2$ (1$^{st}$ dose) and then 500 mg/m$^2$ every 4 weeks for 6 cycles + B at 70 mg/m$^2$ on Days 1 & 2 of each 4-week cycle for 6 cycles. On Arm B, subjects will receive placebo instead of idelalisib. Stratification factors include IGHV mutational status, del17p/p53 mutation status, and refractory/relapsed status. The primary endpoint is PFS and key secondary endpoints include ORR, lymph node response rate, CR rate, and OS. This is an event-driven trial and primary endpoint evaluation will be based on independent central review. For the primary efficacy analysis, the difference in PFS between the treatment arms will be assessed in the ITT analysis set. The study was initiated in June 2012. Clinical trial information: NCT01569295.

**TPS7128^ General Poster Session (Board #408B), Mon, 1:15 PM-5:00 PM**

**RESPONSE 2: A phase 3b study evaluating the efficacy and safety of ruxolitinib in patients with hydroxyurea (HU)-resistant/intolerant polycythemia vera (PV) versus best available therapy (BAT).** *Presenting Author: Francesco Passamonti, Ospedale di Circolo e Fondazione Macchi, Varese, Italy*

**Background:** PV is a myeloproliferative neoplasm characterized by clonal stem cell proliferation, hyperviscous blood, significant morbidity, and reduced life span. Advanced PV results in splenomegaly, severe constitutional symptoms, and possible evolution to myelofibrosis and acute myeloid leukemia (AML). Nearly all patients (pts) have a mutation in *JAK2*, and > 95% have the *JAK2* V617F allele. HU is the myelosuppressive agent of choice in high-risk pts, but it often loses efficacy over time and may cause unacceptable skin toxicities. Therapeutic options in the case of HU resistance are limited, and survival is significantly reduced. A phase 2 study in HU-resistant/-intolerant PV pts showed that ruxolitinib, a potent and selective JAK1/JAK2 inhibitor, was well tolerated and achieved rapid and durable clinical responses, including hematocrit (Hct) normalization, phlebotomy independence, resolution of splenomegaly, and improvements in symptoms (Verstovsek et al, *Cancer,* 2013). RESPONSE, a phase 3 trial, was designed to compare the efficacy and safety of ruxolitinib with best available therapy (BAT) in HU-resistant/-intolerant PV pts with splenomegaly. **Methods:** RESPONSE 2 is an open-label, randomized (1:1), phase 3b study (NCT02038036) designed to compare the efficacy and safety of ruxolitinib with BAT in PV pts (per revised WHO criteria) who require phlebotomy and are HU-resistant/-intolerant. Target enrollment is 104 pts and includes pts without splenomegaly, expanding the RESPONSE patient population. The primary endpoint is the achievement of Hct control, defined as Hct < 45% at week 16 and maintained until week 28, and no phlebotomy from week 4 to week 28, with ≤ 1 phlebotomy postrandomization and prior to week 4. Secondary endpoints include peripheral blood count remission, partial remission (ELN and IWG-MRT criteria), and resolution of symptoms in MPN-SAF TSS at week 28. The BAT group may cross over to ruxolitinib on or after week 28 if they have Hct > 45%, receive phlebotomy, or need to discontinue BAT. Pts will be treated for 52 weeks to assess safety and durability of response. Clinical trial information: NCT02038036.

**7500 Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**A multinational phase III randomized trial with or without consolidation chemotherapy using docetaxel and cisplatin after concurrent chemoradiation in inoperable stage III non-small cell lung cancer (CCheIN).** *Presenting Author: Keunchil Park, Department of Medicine, Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

**Background:** Currently, the recommended treatment for inoperable stage III non-small cell lung cancer (NSCLC) is concurrent chemoradiotherapy (CCRT). The efficacy of consolidation chemotherapy after CCRT needs to be confirmed. The aim of this phase III randomized trial is to determine the efficacy of consolidation chemotherapy with docetaxel (D) and cisplatin (P) following definitive CCRT with the same agents in stage III inoperable NSCLC. **Methods:** Patients with inoperable stage III NSCLC were randomized to either CCRT alone (observation arm) or CCRT followed by consolidation chemotherapy (consolidation arm). N2 or N3 disease was confirmed by PET and/or pathology. CCRT with D (20 mg/m$^2$) and P (20 mg/m$^2$) was administered every week for 6 weeks with a total dose of 66 Gy of thoracic RT as 33 fractions. In the consolidation arm, patients were further treated with 3 cycles of D and P (35 mg/m$^2$each on day 1 and 8, every 3 weeks). The primary endpoint is progression-free survival (PFS). The secondary endpoints are overall survival, response rate, pattern of failure, and safety. Total target number of patients is 434. **Results:** From Oct 2005 to Apr 2011, 437 patients were enrolled and randomized. 419 patients completed CCRT phase (intent-to-treat population; observation 208, consolidation 211). Patients' characteristics were well-balanced in both arms. In the consolidation arm, 142 patients (67%) received consolidation chemotherapy, of whom 95 (67%) completed 3 planned cycles. The median PFS was 8.0 months (95% CI, 7.5 ~ 8.8) in the observation arm and 9.1 months (95% CI, 7.9 ~ 10.9) in the consolidation arm (P=0.38). Median overall survival was 20.6 (95% CI, 17.5 ~ 26.3) and 21.2 months (95% CI, 17.7 ~ 24.7), respectively (P=0.48). Exploratory biomarker study using tissue and blood is under way. **Conclusions:** This study suggests that consolidation chemotherapy with DP after CCRT with weekly DP in stage III NSCLC does not prolong PFS. Clinical trial information: NCT00326378.

**7501 Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**A randomized, double-blind phase 3 trial of adjuvant erlotinib (E) versus placebo (P) following complete tumor resection with or without adjuvant chemotherapy in patients (pts) with stage IB-IIIA EGFR positive (IHC/FISH) non-small cell lung cancer (NSCLC): RADIANT results.** *Presenting Author: Karen Kelly, UC Davis Comprehensive Cancer Center, Sacramento, CA*

**Background:** The proven efficacy of E in advanced NSCLC warranted its evaluation in the adjuvant setting. BR.21 data suggested pts with EGFR positive tumors (IHC/FISH) were more likely to benefit from E. **Methods:** Completely resected IB-IIIA NSCLC pts were randomized 2:1 to receive E 150 mg qd or P for 2 years. Pts were stratified according to stage, histology, prior adjuvant chemotherapy, smoking status, *EGFR* FISH status, and country. The primary endpoint was disease free survival (DFS) in the full analysis set (FAS). Secondary endpoints included overall survival (OS) in the FAS and DFS and OS in the *EGFR* mutation (*EGFR* M+) subset (del19/L858R). Hierarchical testing procedure was used. **Results:** Between NOV 2007 and JUL 2010, 973 pts were randomized. Baseline characteristics were balanced between arms (age > 65 41%; female 41%; stage IB 51%, II 33%, IIIA 16% [AJCC 6$^{th}$ ed]; adenocarcinoma 59%; prior adjuvant chemotherapy 53%; never smoker 20%; Asian 17%; *EGFR* FISH+ 72% and *EGFR* M+ 16.5%). The planned number of events (410) for the final DFS analysis was reached in APR 2013; 277 (28%) pts had died. Median follow-up was 47 months (m). No statistically significant difference in DFS was observed in FAS; hierarchical testing rendered all secondary endpoints non-significant. The median treatment duration was 12 m for E and 22 m for P in FAS. Rash and diarrhea occurred in 58% and 52% pts for E vs 17% and 16% for P. Grade ≥3 rash and diarrhea occurred in 12.6% and 6.2% pts for E vs 0.3% and 0.3% for P. No drug-related adverse events led to death. **Conclusions:** Adjuvant E did not prolong DFS in the overall population. Further investigation in *EGFR* M+ pts is warranted. The safety profile of E was consistent with that in advanced disease. Clinical trial information: NCT00373425.

**Full analysis set.**

| | Median (m) | | | |
|---|---|---|---|---|
| | E (N=623) | P (N=350) | HR (95% CI) | P value |
| **DFS** | 50.5 | 48.2 | 0.90 (0.741-1.104) | 0.3235 |
| **OS** | NR | NR | 1.13 (0.881-1.448) | 0.3350 |

**EGFR M+ subset**

| | Median (m) | | | |
|---|---|---|---|---|
| | E (N=102) | P (N=59) | HR (95% CI) | P value |
| **DFS** | 46.4 | 28.5 | 0.61 (0.384-0.981) | 0.0391* |
| **OS** | NR | NR | 1.09 (0.545-2.161) | 0.8153 |

Abbreviations: HR, hazard ratio; NR, not reached. *Not significant due to hierarchical testing.

**7502 Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**Randomized trial on thoracic radiotherapy (TRT) in extensive-stage small cell lung cancer.** *Presenting Author: Ben J. Slotman, VU University Medical Center, Amsterdam, Netherlands*

**Background:** Prophylactic cranial irradiation (PCI) reduces the risk of brain metastases and improves survival in ES-SCLC after response to chemotherapy. As a majority of patients have intrathoracic disease after chemotherapy, this randomized study assesses the role of TRT in ES-SCLC. **Methods:** Patients (WHO 0-2) with confirmed ES-SCLC with a response after 4-6 cycles of standard chemotherapy were randomized to receive TRT (30 Gy/10fx) or no TRT. All received PCI. Primary study endpoint was overall survival. Acute toxicity was graded using CTCAE v3.0. The study had 80% power to detect a hazard ratio of 0.76 at 1 year (2-sided 5% signif.). Accounting for 5% dropout before treatment, 483 patients had to be randomized. Analysis was based on intent to treat. **Results:** Between Feb'09 and Dec'12, 498 patients were enrolled (249 per arm); Median follow-up was 24 months. 88% had residual intrathoracic disease. Baseline characteristics were well balanced. Mean age was 63 year (range 36-85), 89% had WHO 0-1; 11% WHO2. Mean interval between start of chemotherapy and randomization was 16 weeks. Three patients subsequently withdrew informed consent leaving 247 (TRT) versus 248 patients (control arm). In the TRT arm, 5 patients did not receive TRT due to progression or refusal. No severe toxicities were observed. At the time of analysis (Dec'13), 76 patients were still alive. Progression-free survival was longer in the TRT-arm (HR=0.73, CI 0.61-0.87; p=0.001). Curves for overall survival overlapped during the first 9 months and then diverged in favour of the TRT-arm. The survival difference at 1 year was not statistically significant (33% vs 28%; HR=0.84, CI 0.69-1.01; p=0.066). Survival at 2 years was 13% (CI 9-19) for the TRT and 3% (CI 2-8%) for the control arm (P=0.004). **Conclusions:** TRT improves progression-free survival. Although TRT did not influence the risk of death in the first year, it led to a significant increase in 2-year survival. TRT should therefore be offered to all ES-SCLC patients with a response to initial chemotherapy. This study was supported by grants from the Dutch Cancer Society (CKTO) and Cancer Research UK and supported by the Dutch Lung Cancer Research Group and The Christie NHS Foundation Trust Clinical Trials Unit. Clinical trial information: NTR1527.

**7503 Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**Prophylactic cranial irradiation (PCI) has a detrimental effect on the overall survival (OS) of patients (pts) with extensive disease small cell lung cancer (ED-SCLC): Results of a Japanese randomized phase III trial.** *Presenting Author: Takashi Seto, Department of Thoracic Oncology, National Kyushu Cancer Center, Fukuoka, Japan*

**Background:** A previous study has shown that PCI reduced the risk of brain metastases (BM) and prolonged the OS of patients with ED-SCLC (Slotman B et al, NEJM 2007). There were, however, several concerns that arose in association with that study, including the lack of magnetic resonance imaging (MRI) assessment to confirm the absence of BM before enrollment, the use of induction chemotherapy other than platinum, and variations in the radiation doses. **Methods:** From March 2009, pts with ED-SCLC who had any response to first-line platinum doublet chemotherapy were randomized to either PCI (25Gy/10 fractions) or observation (Obs) alone. The patients were required to prove the absence of BM by MRI prior to enrollment. The primary endpoint was OS and a planned sample size of 330 was determined to detect the hazard ratio (HR) of 0.75 at a significance level of 0.05 and a power of 80%. Secondary endpoints included time to BM (evaluated every 3 months by imaging), progression-free survival (PFS), and adverse effects (AEs). **Results:** In July 2013, a preplanned interim analysis was conducted for the survival data of 163 pts from 41 centers. The study was terminated because of futility; with a median follow-up of 9.4 months and 111 observed deaths, the median OS was 10.1 and 15.1 months for PCI ($n$=84) and Obs ($n$=79), respectively (HR=1.38, 95%CI= 0.95-2.01; stratified log-rank test, $P$=0.091). Bayesian predictive probability of showing superiority of PCI over Obs was 0.01%. PCI significantly reduced the risk of BM as compared to Obs (32.4% vs 58.0% at 12 months; Gray's test, $P$<0.001), whereas PFS was comparable between the two arms (median, 2.2 vs. 2.4 months; HR=1.12, 95%CI=0.82-1.54). No significant difference in AEs greater than Grade 2 was observed between the two arms. **Conclusions:** PCI after response to chemotherapy had a negative impact on OS in pts with ED-SCLC. Clinical trial information: 000001755.

**7504** **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**A randomized phase III study of cisplatin (CDDP), etoposide (ETOP) and irinotecan versus topotecan as second-line chemotherapy in patients with sensitive relapsed small-cell lung cancer (SCLC): Japan Clinical Oncology Group study JCOG0605** *Presenting Author: Koichi Goto, Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

**Background:** ETOP and irinotecan are drugs known to exert promising activity in SCLC. A phase II study of weekly chemotherapy using a combination of CDDP, ETOP and irinotecan (PEI), which are known to inhibit both topoisomerase I and II, showed quite favorable outcome in patients with sensitive relapsed SCLC. A phase III study confirming the superiority of PEI over topotecan as second-line chemotherapy in patients with sensitive relapsed SCLC was conducted. **Methods:** SCLC patients who responded to first-line treatment and relapsed/progressed more than 90 days after the completion of first-line treatment were eligible for this study. Additional eligibility criteria included age 20-75 years, PS of 0-2, and adequate organ functions. Patients were randomized 1:1 to PEI, which consisted of CDDP (25 mg/m$^2$) weekly for 10 weeks, ETOP (60 mg/m$^2$) for 3 days on weeks 1, 3, 5, 7, and 9, and irinotecan (90 mg/m$^2$) on weeks 2, 4, 6, 8 and 10 with granulocyte colony-stimulating factor support, or to topotecan (1.0 mg/m$^2$) on days 1-5, every 3 weeks for 4 courses. The primary endpoint was overall survival. The planned sample size was 180 patients, to attain 80% power with a one-sided alpha of 5%. **Results:** From Sep. 2007 to Nov. 2012, 180 patients were randomized to topotecan (n=90) and PEI (n=90): median age 64 (44-75) years; M/F 155/25; LD/ED 45/135; PS 0-1/2 175/5. The overall survival was significantly longer in the PEI arm than in the topotecan arm (HR 0.67; 90% CI 0.51-0.88; p=0.0079) with MST 18.2 months vs. 12.5 months. PFS was also significantly longer in the PEI arm (HR 0.50; 95% CI 0.37-0.68; p<0.0001) with the median PFS 5.7 months vs. 3.6 months. Grade 3/4 adverse events in PEI and topotecan arms, respectively, were: neutropenia 83.3% vs. 85.6%; anemia 84.4% vs. 27.8%; thrombocytopenia 41.1% vs. 27.8%; diarrhea 7.8% vs. 0%; febrile neutropenia 31.1% vs. 6.7%. There was 1 treatment-related death in the PEI arm, and 2 in the topotecan arm. **Conclusions:** The combination chemotherapy with CDDP, ETOP and irinotecan should be considered as the standard second-line chemotherapy for sensitive relapsed SCLC. Clinical trial information: 000000828.

**7505** **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**Randomized phase II-III study of bevacizumab in combination with chemotherapy in previously untreated extensive small-cell lung cancer: Results from the IFCT-0802 trial.** *Presenting Author: Jean-Louis Pujol, Centre Hospitalier Universitaire, Maladies Respiratoires, Montpellier, France*

**Background:** A randomized phase II-III trial was designed to assess efficacy and safety of adding bevacizumab (Bev) to first-line standard chemotherapy (CT) in extensive small-cell lung cancer (SCLC). **Methods:** Patients with SCLC were enrolled and then received two induction cycles of CT, three weeks apart (cisplatin - etoposide, or cisplatin - cyclophosphamide - epidoxorubicin - etoposide [PCDE]). Responders were randomly assigned 1:1 to receive 4 additional cycles of CT alone or CT plus Bev (7.5 mg/kg) followed by single-agent Bev until progression or unacceptable toxicity. The primary endpoint was response rate (RR) after 4 cycles (i.e. two cycles after randomization). **Results:** 147 patients were enrolled. After the 2 first CT cycles, RR was observed in 99 patients (67.3%) and among them, 74 patients were eligible for Bev and randomly assigned to CT only (n = 37) or CT plus Bev (n = 37). Median number of CT was 6 in CT alone group and 6 in CT plus Bev group. The median number of additional Bev administrations in the latter group was 4. The percentage of still-responder patients after 4 cycles, including 2 with bevacizumab in the experimental arm, did not differ between the CT arm (89.2%) and the CT+bevacizumab arm (91.9%). Neither progression-free survival (PFS) nor overall survival (OS) significantly differed (median PFS : 5.5 and 5.3 months; median OS: 13.0 and 11.1 months, in CT alone and CT plus Bev groups respectively). In the CT alone group and the CT plus Bev group, 22 (59.5%) versus 23 (62.2%) of patients respectively, experienced one or more grade 3-4 adverse events. Specific Bev-induced toxicity was observed in 15 (40.5%) patients; one unexpected toxicity (fatal subdural hematoma) was reported in the combination group. Evaluation of serum biomarkers will be presented. **Conclusions:** Bev did not increase the proportion of responder patients at cycle 4. This phase II study failed to demonstrate any signal suggesting an outcome improvement in extensive-SCLC. Consequently this trial will not go further the phase 3 part of the program. Clinical trial information: NCT00930891.

**7506** **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**A randomized double-blind phase II trial of platinum (P) plus etoposide (E) with or without concurrent ZD6474 (Z) in patients (pts) with previously untreated extensive-stage (ES) small cell lung cancer (SCLC): Hoosier Oncology Group LUN06-113.** *Presenting Author: Rachel E. Sanborn, Earle A. Chiles Research Institute and Providence Cancer Center, Portland, OR*

**Background:** Standard treatment with P + E results in median survival for ES SCLC 10 months. Dose escalation, addition of third cytotoxic agents, and maintenance therapy have failed to improve outcomes. Overexpression of VEGF is associated with poor prognosis in SCLC. This trial evaluated the efficacy and tolerability with the addition of Z (dual VEGF and EGFR inhibitor) to PE. **Methods:** Randomized, double blind, placebo controlled study of P (cisplatin 60 mg/m$^2$ or carboplatin AUC 5) day 1, E (120 mg/m$^2$ with cis or 100 mg/m$^2$with carbo) IV days 1-3, with Z (100 mg) or placebo po daily, q3 wks for 4 cycles. 6 pts were initially enrolled on P+E+Z for safety assessment. Pts with untreated ES SCLC or high grade poorly differentiated neuroendocrine tumors and ECOG 0-1 were eligible. Pts with symptomatic brain metastases (mets) or prolonged QTc were ineligible. 1°endpoint was time to disease progression (TTP). Secondary endpoints were safety, response rate (RR), disease control rate (DCR), and overall survival (OS). VEGF polymorphisms were also evaluated. **Results:** 74 pts enrolled (33 placebo, arm A; 41 Z, arm B) Median age 63/64 A/B; female/male 48.5%/51.5% A, 41.5%/58.5% B; ECOG 0/1 36%/64% A, 34%/66% B. Brain mets at diagnosis, 30% A, 39% B. Median number of cycles received was 4 (both arms). Cisplatin/carboplatin 51.5%/48.5% A, 61%/39% B. All Grade (Gr) 3-4 toxicity: 37% A, 69% B (heme, 20% A; 30% B, mainly neutropenia both arms; non-heme, 17% A; 33% B). Gr 5 toxicity, 1 each: A, 3 (cardiac infarct, pulmonary hemorrhage, pneumonitis); B, 2 (infection, respiratory failure). No differences were seen in bleeding/hemorrhage (1 gr 3/4 each, 1 gr 5 A). 3 pts had Gr 3/4 hypertension in B (0 in A). RR 65.4% A, 51.4% B; P=0.31. DCR 73% A, 74% B; P=1.0. Median OS 10.2 months (mo) A, 10.7 mo B; P=0.90; HR 0.78 (B v A). Median TTP 5.6 mo A, 5.5 mo B; P=0.66; HR 1.13 (B v A). **Conclusions:** The addition of Z to PE did not improve TTP, RR, DCR, or OS for patients with extensive SCLC. An increase in toxicity was seen with Z compared with placebo. Z in combination with PE cannot be recommended for further study in unselected pts with ES SCLC. Clinical trial information: NCT00613626.

**7507** **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

**Randomized trial of arginine deprivation with pegylated arginine deiminase in patients with malignant pleural mesothelioma.** *Presenting Author: Peter Wojciech Szlosarek, St. Bartholomew's Hospital, London, United Kingdom*

**Background:** Argininosuccinate synthetase 1 (ASS1)-deficient malignant pleural mesothelioma (MPM) cells are sensitive to arginine deprivation. We examined the efficacy and safety of the arginine-lowering agent pegylated arginine deiminase (ADI-PEG20, Polaris Group, US) among patients with MPM. **Methods:** Patients with good performance status (0-1), non-resectable disease, ASS1-deficient MPM, and measurable disease by modified RECIST were randomized (2:1) in a multicenter phase II trial. They received best supportive care (BSC) or BSC plus ADI-PEG20 (i.m. injection 36.8mg/m2, weekly). Primary endpoint was progression-free survival (PFS); target hazard ratio (HR) 0.60. Other endpoints: overall survival (OS), tumor response rate (modified RECIST), and toxicity. We measured plasma [arginine], [citrulline] and [ADI-PEG20 antibody], ASS1 methylation status, and metabolic response by [18F]Fluorodeoxyglucose Positron Emission Tomography (FDG-PET). [ClinicalTrials.gov NCT01279967, funding Cancer Research UK]. **Results:** We screened 214 patients (March 2011-May 2013), and randomized 68 with ASS1-deficient MPM: 44 ADI-PEG20+BSC and 24 BSC alone. PFS HR was 0.53 (95% CI 0.31 to 0.90, p=0.02), median 98 vs. 59 days favouring ADI-PEG20+BSC. The OS HR was 0.81 but the curves crossed, so we used the restricted mean survival times: 390 vs. 317 days (difference +73 days favoring ADI-PEG20+BSC,p=0.20). The best response was stable disease: at 4 months 67% ADI-PEG20+BSC vs. 50% BSC alone. The main grade 3/4 toxicities associated with ADI-PEG20+BSC were: neutropenia (11%), thromobocytopenia (5%), fatigue (7%), anaphylactoid reactions (7%), skin rash (2%), and serum sickness (2%). Plasma arginine levels declined with ADI-PEG20+BSC only, and correlated with the following FDG-PET changes in 39 evaluable ADI-treated patients with aberrant MPM ASS1 methylation: 46% partial response, 31% stable disease, 15% progressive metabolic disease, and 8% mixed metabolic response. **Conclusions:** Arginine deprivation using ADI-PEG20 in patients with ASS1-deficient MPM almost doubled PFS and was generally safe. It should be examined further either alone or in combination with selected therapies. Clinical trial information: NCT01279967.

**7508 Poster Highlights Session (Board #1), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**A randomized trial of prophylactic cranial irradiation versus observation in patients with fully resected stage IIIA N2 non-small cell lung cancer and high risk of cerebral metastases after adjuvant chemotherapy.** *Presenting Author: Si-Yu Wang, Sun Yat-Sen University Cancer Center, Guangzhou, China*

**Background:** Prophylactic cranial irradiation (PCI) significantly decreases the incidence of brain metastases in patients with non-small cell lung cancer (NSCLC), but its impact on survival is uncertain. Previously, we built a mathematical model to predict the risk of developing cerebral metastases in patients with locally advanced NSCLC. The purpose of this study is to evaluate if PCI improves survival in patients with resected stage IIIA N2 NSCLC and high risk of cerebral metastases after adjuvant chemotherapy. **Methods:** In this open-label, randomized trial, patients with fully resected stage IIIA N2 NSCLC and high cerebral metastases risk without recurrence after postoperative adjuvant chemotherapy were randomly assigned to receive PCI (30 Gy in 10 fractions) or observation. The primary end point was disease-free survival (DFS). The secondary end points included the incidence of brain metastases, overall survival (OS) and toxicity. **Results:** From January 2005 to January 2009, 156 eligible patients were randomized (81 in PCI group and 75 in control group). This study was terminated early as a result of slow accrual. The PCI group had significantly lengthened DFS compared with the control group, with a median DFS of 28.5 months versus 21.2 months (hazard ratio [HR], 0.67; 95% confidence interval [CI], 0.46-0.98; P=0.037). The 3-year and 5-year DFS were respectively 42.0% and 26.1% with PCI, and 29.8% and 18.5% with observation. PCI was associated with a decrease in risk of brain metastases (5-year brain relapse rate, 13.6% vs 41.3%; odds ratio, 0.223; 95% CI, 0.102-0.489; P<0.001). The median OS was 31.2 months in the PCI group and 27.4 months in the control group (HR, 0.81; 95% CI, 0.56-1.16; P=0.310). The 3-year and 5-year OS were respectively 44.5% and 27.4% with PCI, and 38.7% and 22.8% with observation. While main toxicities were headache, nausea/vomiting and fatigue in the PCI group, they were generally mild. **Conclusions:** In patients with fully resected stage IIIA N2 NSCLC and high risk of cerebral metastases after adjuvant chemotherapy, PCI prolongs DFS and decreases the incidence of brain metastases.

**7509 Poster Highlights Session (Board #2), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Postoperative radiotherapy (PORT) for pathologic N2 non-small cell lung cancer (NSCLC) treated with adjuvant chemotherapy: A review of the National Cancer Database.** *Presenting Author: Cliff Grant Robinson, Washington University School of Medicine in St. Louis, St. Louis, MO*

**Background:** Adjuvant chemotherapy confers a 5% overall survival (OS) benefit for NSCLC patients following resection. Historic trials predating widespread use of chemotherapy suggested no OS benefit to PORT for N2 disease, felt to be from competing risks of older RT techniques and subsequent toxicity. We investigated the impact of modern PORT on OS for N2 NSCLC patients treated nationally with surgery and adjuvant chemotherapy. **Methods:** Patients with pathologic N2 NSCLC who underwent complete (R0) resection and adjuvant chemotherapy from 1998 to 2010 were identified from the National Cancer Database. Only patients for whom complete radiation and chemotherapy details were available were included. Patients were stratified by the use of PORT (≥45 Gy) as coded in the database. A total of 4,585 patients were identified (1,909 PORT, 2,676 no PORT) with a median follow-up of 22 months. The impact of PORT on OS was explored using Cox regression. **Results:** Patients treated with PORT were slightly younger (median 63.5 vs. 65 years, p<0.001) and healthier (Charlson 0 in 60.8% vs. 55.2%, p<0.001), though less likely to be treated at an academic facility (31.6% vs. 40.9%, p<0.001). Patients treated with PORT had fewer pneumonectomies (5.9% vs. 9.9%, p<0.001) and more sublobar resections (16.3% vs. 9.8%, p<0.001), and slightly smaller tumors (34.6 vs. 36.7 mm, p<0.015). On multivariate analysis, factors independently predictive of improved OS for the entire group were younger age, treatment at an academic facility, higher income, lower Charlson score, smaller tumor, ≥ lobectomy, and use of PORT (HR 0.873, 95% C.I. 0.789-0.965). Use of PORT was associated with a significant increase in median and 5-year overall survival compared to no PORT, 45.9 vs. 40.7 months and 39.1% vs. 34.7% (p=0.005), respectively. **Conclusions:** For NSCLC patients with N2 disease following complete resection and adjuvant chemotherapy, modern PORT appears to confer an additional 5% survival advantage beyond that achieved with adjuvant chemotherapy alone. Investigators are encouraged to enroll on prospective trials such as LungART, a randomized trial of modern PORT vs no PORT in resected NSCLC.

**7510 Poster Highlights Session (Board #3), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Phase III study of surgery (S) versus definitive concurrent chemoradiotherapy boost (def ccCRTx-BOx) in patients (pts) with operable (OP+) stage IIIA(N2)/selected IIIb (sel IIIB) non-small cell lung cancer (NSCLC) following induction (IND) chemotherapy (CTx) and concurrent CRTx (ESPATUE).** *Presenting Author: Wilfried Ernst Erich Eberhardt, Department of Medical Oncology, Ruhrlandklinik, West German Cancer Center, University Hospital Essen. University Duisburg-Essen, Essen, Germany*

**Background:** Def ccCRTx or ccCRTx + S are accepted therapies (Tx) for OP+ stage IIIA(N2) NSCLC (Albain 2009). Our multicenter phase-II showed efficacy of CTx + ccCRTx + S in IIIA(N2) / sel IIIB (CISTAXOL: Eberhardt 2013). Here we compared S with ccCRTx-BOx in OP+ stage III NSCLC following IND. With 246/500 planned pts (1/04-8/12) trial closed for slow accrual + futility. Here we report final analysis (29-Jan-2014). **Methods:** Pathologically proven OP+ IIIA(N2) / sel IIIB NSCLC pts, adequate organ function / functional OP+, received IND CTx (3 cycles CDDP/taxol) and ccCRTx to 45 Gy (1.5Gy bid/cc CDDP/vinorelbine). Pts were reevaluated in last week ccCRTx (PET-CT) and discussed by multidisciplinary board. OP+ pts were randomized (rand) to def ccCRTx-BOx risk adapted to 65/71 Gy (arm A) or S (arm B). Primary endpoint: overall survival (OS). **Results:** 246 pts (70 F 176 M; T1-3N2 75 T4N0-1 80 T4N2/anyT N3 91; age 59 (33-74); SQC 95 ADC 107, other 44) enrolled at 5 centers. 245 started IND, 161/246 OP+ pts (65.4%) were rand to arm A or B (strata: TN-group, PCI-policy, region) - post rand crossover due pts preference: 6.8%. 46 non-rand pts received def ccCRTx-BOx. Pts characteristics were well balanced. Pneumonectomy in 26%, R0-Res in 81% of arm B. Med F-UP post rand 78.2 mo. 36 are actually long-term surv with F-UP > 5 y. OS did not differ between arms ( logrank p = 0.31 ). OS at 5 y 34.1% (27.6-40.8) in 246 initially recruited (IR) and 216 (87.8%) received def local Tx. **Conclusions:** Long-term OS at 5 y in rand OP+ pts was excellent with both Tx. These high-volume center data confirm earlier trials: Both options are acceptable and should be discussed with individual pts. Clinical trial information: 70-3070-Eb.

| | All IR | 246 |
|---|---|---|
| | Completed IND | 227 |
| | OP+ / rand | 161 |
| | A: BOx 80 | B: S 81 |
| **1 Y-OS%** | 82.5 (72.2-89.2) | 77.8 (67.1-85.4) |
| **3 Y-OS%** | 49.9 (38.0-60.6) | 58.4 (46.4-68.6) |
| **5 Y-OS%** | 40.6 (28.7-52.2) | 44.2 (31.6-56.2) |
| **TRD%** | 2.5 | 6.2 |

**7511^ Poster Highlights Session (Board #4), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Phase II study of cetuximab, pemetrexed, cisplatin and concurrent radiotherapy in patients with locally advanced, unresectable, stage III, non-squamous, non-small cell lung cancer (NSCLC): Results of the IFCT-0803 trial.** *Presenting Author: Jean Tredaniel, Groupe Hospitalier Paris Saint-Joseph, Paris, France*

**Background:** Cisplatin-based chemotherapy and concurrent radiotherapy, the standard treatments for locally advanced unresectable NSCLC have reach a plateau. New therapeutic combinations of molecular targeted drugs are needed. IFCT-0803 phase II trial aimed to evaluate the benefit of adding cetuximab to a combination of radio and concomitant chemotherapy with cisplatin and pemetrexed in patients with stage III, non-squamous NSCLC. **Methods:** Based on a 2-stage Simon approach, a total of 106 patients were to accrue. An interim analysis of the first 34 patients authorized the continuation of the study. Eligible patients receive thoracic radiation (66 Gy) along with cisplatin (75 mg/m$^2$) and pemetrexed (500 mg/m$^2$) on D1 administered every 21 days for four cycles; weekly cetuximab (400 mg/m$^2$) for the first week, then 250 mg/m$^2$) is added from the first week of therapy for a total of 12 doses. The primary objective is to assess the disease control rate at the 16th week (16W-DCR), one month after the treatment completion. **Results:** 99 patients at inclusion were: 60 male, 57 years (median age), PS 0 = 60, ever smoker = 7, stage IIIA = 48 and IIIB = 49, adenocarcinoma = 77. Compliance was good for the first 92 eligible patients : Day 1 chemotherapy was administered to 100% of patients on cycle 1, 98.9% on cycle 2, 93.4% on cycle 3 and 84.8% on cycle 4. Radiotherapy protocol was respected: median was 33 for number of fractions, 66 Gy for total dose, 48 days for treatment duration. The endpoint 16W-DCR was 93.3 % (IC95% : 88.1 - 98.5). 30 patients had a maximal toxicity of grade 3 and 10 of grade 4. Two toxic deaths were observed, one by a traumatic subdural hematoma, as the patient experienced a grade 4 thrombocytemia, another occuring two months post-treatment completion, caused by a grade 4 radiation pneumonia, whereas concurrent cancer progression was documented. **Conclusions:** IFCT-0803 trial showed both the feasability and high DCR for radiation, cisplatin, pemetrexed and cetuximab combination, with a tolerable toxicity profile. Our data will be updated at the ASCO meeting, the accrual goal (106 pts) being reached on Jan. 2014. Clinical trial information: NCT01102231.

**7512 Poster Highlights Session (Board #5), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Multidisciplinary treatment for stage IIIA non-small cell lung cancer (NSCLC): Does institution matter?** *Presenting Author: Pamela Samson, Washington University in St. Louis, St. Louis, MO*

**Background:** It has been reported that survival is improved for early stage NSCLC when surgery is performed at high volume academic centers. However, the impact of institution has not been well described in the setting of surgery for stage IIIA NSCLC, in which a wide variety of neo-/adjuvant therapies are often employed. **Methods:** Treatment data of clinical stage IIIA NSCLC patients undergoing resection was obtained from the National Cancer Database (NCDB). Information on patient and tumor-related variables, therapy modalities, 30-day mortality, and survival was abstracted. Multivariable regression models were fitted to evaluate variables influencing 30-day mortality and overall survival (OS). **Results:** From 1998-2010, 11,492 clinical stage IIIA NSCLC patients were treated at community centers, while 7,743 patients were treated at academic centers. Academic center patients were more likely to be younger, female, non-Caucasian, live in an urban area, have a lower Charlson Comorbidity Index (CCI), and have a higher income and travel distance (all $p < 0.001$). Academic center patients were more likely to receive neoadjuvant chemotherapy (49.6% vs. 40.6%, $p < 0.001$). Increased 30-day mortality was associated with increasing age, male gender, pre-operative radiation therapy, increased CCI, and pneumonectomy. Patients undergoing surgery at academic centers experienced decreased 30-day mortality (OR 0.75, 95% CI 0.60 – 0.93, 3.3% vs. 4.5%, $p < 0.001$). Decreased long term survival was associated with increasing age, male gender, increased CCI, larger tumors, and pre-operative radiation therapy. Neoadjuvant chemotherapy (HR 0.66, 95% CI 0.62-0.70), surgery at an academic center (HR 0.92, 95% CI 0.88 – 0.97), and surgical treatment with lobectomy (HR 0.72, 95% CI 0.67 – 0.77) were associated with improved OS. Median OS for academic center patients was longer (33.8 vs. 28.9 months, $p < 0.001$). **Conclusions:** Stage IIIA NSCLC patients treated with pulmonary resection at academic centers had a lower 30-day mortality rate and increased OS compared to patients treated at community centers. Possible contributing factors include high-volume surgical centers and an increased rate of neoadjuvant chemotherapy.

**7513 Poster Highlights Session (Board #6), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Adjuvant erlotinib (E) versus placebo (P) in non-small cell lung cancer (NSCLC) patients (pts) with tumors carrying *EGFR*-sensitizing mutations from the RADIANT trial.** *Presenting Author: Frances A. Shepherd, Princess Margaret Cancer Centre, Toronto, ON, Canada*

**Background:** E, anEGFR TKI, prolongs survival in pts with advanced NSCLC. Pts with tumors carrying *EGFR* exon 19 del or 21 L858R mutations are particularly sensitive to EGFR TKIs. **Methods:** RADIANT was a randomized trial of postoperative E *v* P in pts with completely resected stage IB-IIIA NSCLC. Pts were stratified by histology (adenocarcinoma, other), stage (IB, II, IIIA), adjuvant chemotherapy (yes, no), smoking history (never, current/former), *EGFR* FISH (positive, negative/undetermined) and country. Pts were randomized 2:1 to receive E 150mg/day or P for up to 2 yr. Among 973 randomized pts, *EGFR* mutation status was determined for 921 (95%); 161 (17%) had mutations (55% exon 19 del, 45% exon 21 L858R). These pts form the basis of this report. **Results:** Pts with mutations were more frequently female (65%) and non-smokers (63%); 47% had stage IB, 29% stage II, 22% stage IIIA; 49% received adjuvant chemotherapy; 47% were Asian. Some imbalances were observed (E: less chemo and lower stage; P: smaller tumor size). There were 102 pts randomized to E and 59 to P. Median duration (range) of treatment was 21.2 (0.16-22.93) m for E and 21.9 (2.43-22.93) m for P; 34 (34%) and 24 (41%) pts completed >22 m of E and P, respectively. DFS events occurred in 71 (44%) pts. Pts on E had longer disease-free survival (DFS) *v* P (median 46.4 *v* 28.5 m; HR 0.61, 95% CI 0.38-0.98, p=0.039); however, this result is not statistically significant due to the hierarchical testing procedure. The effect on DFS remained consistent after adjusting for other prognostic variables via an exploratory multivariate Cox model (HR 0.60, 95% CI 0.36-0.98, p=0.046). There were more brain relapses on E (40%) *v* P (13%), and fewer bone relapses 14% *v* 29%. Deaths occurred in 35 (21.7%) pts. There was no significant difference in overall survival (OS median not reached in either arm; HR 1.09, 95% CI 0.56-2.16, p=0.815). For drug-related events, AE, serious AE and discontinuations for AE were higher with E compared to P (98% *v* 61%; 4% *v* 0%; 25% *v* 0%, respectively). **Conclusions:** Although not statistically significant, these data suggest adjuvant E prolongs DFS in pts with completely resected *EGFR* mutated NSCLC. OS interpretation is limited. Clinical trial information: NCT00373425.

**7514 Poster Highlights Session (Board #7), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**SELECT: A multicenter phase II trial of adjuvant erlotinib in resected early-stage EGFR mutation-positive NSCLC.** *Presenting Author: Nathan A. Pennell, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH*

**Background:** EGFR mutant NSCLC is exquisitely sensitive to EGFR tyrosine kinase inhibitors (TKIs). Retrospective data suggests adjuvant TKIs may improve outcomes. This trial is the first to prospectively test the efficacy of adjuvant erlotinib in EGFR-mutant NSCLC. **Methods:** Eligible pts had resected stage IA-IIIA NSCLC harboring a TKI-sensitizing EGFR mutation. Pts were treated with erlotinib 150 mg/day for 2 years after completion of standard adjuvant chemotherapy and/or radiotherapy. With a sample size of 100 pts the study was powered to demonstrate a primary endpoint of 2-year disease free survival (DFS) >85%, compared to a historical control of 76% in resected early-stage EGFR-mutant NSCLC. **Results:** 100 pts were enrolled at 7 sites between 1/08 and 5/12; 45% stage I; 27% stage II; 28% stage IIIA. 89 pts have reached 2 year follow-up (2 year follow-up on the entire cohort will be presented at the annual meeting). Toxicities were typical of erlotinib with no G4/5 events and 1 G2 pulmonary fibrosis. 40% of pts required dose reduction to 100 mg/day and 16% two dose reductions to 50 mg/day. 69% of pts completed at least 22 months of erlotinib. With median follow-up of 3 years, the 2-year DFS is 90% (97% stage 1, 73% stage 2, 92% stage 3). Median DFS and OS have not been reached. 24 pts have recurred, only 2 during erlotinib treatment and 22 after stopping erlotinib with a median time to recurrence of 12 months after stopping erlotinib. 63% (n=15) of pts with recurrence underwent repeat biopsy, and only 1 T790M was detected. 71% (n=17) of recurrent pts were re-treated with erlotinib with 10 pts remaining on erlotinib, treatment range 2-42 months. 8 pts have died. **Conclusions:** Pts with EGFR mutation-positive NSCLC treated with adjuvant erlotinib have an improved 2-year DFS compared to historical genotype-matched controls. Recurrences are rare on erlotinib and most occur in the 12m after discontinuation, suggesting longer duration of adjuvant treatment may be beneficial. Recurrent cases after adjuvant erlotinib remain generally sensitive to EGFR TKIs. Clinical trial information: NCT00567359.

**7515 Poster Highlights Session (Board #8), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**NEOSCAN: Phase II trial of neoadjuvant chemotherapy for resectable lung cancers with switch to chemo alternative in $^{18}$F-FDG PET nonresponders.** *Presenting Author: Mark G. Kris, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Perioperative chemotherapy improves survival in pts with resectable lung cancers. Administering chemotherapy prior to surgery enables assessment of response and opportunity to switch non-responding pts to potentially more effective regimens. Response measured by PET correlates better than CT with clinical outcomes. This trial assessed PET-guided neoadjuvant chemotherapy, assigning pts with suboptimal PET response after 2 cycles of platinum-based therapy to alternative "switch" chemotherapy. **Methods:** We enrolled pts with clinical stage IB-IIIA NSCLCs (primary tumor >2 cm and SUVmax≥4.5) deemed to be resectable by a thoracic surgeon. All pts had a pretreatment PET. Pts received 2 cycles of cisplatin (or carboplatin) + gemcitabine (squamous) or pemetrexed (adenocarcinoma/other), followed by repeat PET. If PET showed ≥35% decrease in SUVmax, pts continued on platinum-based therapy. Pts with suboptimal response (<35% decrease) were switched to vinorelbine + docetaxel q2 weeks (2 doses = 1 cycle). The primary endpoint was partial metabolic response after 2 cycles of "switch" therapy as assessed by PERCIST (SUVmax decrease ≥30% using the pre-switch scan as new baseline). We powered the study to detect a 30% response rate to "switch" chemotherapy (≥6 responses in ≤25 pts who received vinorelbine + docetaxel). **Results:** 32 pts were enrolled (7 gemcitabine, 25 pemetrexed). 21 (66%) had >35% decrease in SUVmax and continued platinum-based therapy. 11 (34%) had <35% decrease and switched therapy. The study met its primary endpoint when 6 of 9 pts (66%, 95% CI 35-88%) who received vinorelbine + docetaxel had a PERCIST partial metabolic response. 27 pts have been surgically explored with 23 (85%) $R_0$ resections, including 7 of 7 who switched chemotherapy and were explored. There were no on-study deaths. **Conclusions:** Pts with resectable lung cancers who have a suboptimal PET response to histology-selected, platinum-doublet neoadjuvant chemotherapy can be effectively treated with vinorelbine and docetaxel followed by surgery. We now plan to correlate pathologic response in resected tumors with SUV change. Clinical trial information: NCT01443078.

**7516 Poster Highlights Session (Board #9), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Driver mutations associated with smoking and other environmental factors: Prospective and integrative genomic analysis from the Japan Molecularepidemiology for Lung Cancer Study (JME).** *Presenting Author: Norimasa Ito, National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka, Japan*

**Background:** Driver mutations are critical for lung cancer development as well as therapeutic targets. Its associations with environmental factors, sex hormones and virus remain elusive. **Methods:** This is a prospective, multicenter study on molecular epidemiology sponsored by the Japanese National Hospital Organization. Eligible are newly diagnosed patients with stage I to IIIB non-small cell lung cancer (NSCLC) who underwent surgery. Somatic mutations were examined by multiplex targeted deep sequencing (Illumina), validated by sensitive PCR methods, in surgical specimens, and human papilloma virus (HPV) using a PCR-based microarray system. The SWOG 0424 questionnaire was used to obtain information on patient demographics and detailed environmental factors. The sample size was 900 cases consisting of 450 ever-smokers and 450 never-smokers. **Results:** From July 2012 to December 2013, 958 patients were accrued from 43 institutions, and 901 samples were successfully tested for molecular analyses. Histology was adenocarcinoma (77 %), squamous cell carcinoma (16 %) and others (7 %). At least one somatic mutation was identified in 67 % of ever-smokers and 69 % of never-smokers. Common mutations were shown in the Table. 899 cases were also examined by Scorpion-ARMS method for KRAS and 864 cases by Cycleave method for EGFR, and the concordance rate between the deep sequencing and the PCR methods was 79.0 % in KRAS and 93.4 % in EGFR. Only 2 cases (0.3 %) were HPV-positive. **Conclusions:** The mutational spectrum showed a unique signature of exposure to smoking and other environmental factors. Little evidence was observed for an association between HPV and NSCLC. International collaboration with SWOG 0424 is planned to clarify the mechanisms of lung cancer development. Clinical trial information: UMIN000008177.

| Variable | | EGFR | TP53 | KRAS | PIC3CA | CTNNB1 |
|---|---|---|---|---|---|---|
| **Ever-smoker** | Male (N=371) | 17% | 39% | 13% | 4% | 1% |
| | Female (N=74) | 32% | 32% | 9% | 3% | 1% |
| **Never-smoker** | Male (N=59) | 47% | 14% | 3% | 2% | 0% |
| | Female (N=397) | 61% | 15% | 4% | 2% | 3% |
| **Never-smoker** | Passive smoking (+) (N=397) | 61% | 15% | 4% | 2% | 3% |
| | Passive smoking (-) (N=52) | 52% | 17% | 4% | 2% | 2% |
| **Female** | Age at menopause | | | | | |
| | 45 years old ≥ (N=64) | 64% | 20% | 3% | 0% | 2% |
| | 45 years old < (N=367) | 57% | 18% | 6% | 3% | 3% |

**7517 Poster Highlights Session (Board #10), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**PD-L1 expression and genotype in non-small cell lung cancer (NSCLC).** *Presenting Author: Sascha Ansen, Department I of Internal Medicine, Center for Integrated Oncology, University Hospital of Cologne, Cologne, Germany*

**Background:** Tumor cells expressing programmed cell death 1 ligand (PD-L1) are believed to suppress immune responses through activation of the PD-1/PD-L1 pathway. Recent data indicate that PD-L1 tumor status might be predictive for responses to PD-1- and PD-L1- directed therapies. **Methods:** PD-L1 expression was evaluated in genomically annotated 259 adenocarcinomas (AD) and 180 squamous cell carcinomas of the lung (SQ) using immunohistochemistry (IHC). Moreover, PD-L1 expression and its correlation with clinical data, histology and genotype were analyzed. **Results:** Tumors were considered PD-L1 positive if tumor cells showed at least weak membranous staining by IHC. 83 of 259 patients (pts.) with AD were positive for PD-L1 surface expression (=32,0%). The observed staining intensity was weak, intermediate and strong in 38, 33 and 12 cases respectively. 55 of 180 pts. with SQ were PD-L1$^{+}$(=30,6%). The observed staining intensity was weak, intermediate and strong in 27, 21 and 7 cases respectively. For AD and SQ no significant association between PD-L1 expression and clinical characteristics (gender, smoking history, stage) could be found. PD-L1 expression in AD or SQ was not significantly associated with ALK translocation (n=178; n=138), BRAF mutation (mut.) (n=113; n=98), DDR2 mut. (n=59; n=64), EGFR mut. (n=124; n=101), FGFR2 mut. (n= 117; n=91), HRAS mut. (n=94; n=73), KRAS mut. (SQ, n=101), NFE2L2_exon2 mut. (AD, n=97), NRAS mut. (n=109; n=81), PIK3CA mut. (n=121; n=99), STK11 mut. (SQ, n=101), TP53 mut. (n=124; n=101) or RB1 deletion (SQ, n=109). However, PD-L1 expression in AD is significantly more frequent in KRAS mutated than in KRAS wild-type samples (n=126; p=0,002) and significantly more frequent in samples with deletion of RB1 (n=143; p=0,024). On the contrary, PD-L1 expression in AD is significantly less frequent in samples with STK11 mutations (n=122; p=0,022). Finally, PD-L1 expression in SQ is significantly more frequent in samples with a mutation in exon 2 of NFE2L2 (n=88; p=0,025). **Conclusions:** PD-L1 expression in the two most common histological NSCLC subtypes is associated with distinct genotypes that might further facilitate identification of pts. most suitable for therapeutic anti PD-1 and anti PD-L1 intervention.

**7518 Poster Highlights Session (Board #11), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Second primary lung cancers: Analysis of E5597 selenium chemoprevention study.** *Presenting Author: Rathi Narayana Pillai, The Winship Cancer Institute of Emory University, Atlanta, GA*

**Background:** Non-small cell lung cancer (NSCLC) patients that undergo curative resection are at risk for development of second primary lung cancer (SPLC). The E5597 trial is the largest placebo-controlled lung cancer chemoprevention study conducted in the US. We report on the SPLC diagnosed in this cohort. **Methods:** E5597 randomized 1,561 (2:1) patients with resected stage I NSCLC to selenium or placebo for a total of four years with the primary objective of decreasing the incidence of SPLC. The study was stopped at first interim analysis for futility in October 2009. The participants were followed for incidence of all second primary tumors (SPT). **Results:** There were 290 (19%) incidences of SPT, of which 113 (7.2%) were SPLC among 112 cases (1 case with 2 incidences) as of January 2014 with median follow-up time of 5.6 years. 82 incidences in 81 cases occurred in the selenium arm (S) and 31 cases in the placebo arm (P). The median age was 67 years, and there were a higher proportion of women (52.7%). Although several patients continued smoking or had only quit within a year of SPLC (40.2%), most patients had quit smoking for at least one year (57.2%). The most common histology was adenocarcinoma (40.7%), followed by other (30.1%), squamous cell (25.6%), and large cell (1.8%). Almost all SPLC cases were detected by imaging (88.5%), but 31.9% were also clinically evident. Nearly two thirds of SPLC were stage I-II (61%). The incidence rates of SPLC were higher in the S arm compared to P arm: 1.42 versus 1.05 per 100 person years, respectively (95% CI 0.77-2.38). The median time to SPLC from randomization was 3.0 years (range 0.9-9.3 years) and from initial diagnosis of lung cancer was 4.2 years (range 0.8-28.5). **Conclusions:** SPLC is the most common second primary cancer in NSCLC patients. Continued surveillance even after tobacco cessation, is warranted for earlier detection of SPLC.

**7519 Poster Highlights Session (Board #12), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Randomized phase III trial in extensive-disease small cell lung cancer comparing first-line etoposide to topotecan in combination with platinum.** *Presenting Author: Morten Mau-Soerensen, Department of Oncology, Rigshospitalet, Copenhagen, Denmark*

**Background:** Randomized trials in extensive disease (ED) small cell lung cancer (SCLC) comparing the camptothecins to standard etoposide based chemotherapy have reached conflicting results. Here we report the results of an interim analysis of a phase III trial randomly allocating patients (pts) with ED SCLC to etoposide or topotecan in combination with platinum. **Methods:** Previously untreated pts with ED SCLC were randomized to six cycles of T (topotecan 2.0 mg/m$^2$ IV, day 1-3; cisplatin 50 mg/m$^2$ IV, day 3) or E (etoposide 120 mg/m$^2$, day 1-3; carboplatin IV AUC = 5, day 1) every 3 weeks. Primary end-point was overall survival (OS) and secondary end-points were response, progression-free survival (PFS), and safety. A sample size of 380 pts was estimated to detect an increase in 2-year survival from 7.5 to 15 % ($\alpha$=0.05, $\beta$=0.20.) ClinicalTrials.gov NCT 00812266. **Results:** The trial was prematurely stopped due to poor accrual according to a pre-planned interim analysis after the accrual of 281 pts reducing power to 0.66. Prognostic factors were equally balanced between arms. WHO performance status > 2 were recorded in 20.0% and 50% were females. Median age was 64 years (40 – 82). Most frequent grade 3/4 non-hematological adverse events (AEs) were infections (E 17.1 vs T 12.1%) and fatigue (E 14.2 vs T 12.7%). Most common grade 1/2 non-hematological AEs were alopecia (E 91.3 vs T 88.0%), nausea (E 55.9 vs T 57.9%) vomiting (E 27.6 vs T 24.1%), auditory toxicity (E 25.2 vs T 33.8%), and neuropathy (E 33.9 vs T 39.8%). Grade 4 leuco- and thrombocytopenia were observed in 21.1 and 12.8% of pts in arm E, respectively, compared to 6.7 and 5.2% in arm T ($p < 0.01$). Overall response rates were 69.1 % in arm E compared to 59.8% in arm T (NS). Median PFS was 6.6 months in E arm and 6.9 month in arm T, HR = 0.93, 95% CI 0.72-1.19, p=0.55. Median OS and 2-yr survival rates were 10.9 months and 9.2% in arm T, compared to 9.8 months and 8.7% in arm E, respectively, HR = 0.87, 95% CI 0.67-1.17, p=0.26. **Conclusions:** No differences in OS or PFS were observed comparing first line E with T in ED SCLC. Significantly more hematological toxicity was noted in the E arm. A biomarker study is planned to identify pts that derive most benefit from either T or E. Clinical trial information: NCT00812266.

**7520 Poster Highlights Session (Board #13), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Randomized phase 2 trial comparing amrubicin (A) with re-challenge of platinum doublet (P) in patients (pts) with sensitive-relapsed small-cell lung cancer (SCLC).** *Presenting Author: Atsushi Nakamura, Sendai Kousei Hospital, Sendai, Japan*

**Background:** When this trial was planned, A was believed to be a promising new anthracycline agent for sensitive-relapsed SCLC. While re-challenge of P that had been used for the first-line treatment was also believed to be effective for sensitive-relapsed SCLC, although prospective evaluation of it had not been reported. Thus this randomized phase 2 study was conducted to select A or P for future phase 3 trial. **Methods:** Sensitive-relapsed SCLC pts were randomized to receive A (40 mg/m2, day1-3, every 3 weeks) or P (every 3-4 weeks). The modification of P such as the 20%-dose reduction of combined third-generation or change of platinum agent from cisplatin to carboplatin according to patients' condition was permitted. The primary endpoint was overall response rate (ORR), and secondary endpoints were progression-free survival (PFS) and toxicity profile. According to the Simon's Two-Stage phase 2 design, 28 pts were required in each arm (p0=0.3, p1=0.5, alpha=0.10, beta=0.20), and the treatment that achieved $>$ 12 out of 28 pts with partial response would be judged as effective. **Results:** From February 2008 to June 2013, 60 pts were enrolled from 14 institutions. Two patients in A arm and one patient in P arm did not receive any protocol treatment due to rapid disease progression. Evaluated patients' characteristics were as follows: Male/Female, 53/4; median age, 66 (range 44-80); Performance status 0/1/2, 32/21/4. The median numbers of treatment cycles were 4 (range 2-8) in A arm and 3 (range 1-7) in P arm. ORRs and disease control rates were 67% (90%CI, 52-82) and 86% for A, and 43% (90%CI, 28-58) and 80% for P, respectively. Median PFS was 5.4 months in A arm and 5.0 months in P arm. Grade 3 toxicity was observed in 33% of patients in A arm including 19% of febrile neutropenia, while 17% in P arm without any febrile neutropenia. There was no grade 4 toxicity or treatment-related death in this trial. **Conclusions:** Both treatments met the primary endpoint. Since A produced higher ORR and median PFS than P with acceptable toxicity, we select A for subsequent phase 3 trial. Clinical trial information: UMIN000002617.

**7521 Poster Highlights Session (Board #14), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Randomized phase 2 study of carboplatin plus irinotecan (CI) versus carboplatin plus amrubicin (CA) for extensive disease small-cell lung cancer (ED-SCLC): NJLCG0901.** *Presenting Author: Yosuke Kawashima, Sendai Kousei Hospital, Sendai, Japan*

**Background:** Cisplatin-based regimens are standard first-line chemotherapy for ED-SCLC. In patients unfit for cisplatin due to advanced age or poor performance status (PS), carboplatin plus etoposide (CE) is as effective as cisplatin plus etoposide (JCOG9702 trial). Carboplatin plus irinotecan (CI) and carboplatin plus amrubicin (CA) are promising new carboplatin-based regimens identified in our previous studies (NJLCG0405 and NJCLG0701). Accordingly, we conducted this randomized phase 2 study to identify the appropriate regimen for comparison with CE in future phase 3 trials. **Methods:** Chemotherapy-naïve ED-SCLC patients were randomly assigned to receive 4–6 cycles of carboplatin (area under the curve [AUC] 5.0, day 1) plus irinotecan (70 mg/m$^2$, days 1 and 8) every 3 weeks (CI arm) or carboplatin (AUC 4.0, day 1) plus amrubicin (35 mg/m$^2$, days 1–3) every 3 weeks (CA arm). The primary endpoint was the overall response rate (ORR). Secondary endpoints were progression-free survival (PFS), overall survival(OS), and toxicity. Assuming that an ORR of 80% in eligible patients indicates potential usefulness and an ORR of 60% is the lower limit of interest, the target sample size was 35 patients in each arm (alpha, 0.05; beta, 0.20). **Results:** Between December 2009 and March 2013, 71 patients were enrolled. One patient in each arm did not receive any protocol treatment due to rapid disease progression. Characteristics of treated patients were as follows: median age, 70 years (range 51–84 years); proportion of males, 84%. The ORRs were 79% (95% confidence interval [CI]: 62–91) and 89% (95%CI: 73–97), median PFS were 5.1 and 6.3 months (hazard ratio [HR] = 0.51, 95%CI: 0.30–0.85, p = 0.01), and median OS were 14.9 and 15.9 months in the CI and CA arms, respectively. Toxicities of grade 3 or higher severity were neutropenia (CI, 53% and CA, 89%), anemia (CI, 26% and CA, 20%), thrombocytopenia (CI, 18% and CA, 14%), and febrile neutropenia (CI, 12% and CA, 29%). No treatment-related deaths were observed. **Conclusions:** CA was numerically effective than CI in chemo-naïve ED-SCLC patients, with acceptable toxicity. CA could be selected for future phase 3 trials. Clinical trial information: UMIN000008970.

**7522 Poster Highlights Session (Board #15), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Safety and antitumor activity of the PARP inhibitor BMN673 in a phase 1 trial recruiting metastatic small-cell lung cancer (SCLC) and germline BRCA-mutation carrier cancer patients.** *Presenting Author: Zev A. Wainberg, David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA*

**Background:** BMN 673 is the most potent inhibitor of PARP1/2 in clinical development (IC50$<$1nM), inducing synthetic lethality in tumors deficient in homologous recombination. Based on preclinical data showing high PARP expression in SCLC models and significant antitumor activity of BMN 673, an expansion cohort of SCLC patients was also studied. **Methods:** Safety, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity of BMN 673 were evaluated in a 2-stage study. In dose escalation (Stage 1), cycle 1 was 6 wks, with drug taken on days 1 and 8-35, for PK and PD assays, followed by daily continuous dosing in 4-wk cycles. Stage 2(expansion at MTD) recruited pts with tumors defective in DNA repair: Previously treated extensive stage SCLC (second line), Ewing's sarcoma (ES), or tumors in germline (g) BRCA mutation (mut) carriers. **Results:** Stage 1: The MTD and Recommended Phase 2 Dose (RP2D) was established at 1 mg/d in 39 pts (33F/6M) treated at doses ranging from 25 to 1100 $\mu$g/d. Dose-limiting thrombocytopenia occurred in 1/6 and 2/5 pts at 900 and 1100 $\mu$g/d, respectively. Stage 2: To date, 54 pts [38F/16M, median age 52 (range 18-78)] have been enrolled: 15 SCLC, 12 ES and 27 gBRCA mut. RECIST confirmed responses have been reported in 2/11 (18%) evaluable previously treated SCLC pts [Clinical Benefit Rate (PR+SD $>$ 8 wks): 6/11 pts (55%); median PFS: 7.4 wks, 95% CI 4.3-19.4]; 12/26 (46%) gBRCA mut ovarian cancer pts (median PFS: 32.3 wks, 95%CI 28.2-38.6); and 8/18 (44%) gBRCA mut breast cancer pts (median PFS: 31 wks, 95% CI 13.1-45.4). No responses were seen in ES pts. Overall, the most frequent adverse events were mild to moderate and included fatigue (all grades=30%), nausea (26%), alopecia (25%), anemia (23%), thrombocytopenia (20%) and neutropenia (14%). **Conclusions:** BMN 673 is well tolerated at the RP2D of 1 mg/d. BMN 673 has antitumor activity in pts with advanced previously treated SCLC and significant activity in pts with gBRCA mut ovarian and breast cancer. A phase 3 trial in gBRCA mut breast cancer is ongoing. Clinical trial information: NCT01286987.

**7523 Poster Highlights Session (Board #16), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**A phase 1 study of veliparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, in combination with cisplatin and etoposide in extensive-stage small cell lung cancer (SCLC) patients: An Eastern Cooperative Oncology Group study (E2511).** *Presenting Author: Taofeek Kunle Owonikoko, The Winship Cancer Institute of Emory University, Atlanta, GA*

**Background:** Veliparib is a small molecule inhibitor of PARP currently in advanced clinical testing. Based on promising preclinical evidence of therapeutic potentiation when combined with cisplatin and etoposide in SCLC, a phase 1 study was conducted to establish the safety of the 3-drug combination. **Methods:** The study employed the 3+3 dose escalation design to establish the safety and recommended phase 2 dose (RP2D) of veliparib when combined with fixed doses of cisplatin (75mg/m$^2$ on D1) and etoposide (100mg/m$^2$on D1-3) without prophylactic growth factor support in a 21-day cycle. The starting dose of Veliparib was 60mg (bid D1-7) with plan to escalate to 100mg (D1-7) if no dose limiting toxicity (DLT) or de-escalate to 40mg (bid D1-7) if DLT was observed in 2 of 3 or $\geq$2 of 6 treated patients. Patients with treatment-naïve, extensive stage SCLC were included. DLT was assessed during cycle 1. **Results:** The study enrolled 9 patients with extensive stage SCLC; Gender: M/F (4/5); Age: median/range (60, 51-78); Race: White/African American (8/1). Veliparib was well tolerated at the 60mg dose (0 of 3 patients with DLT). DLT was seen in 1 of 6 patients treated at the 100mg dose (grade 5 cardiac failure). We established the maximum tolerated dose of veliparib of 100mg bid on D1-7 in combination with standard doses of cisplatin and etoposide as the RP2D. Grades 3-5 adverse events irrespective of attribution included - G3: dehydration (1), febrile neutropenia (1), hyponatremia (1), diarrhea (1), nausea (3), thrombocytopenia (1), fatigue (2), neutropenia (1), leukopenia (3); G4: hyponatremia (1), respiratory failure (1), thrombocytopenia (1), neutropenia (5), leukopenia (2); G5: heart failure (1). Unconfirmed investigator-assessed efficacy outcome in 7 evaluable patients were stable disease in 2/7 (28.6%), partial response in 4/7 (57.1%) and complete response in 1/7 (14.3%) patients. **Conclusions:** The study demonstrated the safety of combining veliparib with cisplatin and etoposide in previously untreated SCLC patients. A randomized phase II efficacy study of this combination is currently ongoing. Clinical trial information: NCT01642251.

**7524 Poster Highlights Session (Board #17), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Analysis of small cell lung cancer (SCLC) patients (Pts) treated on cancer therapy evaluation program (CTEP)-sponsored phase I trials: 1992-2012.** *Presenting Author: Patrick M. Forde, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

**Background:** Platinum-refractory SCLC has a poor prognosis with a median survival of 2-6 months. Second-line and later treatment options are limited and pretreated patients with preserved ECOG performance status (PS) are often considered for early phase clinical trials in solid tumors. We conducted an analysis of the CTEP database and report the largest cohort to date of SCLC pts treated on phase I studies. **Methods:** Data from all SCLC patients enrolled on CTEP-sponsored phase I trials from 1992-2012 were analyzed. Trials were conducted at the National Institutes of Health and other institutions in the United States under CTEP sponsorship. Trials were categorized as chemotherapy (C), biologic therapy (B), combined biologic-chemotherapy therapy (BC) or immunotherapy (I). Demographics, rates of toxicities, response rate (RR), clinical benefit rate (CBR = RR +stable disease rate) and treatment duration were analyzed using descriptive statistics. **Results:** 84 pts enrolled during the specified time period, (median age 59 (interquartile range, IQR 52 – 63) ECOG PS 0-1 86.9%; 2, 11.9%; 3, 1.2%). The cohort was heavily pretreated (median 4 lines (IQR 2 – 5)). Pts received the following treatment types (no. of pts (%)) - C, 47 (56%); B, 18 (21.4%); BC, 14 (16.7%); I, 5 (6%). Treatment-related toxicities occurred as follows – grade 1/2, 71 (84.5%); grade 3/4, 39 (46.4%); grade 5, 1 (1.9%). RR was 6 (7.1%) and the CBR was 23 (27.1%). Responses only occurred with C (4 pts) and BC (2 pts). Median treatment duration was 42 days (IQR 25 – 63). **Conclusions:** Toxicities in phase I SCLC pts are higher than those previously reported in the general population of phase I solid tumor pts (G3/4 toxicity rate 46.4% vs. 36-38% (CTEP & non-CTEP databases)). This may partly reflect a relatively higher proportion of SCLC pts with ECOG PS >1 (13.1% vs. 6% of unselected solid tumor pts on CTEP phase I studies). CBR and median treatment duration are comparable to SCLC pts who have been treated with single agent chemotherapy in the second or subsequent line setting but lower than those observed in the general phase I pt population. Phase I study enrollment represents a reasonable option for pretreated SCLC pts with good ECOG PS.

**7525 Poster Highlights Session (Board #18), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Phase II trial of sunitinib in patients with thymic epithelial tumors (TET).** *Presenting Author: Anish Thomas, National Cancer Institute at the National Institutes of Health, Bethesda, MD*

**Background:** There are no standard treatments for patients with advanced TETs after failure of platinum-based chemotherapy. In thymic carcinoma, KIT over-expression and mutations are found in about 80% and 8% cases respectively. Expression of angiogenic markers correlates with invasiveness of TETs. This non-randomized, phase II trial evaluated the efficacy of sunitinib, whose targets include KIT and vascular endothelial growth factors (VEGFR), in TETs. **Methods:** Patients with TET who had progressive disease following at least one platinum-based chemotherapy were enrolled. Sunitinib was administered orally at 50 mg once daily in 6 week cycles for 4 weeks followed by 2 weeks off until disease progression. Tumor response was assessed by CT scans every 6 weeks. Correlative studies included exome sequencing of 197 cancer related genes and peripheral blood T cell subset analyses. Primary end point was objective response rate in 2 parallel cohorts [thymoma (T) and thymic carcinoma (TC)]. **Results:** Between May 2012 and October 2013, 24 patients with TC [median age 58 (41-81); males 63%] and 16 with T [median age 54 (31-74); males 44%] enrolled. Median of 4 (range, 1-11) and 5 (range, 1-12) cycles were administered in patients with TC and T respectively. Among 23 evaluable patients with TC, there were 6 (26%) partial responses, 15 (65%) stable disease [including 9 (39%) minor responses: 10-29% reduction] and 2 (9%) progressive disease. After median follow up of 13.9 months, the median progression-free survival (mPFS) for TC was 6.7 months and median overall survival (mOS) 16.3 months. In contrast, only 1 of 16 (6%) patients with T had a partial response, 12 (75%) stable disease [including 3 (19%) minor responses] and 3 (19%) progressive disease. After median follow-up of 12.7 months, the mPFS was 8.5 months for T and mOS not reached. Most common grade 3 or 4 sunitinib-related adverse events were lymphopenia, fatigue, oral pain and thrombocytopenia. KIT mutations were absent in 20 tumors assessed, which included 11 TC and 4 partial responders. **Conclusions:** Sunitinib demonstrated anti-tumor activity unprecedented for a targeted agent in previously treated patients with TC. Activity was modest in T. Tumor sequencing and T cell subset analyses will be presented. Clinical trial information: NCT01621568.

**7526 Poster Highlights Session (Board #19), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**A phase II study of milciclib (PHA-848125AC) in patients (pts) with thymic carcinoma (TC).** *Presenting Author: Benjamin Besse, Gustave Roussy, Villejuif, France*

**Background:** TC and B3 thymoma (B3T) are rare malignant tumors of the thymus. Outcomes of clinical trials focusing on TC and B3T have highlighted the challenging nature of this disease and the need to identify new agents. Milciclib is an inhibitor of cyclic-dependent kinase and Src family members, and a limited number of additional kinases. We have initiated a single-arm Phase II study in advanced TC/B3T based on 2 partial responses (PRs, one pt with thymic carcinoma and one pt with B3 thymoma) observed in a phase I study conducted with Milciclib. **Methods:** Pts with histologically confirmed TC/B3T who received only one prior systemic therapy were enrolled. Pts received Milciclib 150 mg daily 7d on/7d off in 2-week cycles. The primary endpoint was progression free survival rate at 3 months (PFS-3 rate). Based on the Simon's 2-stage design, the sample size of 54 evaluable pts confers 80% power to reject the null hypothesis of a PFS-3 rate lower than 33% . At least 14 successes out of 54 evaluable patients were required for Milciclib to deserve further investigation. **Results:** To date, 43 pts have been treated (male/female 18/25; median age 55, range 21-80, TC/B3T 26/9). The second stage of the trial is ongoing and 599 cycles have been administered with a median number of 7 cycles/pts. Out of 30 pts whose data are available and mature, 14 are successes (PFS-3 rate = 46.7%; 95%CI 28.3-65.7%) including a RECIST 1.1 PR. Toxicity was generally moderate. The most common Grade 3-4 AE are nausea and asthenia (8.3%), vomiting, myasthenic syndrome, dehydration, hypophosphatemia, cytolytic hepatitis, plantar fascitis (4.2%). The most common Grade 3-4 hematological and biochemical toxicities are neutropenia (8.4%), creatinine, amylase and lipase increase (5.6%). **Conclusions:** The study has already met its predefined primary endpoint in treated patients and therefore we thought it was useful to report these data in a rare disease although the per protocol analysis is to be done on evaluable patients. This supports its full investigation as potential new therapeutic agent to treat TC/B3T. Clinical trial information: NCT01011439.

**7527 Poster Highlights Session (Board #20), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Phase II study of everolimus in patients with thymoma and thymic carcinoma previously treated with cisplatin-based chemotherapy.** *Presenting Author: Paolo A. Zucali, Humanitas Cancer Center, Rozzano, Italy*

**Background:** Alterations of the serine-threonine kinase mammalian target of rapamycin (mTOR) signalling pathway are common in cancer, and thus mTOR is being actively pursued as a therapeutic target. In particular, mTOR is emerging as a potential target, following tumor responses observed in phase I trials, with recent data from several groups. The aim of this study is to determine the activity of Everolimus monotherapy in patients (pts) with advanced or recurrent thymoma (T) or thymic carcinoma (TC) previously treated with cisplatin-containing chemotherapy. **Methods:** Pre-treated T and TC pts were prospectively enrolled in single arm, single-stage, open label, multicentre, phase II trial. Pts received continuous treatment with oral everolimus 10 mg once daily until documented disease progression, unacceptable toxicity, or patient refusal. Tumour assessment was done every six weeks, safety was assessed every 21 days. A Fleming phase II trial was designed considering a disease control rate (DCR) of 40% or lower as clinically unworthy, whereas a rate of 60% or higher was considered of potential interest, $\alpha=\beta=0.10$. It was calculated that 21 pts with disease control would be observed in the first 41 evaluable pts. Progression free survival (PFS), overall survival (OS), and safety were also evaluated. **Results:** Results of the first 35 enrolled pts are presented. Patient characteristics are as follow: median age is 51 years (range 37;81), male/female 20/15 (57%/43%), TC/T 12/23 (34%/66%), and locally advanced/metastatic disease 9/26 (26%/74%). We observed complete remission (CR) in 1 patient (TC), partial response (PR) in 3 pts (2TC/1T), and stable disease (SD) in 21 pts (16T/5TC), for a total of 25 pts who reached DC.With a median follow up of 10 months, median PFS was 12.1 months, while median OS was 24.0months. Seven pts (20%) presented a serious adverse event but only 3 of them permanently discontinued treatment. **Conclusions:** The primary end-point of this study was reached. These results suggest that Everolimus is able to achieve a satisfactory number of DC in this setting of pts. The efficacy should be better evaluated in subsequent larger study phases. Clinical trial information: NCT02049047.

**7528 Poster Highlights Session (Board #21), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Capecitabine plus gemcitabine in thymic epithelial tumors: Final analysis of a phase II trial.** *Presenting Author: Carlo Buonerba, Department of Clinical Oncology and Endocrinology and Rare Tumors Reference Center Campania Region, University Federico II, Naples, Italy*

**Background:** Thymic epithelial tumors (TETs) are rare malignancies, with an estimated incidence of about 3 cases per 100,000 inhabitants. No standard treatment is available for recurrent disease. In 2005, a multi-institutional phase II trial was started on the combination of gemcitabine and capecitabine in pretreated patients with TETs. Final results of this phase II study are presented. **Methods:** Eligibility criteria for the study were mainly the following: histologic diagnosis of TET by central review; at least one prior systemic chemotherapy treatment; progressive disease. Treatment consisted of oral capecitabine (650 mg/mq twice daily on days 1–14) and i.v. gemcitabine (1000 mg/mq on days 1 and 8) every 3 weeks. The radiographic response rate was chosen as primary end point and employed to calculate the study sample. Secondary end points were progression-free survival, toxicity, and overall survival. **Results:** Thirty patients (18 men, 12 women; median age 57 years, range 48–61 years)were enrolled in this phase II trial from November, 2005 to June 2013. The majority of patients (73%) had thymoma, while the remaining had thymic carcinoma.Of note, 63% of patients showed disease progression within 2 months from the last dose of the last systemic therapy received. The most important grade 3 toxicity was neutropenia in eight patients. Twelve patients had a response (three complete responses and eight partial responses). Among thymic carcinoma patients, we observed three partial responses. Median PFS was 11 months (95% CI 3–17 months). The PFS for patients with thymoma and thymic carcinoma was 11 months (95% CI 6–17 months) and 6 months (95% CI 3–11 months), respectively. Thirteen patients are dead at the time of the analysis (median OS, 16 months). **Conclusions:** Capecitabine and gemcitabine is a highly active combination therapy in thymic epithelial tumors and should be routinely included in the managment of recurrent/metastatic disease.

**7529 Poster Highlights Session (Board #22), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Recurrence of epigenetic gene mutations in thymic epithelial carcinomas revealed by targeted exome sequencing of cancer-associated genes.** *Presenting Author: Yisong Wang, Georgetown University, Washington, DC*

**Background:** Genetic alterations and etiology of thymic epithelial tumors (TET) are largely unknown, hampering development of effective targeted therapies for TET patients. **Methods:** TET patients enrolled in a clinical trial of molecularly-guided targeted therapies underwent exome capture sequencing of 197 cancer-associated genes. Somatic non-synonymous sequence variations including missense, nonsense, splice site mutations and indels were identified by comparative sequence analyses of tumor/blood paired samples. **Results:** Targeted exome capture sequencing of 78 advanced stage TETs (46 thymic carcinomas and 32 thymomas)/blood pairs revealed a total of 134 somatic non-synonymous sequence variations in 68 genes. Somatic non-synonymous sequence variations were found in 50% (39/78) of the TETs analyzed. Thymic carcinomas (67%; 31/46) showed higher incidence of somatic non-synonymous mutations than thymomas (25%; 8/32)($p=0.0002$). TP53 (n = 13; 17%) was the most frequently mutated gene in TETs, and TP53 mutant patients showed poorer overall survival than TP53 wild-type patients ($p < 0.0001$). In thymic carcinomas, genes in epigenetic modification machinery [BAP1 (n = 6; 13%), SETD2 (n = 4; 9%), DNMT3A (n = 3; 7%), TET2 (n = 3; 7%), WT1 (n = 2; 4%), SMARCA4 (n = 2; 4%), and ASXL1 (n = 2; 4%)] were found recurrently mutated, whereas in thymomas, a preponderance of epigenetic gene mutations was not observed. **Conclusions:** Our results highlight the potential importance of epigenetic machinery in thymic carcinoma and indicate that substantial difference in genetic makeup exists between thymic carcinomas and thymomas. Targeting of epigenetic pathways may be of benefit to patients who carry those mutations.

**7530 Poster Highlights Session (Board #23), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Next-generation sequencing in malignant pleural mesothelioma: A retrospective study.** *Presenting Author: Giorgio V. Scagliotti, Department of Oncology, University of Turin AOU San Luigi Gonzaga, Orbassano, Italy*

**Background:** The understanding of molecular pathogenesis of malignant pleural mesothelioma (MPM) has lagged behind other common malignancies. According to the COSMIC database the most frequently mutated genes in MPM include CDKN2A, NF2 and BAP1, followed by other 12 genes having been found mutated in a fraction of MPM cases (c-MET, VHL, WT1, etc). **Methods:** A consecutive series of 123 MPM tissue samples with clinical annotates, collected at two institutions (Orbassano n=93; Alessandria n=30), were retrospectively analyzed through Next-Generation Sequencing (NGS) to explore genomic profiling.Genomic DNA was extracted by tumour microdissected, formalin-fixed, paraffin embedded (FFPE) samples. Amplicons NGS libraries for 50 oncogenes included in Ion AmpliSeq Cancer Hotspot Panel v.2 were generated as indicated, and sequenced in Personal Genome Machine Ion Torrent. Additional customized genomic analyses included all exons of BAP1 and NF2. Variant Caller included in Torrent Suite Software was utilised to identify mutations in the samples, annotation was performed with Annovar software. **Results:** All patients had advanced stage and were treated with pemetrexed-based chemotherapy, 70% were males, 50% current smokers, median age 66.5 (range 36-82) years and histological subtypes were 96/22/5 epithelioid/biphasic/sarcomatous. Synonymous/intronic variations represented 61.2% of all detected mutations. More frequently altered genes were APC, BAP1, CSF1R, FLT3, NF2, KDR, PIK3CA, TP53. Irrespective of allelic frequency, at least 1 variation in top genes was recorded in all patients, and at least 5 mutated genes were detected in 68 patients. KIT3 and PIK3CA mutations are associated with younger age while VHL1 and BAP1 with epithelioid histology. Moreover, BAP1 mutation is associated with negative nuclear protein expression at immunohistochemistry. **Conclusions:** These preliminary data indicate that NGS technology is feasible in FFPE MPM tissues and some of the detected genetic mutations are novel observations of potential prognostic and therapeutic interest.

**7531 Poster Highlights Session (Board #24), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**A phase 2 single-arm study with tremelimumab at an optimized dosing schedule in second-line mesothelioma patients.** *Presenting Author: Luana Calabrò, Medical Oncology and Immunotherapy, University Hospital of Siena, Siena, Italy*

**Background:** We reported encouraging clinical activity of tremelimumab (treme), a fully human IgG 2 monoclonal antibody specific for cytotoxic T lymphocyte-associated antigen 4, at 15 mg/kg q3 months (mos), in second-line malignant mesothelioma (MM) patients (pts). Durable partial responses in 2 pts, 31% disease control, 10.7 mos median overall survival (OS), and 1- and 2-y survivals of 48% and 37% were observed (*Lancet Oncol*, 2013). These findings and pharmacokinetic studies in melanoma pts, led us exploring the activity and safety of treme at an optimized dosing schedule in MM pts in the MESOT-TREM-2012 study (ClinicalTrials.gov Id NCT01655888). **Methods:** MM pts progressing on a first-line platinum-based regimen received treme at 10 mg/kg i.v. on day 1, q4 weeks (wks) for 6 doses (induction phase), followed by q12-week dosing (maintenance phase), until progressing disease (PD) or severe toxicity. Primary endpoint was objective response (OR) rate; among secondary were DCR, OS, and safety. Tumor assessment *per* immune-related (Ir) RECIST Criteria was done at screening and q12 wks. Adverse events (AEs) were collected according to the CTC v3.0. **Results:** From July 2012 to July 2013, 29 MM pts, 20 males and 9 females, median age 65 (42-78) years, 11 stage III and 18 stage IV, ECOG performance status 0-1 (23 pts) or 2 (6 pts), were treated. Nineteen pts had a good EORTC prognostic score; 21 pts had epithelioid histotype, 6 biphasic, 1 sarcomatoid, and 1 undefined. As of Jan 2014, all pts received at least 1 dose of treme (median 6, range 1-10). The study met its primary endpoint since at a median follow-up of 14.5 mos 4 irPR were observed. Eleven pts had stable disease of median duration 7.7 mos (range 2.6-16.6+), and the irDCR was 51.7%. Median OS was 11.3 mos (95% CI: 5.6-17.0). Grade 1-2 and 3 treatment-related AEs occurred in 89.6% and 3.4% of pts, respectively; no grade 4 AEs occurred. Most common treatment-related AEs were gastrointestinal (65.5%), dermatologic (48.2%), and fever (34.4%). **Conclusions:** At an optimized dosing schedule treme continues to show clinical activity and an acceptable safety profile in MM pts. A phase 2b global trial is ongoing. Clinical trial information: NCT01655888.

**7532 Poster Highlights Session (Board #25), Sun, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Antimesothelin vaccine CRS-207 plus chemotherapy as front-line treatment for malignant pleural mesothelioma (MPM).** *Presenting Author: Raffit Hassan, National Cancer Institute at the National Institutes of Health, Bethesda, MD*

**Background:** CRS-207 is live-attenuated *Listeria monocytogenes* engineered to express the tumor-associated antigen mesothelin which is highly expressed in malignant pleural mesothelioma (MPM). CRS-207 stimulates potent innate and adaptive cellular immunity. Chemotherapy may act synergistically in combination with CRS-207 by altering the tumor environment to be more susceptible to immune-mediated killing. **Methods:** Key eligibility criteria included patients who were chemotherapy-naïve, had unresectable MPM, good performance status (ECOG 0 or 1) and adequate organ function. Eligible patients received 2 prime vaccinations with CRS-207 ($1 \times 10^9$ CFU; 250 mL IV over 2 hours) 2 weeks apart, followed by up to 6 cycles of pemetrexed (500 mg/m$^2$) and cisplatin (75 mg/m$^2$) 3 weeks apart and 2 CRS-207 boost vaccinations 3 weeks apart. Subjects were followed every 8 weeks until disease progression. Clinically stable patients could continue CRS-207 maintenance vaccinations every 8 weeks. Objectives of the study were safety, immunogenicity, objective tumor responses and tumor marker kinetics. **Results:** Sixteen subjects (88% male; median age: 69) have been enrolled and as of Feb 1 2014, 13/16 are still on treatment. Median time on treatment was 134 days (range: 0-330 days). No treatment-related serious adverse events or unexpected toxicities have been observed. The most common adverse events related to CRS-207 were Grades 1/2 infusion-related fever, chills/rigors, hypotension and nausea/vomiting. Of 15 subjects evaluable for response, 60% (9/15) had confirmed partial response (PR) post CRS-207 and chemotherapy and 27% (4/15) had stable disease (SD). Treatment, follow-up and immune response evaluations are ongoing. **Conclusions:** CRS-207 can be safely combined with standard of care chemotherapy and showed encouraging anti-tumor activity with 9 out of 15 subjects having confirmed durable PR and 4 SD. These results are considerably better than those expected with chemotherapy alone and warrant further evaluation. Clinical trial information: NCT01675765.

**7533 General Poster Session (Board #141), Sat, 1:15 PM-5:00 PM**

**Postoperative chemotherapy as effective as preoperative for N2-positive stage III non-small cell lung cancer.** *Presenting Author: Daniel J Boffa, Yale School of Medicine, New Haven, CT*

**Background:** Neoadjuvant chemotherapy followed by surgery is superior to surgery alone for stage III non-small cell lung cancer (NSCLC) with mediastinal (N2) lymph node involvement. It is unclear, however, if postoperative (adjuvant) chemotherapy is as effective as preoperative (neoadjuvant) chemotherapy in this setting. The objective of this study was to determine the survival of resected stage III NSCLC according to the timing of chemotherapy. **Methods:** The National Cancer Database (NCDB) was queried for patients with clinical T1-4N2M0 NSCLC (clinical Stage III - N2) undergoing resection via lobectomy or pneumonectomy between 2003 and 2006. **Results:** The efficacy of post-operative (adjuvant) therapy in clinical Stage III - N2 NSCLC was evaluated in two ways. First we examined a cohort of 698 treatment-naïve (no preoperative treatment) clinical N2 patients confirmed to be pathologic N2 by the surgical resection of primary tumor (cN2pN2). We compared surgery "alone" to surgery followed by adjuvant chemotherapy. The 5-year survival of cN2pN2 patients was significantly higher with adjuvant chemotherapy (36%, n= 212) or chemoradiation (33%, n= 230) than surgery alone (21%, n= 256, p<.0001). In a multivariable analysis adjusting for patient demographics, tumor attributes, a modified Charlson comorbidity index and type of resection, the use of postoperative chemotherapy (HR, 0.66 95%CI [0.52-0.84], *p*=.0005) and chemoradiation (HR 0.75, 95%CI [0.59-0.95], *p*=.016) were both superior to surgery alone. There was no significant difference between chemotherapy and chemoradiation. We next directly compared postoperative chemotherapy (adjuvant) to preoperative therapy (neoadjuvant) in clinically staged III – clinical N2 NSCLC. A multivariable Cox model including variables noted above indicated that adjuvant therapy (n = 649) was associated with a similar outcome to neoadjuvant therapy (n = 1,356) HR 1.05, 95% CI [.92 – 1.18], p = .475). **Conclusions:** Chemotherapy appears to be similarly effective in stage III NSCLC patients with N2 disease when given before or after resection in the NCDB. This finding, could impact the role preoperative mediastinal staging in operable stage III lung cancer.

**7534 General Poster Session (Board #142), Sat, 1:15 PM-5:00 PM**

**When is a pathologic diagnosis preferred before stereotactic ablative radiotherapy for stage I lung cancer? A decision analysis.** *Presenting Author: Alexander V. Louie, Department of Radiation Oncology, London Regional Cancer Program, London, ON, Canada*

**Background:** The practice of treating a solitary pulmonary nodule (SPN) suspicious for stage I NSCLC with stereotactic ablative radiotherapy (SABR) in the absence of pathologic confirmation of malignancy is growing. In the absence of randomized evidence, the appropriate lung cancer prevalence threshold of when such a strategy is warranted can be informed using decision analysis. **Methods:** A decision tree and Markov model were constructed to evaluate the relative merits of observation, performing SABR without pathology, or performing a biopsy prior to SABR, when faced with a SPN at different lung cancer prevalences. Diagnostic characteristics, as well as disease, treatment, and toxicity parameters were extracted from the literature. Toxicity, recurrence rates, and health utilities (derived via mapping procedures) were abstracted from a prospectively collected database of 382 patients receiving SABR for confirmed or suspected stage I NSCLC. Deterministic analysis and probabilistic sensitivity analyses on all model inputs were performed to inform the appropriate lung cancer prevalence threshold between treatment strategies. The model was validated internally and externally. A 5-year time horizon using a cycle length of one month was employed and quality adjusted life years (QALYs) were discounted at a rate of 3%. **Results:** At a lung cancer prevalence of 65%, performing a biopsy was the preferred treatment strategy, yielding 2.640 QALYs, compared to 2.563 and 2.086 for the no biopsy and observation strategies, respectively. The prevalence threshold between observation and performing a biopsy was 17.0%; and between performing SABR without pathology and performing a biopsy prior to SABR was 85.0%. The latter finding was confirmed on probabilistic sensitivity analysis (85.2%; 95% CI: 80.0%–87.2%). This predicted lung cancer prevalence threshold was most sensitive to the diagnostic sensitivity of transthoracic biopsy (range: 77.2–94.0%). **Conclusions:** This model suggests that if there are concerns about increased morbidity related to biopsy for a SPN, SABR is warranted as a treatment strategy when the prevalence of lung cancer exceeds a point estimate of 85%.

**7535 General Poster Session (Board #143), Sat, 1:15 PM-5:00 PM**

**Analysis of treatment duration and safety of adjuvant erlotinib (E) versus placebo (P) after surgery in patients (pts) with non-small cell lung cancer (NSCLC): RADIANT trial.** *Presenting Author: Mary E.R. O'Brien, The Royal Marsden Hospital, Sutton, United Kingdom*

**Background:** We describe treatment duration and safety in the safety full analysis set (sFAS) and in the subset of pts with *EGFR* del19 and L858R mutations (*EGFR* M+). **Methods:** RADIANT was a randomized trial of adjuvant E *v* P in pts with stage IB-IIIA NSCLC following complete tumor resection w/ or w/o adjuvant chemotherapy. Pts were randomized (2:1) to receive up to 2 years of E 150mg/day or P. AEs were graded with NCI CTCAE v3.0. Dose reductions to 100mg and then 50mg were allowed; pts not tolerating 50mg/day were discontinued. **Results:** The sFAS included 954 pts, of whom 159 (16.7%) were *EGFR* M+. AEs led to treatment termination in 33.6% of pts on E versus 8.5% on P in sFAS, and 30% versus 5.1% in the *EGFR* M+ subset. In sFAS, 22.6% of E pts had Gr ≥3 skin disorders (rash, dermatitis acneiform, pruritus, etc.) and 6.2% had Gr ≥3 diarrhoea. The figures were similar for *EGFR* M+ pts. In sFAS, pts received 11.9 versus 21.9 m (median) of E versus P, and 27% *v* 46% were treated for >22 m. For *EGFR* M+ pts median treatment duration was 21-22 m in both arms and 34% versus 40.7% (E vs P) received >22 m of therapy. In sFAS, 26.7% versus 10.8% (E vs P) pts in received <3 m of therapy, as did 21% versus 8.5% *EGFR* M+ pts. AEs led to dose interruption, reduction, or both in 18.5, 24.5, 25.5% in sFAS; the figures were generally similar for *EGFR* M+ pts. **Conclusions:** The safety profile of E was consistent with that in advanced disease, although Gr ≥3 skin disorders was more frequent than previously reported in advanced NSCLC (9-14%). For E, AE frequency was similar between sFAS and *EGFR* M+ subset. While treatment duration was longer in the *EGFR* M+ subset than sFAS, frequency of AE leading to treatment termination was similar. Further investigation of E in *EGFR* M+ is warranted. Clinical trial information: NCT00373425.

| | sFAS | | *EGFR* M+ | |
|---|---|---|---|---|
| | E | P | E | P |
| **N** | 611 | 343 | 100 | 59 |
| **AEs leading to treatment termination %** | | | | |
| **Any** | 33.6 | 8.5 | 30 | 5.1 |
| **Drug-related** | 26.7 | 2.3 | 25 | 0 |
| **AEs leading to dose** | | | | |
| **Interruption** | 18.5 | 6.7 | 22 | 6.8 |
| **Reduction** | 24.5 | 2.6 | 22 | 1.7 |
| **Both %** | 25.5 | 1.5 | 34 | 1.7 |
| **Gr≥3 skin disorder %** | 22.6 | 0.3 | 20 | 0 |
| **Gr≥3 diarrhea %** | 6.2 | 0.3 | 5 | 0 |
| **Median treatment duration (m)** | 11.9 | 21.9 | 21.2 | 21.9 |
| **>22m of treatment %** | 27.5 | 45.8 | 34 | 40.7 |

**7536 General Poster Session (Board #144), Sat, 1:15 PM-5:00 PM**

**Nonadherence of adjuvant radiation in NSCLC patients with N2 disease after lobectomy.** *Presenting Author: Yan Xing, Department of Medicine, Harvard Medical School, Mount Auburn Hospital, Cambridge, MA*

**Background:** National Comprehensive Cancer Network (NCCN) guidelines recommend adjuvant radiotherapy (XRT) for NSCLC patients with N2 disease after lobectomy. The purpose of this study is to identify factors associated with non-adherence if any to NCCN guidelines for the above patients in a large population database. **Methods:** SEER registry was queried for NSCLC patients with N2 disease and lobectomy, diagnosed between 2004-2010. Patients with distant metastases were excluded. The study period was divided in two eras (2004-2006 and 2007-2010) because the landmark publication in this field by Lally et al. was published on Jun 12, 2006. Multivariate logistic regression analyses were performed to identify factors predicting non-adherence. **Results:** A total of 2,112 N2 NSCLC patients who had lobectomy were included in the final cohort, 773 (36.6%) of whom received adjuvant XRT according to NCCN guidelines. There were 34.3% and 38.3% of N2 NSCLC patients who received adjuvant XRT in 2004-2006 and 2007-2010 respectively. 40.3% of patients who had larger lymph nodes (LN) burden (≥ 20% LNs removed were positive) received adjuvant XRT compared to 28.2% in patients with small LN burden. Multivariate analyses revealed that age ≥ 70 years, unmarried, west region, diagnosed in early period (2004-2006), T1 and smaller LN burden were associated with non-adherence with guidelines (Table). **Conclusions:** Although treatment trends are improving since 2007, adjuvant XRT for NSCLC patients with N2 disease continues to be underutilized, particularly in the elderly, unmarried, west regions of the United States, T1 and smaller LN burden.

**Factors associated with no adjuvant XRT in N2 NSCLC patients after lobectomy.**

| Variables | OR | 95% CI | p |
|---|---|---|---|
| **Age** | | | |
| **60-69 vs. <60** | 1.37 | 1.09 - 1.71 | 0.006 |
| **≥70 vs. <60** | 2.01 | 1.61 - 2.53 | <0.001 |
| **Marital status** | | | |
| **Unmarried vs. married** | 1.31 | 1.08 - 1.59 | 0.005 |
| **Unknown vs. married** | 1.73 | 0.87 - 3.44 | NS |
| **Region** | | | |
| **West vs. South** | 1.49 | 1.19 - 1.86 | <0.001 |
| **Midwest vs. South** | 1.32 | 0.95 - 1.85 | NS |
| **Northeast vs. South** | 1.19 | 0.91 - 1.57 | NS |
| **Year of diagnosis** | | | |
| **2004-2006 vs. 2007-2010** | 1.23 | 1.02 - 1.48 | 0.028 |
| **T stage** | | | |
| **T2 vs. T1** | 0.95 | 0.77 - 1.17 | NS |
| **T3 vs. T1** | 0.75 | 0.56 - 0.99 | 0.045 |
| **T4 vs. T1** | 0.81 | 0.50 - 1.29 | |
| **% of positive LN in removed LN** | | | |
| **< 20% vs. ≥ 20%** | 1.79 | 1.46 - 2.20 | <0.001 |

Abbreviations: NS, not significant.

**7537 General Poster Session (Board #145), Sat, 1:15 PM-5:00 PM**

**KIF5B-RET fusion gene and oncogenic mutations of EGFR or KRAS gene in lung adenocarcinomas.** *Presenting Author: Jin Hyoung Kang, Division of Medical Oncology, Department of Internal Medicine,Seoul St.Mary's Hospital, The Catholic University, Seoul, South Korea*

**Background:** The KIF5B-RET rearrangement is detected with the frequency of 1~2% in 'triple marker'-negative lung adenocarcinomas, i.e., EGFR, KRAS and EML4-ALK wild type. These mutational changes are known to be mutually exclusive, but the co-existence of ALK rearrangement with activating mutations of EGFR is rarely found. **Methods:** We examined the KIF5B-RET fusion gene in frozen tissues from 156 surgically resected lung tumors using RT-PCR with direct sequencing and the mutation status of EGFR and KRAS genes using PNA clamping (PANAGENE, KOREA). We tested KIF5B-RET translocation in FFPE (Formalin Fixed Paraffin Embedded) using fluorescence in situ hybridization (FISH) with Zytolight Spec RET dual color break-apart probe (zytovision) and KIF5B-RET SY translocation FISH probe (abnova). We also measured c-RET mRNA and protein expression by qRT-PCR and immunohistochemistry (IHC), respectively. **Results:** The existence of KIF5B-RET fusion gene was identified in 11 pts (7.1 %). The mean age was 64.8(52~82) and M: F ratio 5:6. Of 11 pts, 3 pts (27.3 %) harbored wild type of EGFR and KRAS gene. However, KIF5B-RET fusion gene coincided with EGFR or KRAS mutation in 8 pts (72.7 %). These eight pts were also positive for both KIF5B-RET fusion (41.9%, 22.2~72.4 %) and RET break-apart probes (23.7%, 14.3~37.8 %). However, there were no correlations between RET mRNA and protein expression in the KIF5B-RET-positive pts. The median DFS and OS were 23.0 months (8.0~111) and 27.8 months (2.6~114.5), respectively. **Conclusions:** Taken together, our data suggest one-step screening platform for KIF5B-RET as well as EGFR, K-RAS, ALK oncogenic mutations be necessary for lung adenocarcinoma pts because EGFR or KRAS mutation are not infrequently found in KIF5B-RET-positive pts. Now, we are undergoing the clinical study for combined treatment of EGFR TKIs with RET inhibitors for lung adenocarcinoma pts harboring both KIF5B-RET rearrangement and EGFR mutation.

**7538 General Poster Session (Board #146), Sat, 1:15 PM-5:00 PM**

**A novel gene signature to predict distant metastasis in stage I lung cancer patient following local therapy with surgery or stereotactic body radiation therapy (SBRT).** *Presenting Author: Sungjune Kim, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

**Background:** The standard management for stage I non-small cell lung cancer is surgical resection and SBRT. Adjuvant therapy is typically not given in this group of lung cancer patients. Unfortunately, 14% to 23% who undergo surgery for a stage I NSCLC ultimately fail distantly. **Methods:** Moffitt Cancer Center (MCC) has launched a major initiative termed Total Cancer Care (TCC) to innovate personalized compiling 40,000 tumor microarray databank linked to longitudinal clinical data. We conducted a retrospective chart review of pathologic T1-T2N0 NSCLC patients in the TCC database, and classified patients according to their recurrence pattern. CEL files from Affymetrix microarray from pathologic specimens from these patients were obtained from TCC, and gene expression profile was analyzed. **Results:** We identified a cohort of 143 patient treated with surgical resection. 56 patients were without evidence of disease at least 3 years following surgery (Control cohort), 34 patients failed locally and in regional lymph nodes (Loco-regional failure cohort), and 53 patients developed distant metastasis (distant failure cohort). 144 genes were identified that showed significant differences in RNA expression level between control cohort vs. distant failure cohort. However, only 1 gene was associated with loco-regional failure. 144 genes identified were validated against the Director's Challenge database. Over 90% of the genes identified from this study correctly predicted survival outcome from the Director's Challenge database. **Conclusions:** We have identified a group of genes that predict distant metastasis among surgically resected pathologic T1-T2N0 adenocarcinoma of the lung. We are currently developing the scoring system to classify this earliest stage lung adenocarcinoma patients into 3 groups, low risk, intermediate risk, and high risk for distant failure based on our gene signature. The outcome of this study will identify a select group of stage I lung adenocarcinoma patients who will benefit from adjuvant chemotherapy after local therapy with surgery or SBRT. Ultimately, we are planning to translate these findings to a clinical trial.

**7539^ General Poster Session (Board #147), Sat, 1:15 PM-5:00 PM**

**Final overall survival (OS) results from a phase II study of pemetrexed (Pem) and cisplatin (Cis) with concurrent thoracic radiation (RT) after Pem-Cis induction in patients with unresectable locally advanced (LA) nonsquamous non-small cell lung cancer (NS-NSCLC).** *Presenting Author: Silvia Novello, S. Luigi Hospital, University of Turin, Orbassano, Italy*

**Background:** This single arm multicenter phase II study assessed the efficacy and safety of Pem-Cis induction chemotherapy (CT) followed by full-dose Pem-Cis + concurrent RT in patients (pts) with LA NS-NSCLC. The 1yr PFS rate (primary endpoint) was 51.3% (ECCO 2013), incidences of Grade (G)3/4 (esophagitis 12%, neutropenia 11%) and G1/2 toxicities were low during CT and CT+RT (ECCO 2013, WCLC 2013). Here we report the final results after 2yr follow-up. **Methods:** Pts with unresectable Stage IIIA/B NS-NSCLC (AJCC V6) and ECOG-PS 0-1 received 2 cycles of Pem 500/Cis 75mg/m$^2$on Day (d)1, q21d. Pts who did not progress, with no residual neurological toxicity >G2, ECOG-PS 0-1 and lung V20<35% continued with 2 cycles of full dose Pem-Cis + concurrent RT (2Gy/fraction, 66Gy total). All pts received vitamin supplementation/dexamethasone prophylaxis as per Pem label. **Results:** Of 90 pts enrolled (all treated), 75 (83.3%) completed induction CT and started concurrent CT+RT (baseline for 90/75 pts: median age 61/62yrs, male 57%/53%, ECOG-PS 0 66%/65%, mean (SD) FEV 2.3(0.62)/2.3(0.59)L, adeno 90%/92%, Stage IIIA 36%/37%). Post discontinuation, 16.7% of pts had surgery, 26.7% RT, and 36.7% systemic CT. Median OS was 26.2mo (table). Tumor response rate (table) included 9 CRs (10.0%; 6 after surgery, 3 after CT-RT only), all were still progression-free at study end (CR for 3.8-19.6mo). Late toxicities included serious adverse events (SAE) related to study drug (3 pts: G3 leukopenia, G3 hypoacusis, G2 pulmonary embolism) and SAEs of radiation pneumonitis (2 pts: 1 G3, 1 G2). **Conclusions:** Pem-Cis induction CT followed by full-dose Pem-Cis and concurrent RT was effective (median OS 26mo), acute and late toxicity was manageable during both induction CT and concurrent CT+RT. Clinical trial information: NCT01000480.

| | All pts (ITT) N=90 | Started concurrent CT+RT (N=75) |
|---|---|---|
| **Kaplan-Meier estimate, months (95%CI)** | | |
| **mPFs** | 10.6 (8.6, 17.3) | 12.5 (9.6, 19.0) |
| **mOS** | 26.2 (16.7, n.e.) | 30.0 (21.3, n.e.) |
| **Tumor response, % (95%CI)** | | |
| **Response rate** | 60.0 (49.1, 70.2) | 72.0 (60.4, 81.8) |
| **Disease control rate** | 77.8 (67.8, 85.9) | 93.3 (85.1, 97.8) |

**7540 General Poster Session (Board #148), Sat, 1:15 PM-5:00 PM**

**Impact of comorbidity and age on survival among older veterans with early stage non-small cell lung cancer (NSCLC).** *Presenting Author: Melisa L. Wong, University of California, San Francisco and San Francisco VA Medical Center, San Francisco, CA*

**Background:** Older age has been shown to be a stronger predictor of treatment receipt than comorbidity for NSCLC of all stages. We hypothesized that comorbidity would be a stronger predictor of survival than age among veterans with early stage NSCLC. **Methods:** We obtained first-line treatment and overall survival to 5 years from the Veterans Affairs Central Cancer Registry for 6,361 veterans age ≥ 65 diagnosed with stage I-II NSCLC from 2003-2008. Veterans were grouped by age (65-74, ≥ 75), Charlson comorbidity index (CCI 0, 1-3, ≥ 4), and stratified by first-line treatment. Log-rank tests and Cox proportional hazards models were used to identify differences in 5-year survival according to comorbidity and age. **Results:** Median age at diagnosis was 74 and median CCI was 2 (range 0-13). 2,840 (45%) patients received surgery: 2,219 lobectomies (includes 135 pneumonectomies) and 621 sublobar resections. 1,645 (26%) patients received radiation and 1,876 (29%) received other/no treatment. When stratified by age and comorbidity, veterans with CCI 0 who underwent surgery had similar 5-year survival regardless of age and veterans with CCI ≥ 4 had the worst 5-year survival across all treatment groups. In the lobectomy group, 5-year survival for veterans with CCI 0 was 64% for age 65-74 and 59% for age ≥ 75; for veterans with CCI ≥ 4, 5-year survival was 49% for age 65-74 and 50% for age ≥ 75 (log-rank test, p = .002). In multivariable analysis, severe comorbidity was one of the strongest predictors of 5-year survival for all treatment groups along with stage and geographic region. The hazard ratio for 5-year mortality for CCI ≥ 4 was 1.45 (95% CI 1.16-1.83) in the lobectomy group and 1.75 (95% CI 1.11-2.75) in the sublobar resection group. Age had only a modest effect on mortality in the lobectomy group (HR 1.16; 95% CI 1.01-1.34) and radiation group (HR 1.15; 95% CI 1.01-1.31) but was not prognostic in the other treatment groups. **Conclusions:** Severe comorbidity is a much stronger predictor of overall survival than age in early stage NSCLC. Therefore, elderly patients with minimal comorbidity should be considered for surgical evaluation.

**7541 General Poster Session (Board #149), Sat, 1:15 PM-5:00 PM**

**Patterns of surveillance after curative intent surgery in elderly stage I-IIIA non-small cell lung cancer patients.** *Presenting Author: Christine Agnes Ciunci, Hospital of the University of Pennsylvania, Philadelphia, PA*

**Background:** The optimal strategy for imaging surveillance of stage I-IIIA non-small cell lung cancer (NSCLC) patients (pts) after curative intent surgery is unknown. In general, current guidelines recommend imaging with chest CT every 6-12 months for the first 2 years, then annually. In the absence of strong evidence to implement guidelines, variability in imaging has been noted in limited survey data. There are no population studies identifying how pts are being followed in practice. **Methods:** We performed an observational retrospective cohort study using the Surveillance, Epidemiology and End Results (SEER)-Medicare database to determine the primary surveillance modality, either chest CT or chest x-ray (CXR), in elderly stage I-IIIA NSCLC pts who underwent lobectomy or pneumonectomy. We defined the primary modality as CT for pts undergoing at least 1 CT in both years 1 and 2 of surveillance, and as CXR for pts who did not fit the CT criteria, and who had at least 2 CXR's in both years 1 and 2 of surveillance. **Results:** 10,959pts were identified as undergoing curative intent surgery, of whom 94% had lobectomy and 6% had pneumonectomy. 58% of pts were ages 65-74, and 42% were 75 or older. 50% of pts were female. 70%, 16% and 14% of pts were stage I, II and IIIA respectively. 68% had non-squamous histology and 32% had squamous. 5,714 (52%) pts were followed by CT surveillance, and 2,491 (23%) were followed by CXR. 2,754 (25%) pts did not fit the criteria for either.Despite current guidelines, only 47% of stage I, 63% of stage II, and 66% of stage IIIA pts completed at least 1 CT in both years 1 and 2 after surgery. In this population, as stage and age decreased, surveillance of some sort was used less frequently ($p<0.001$), and CXR over CT surveillance increased ($p<0.001$). Pneumonectomy pts were more likely than lobectomy pts to have surveillance ($p=0.002$). **Conclusions:** This is the first population-based study to characterize the patterns of surveillance after curative intent surgery in elderly NSCLC pts. More evidence is needed to evaluate the effectiveness of different surveillance strategies to better shape guidelines and practice.

**7542 General Poster Session (Board #150), Sat, 1:15 PM-5:00 PM**

**Phase II study of induction chemotherapy with carboplatin, paclitaxel, and bevacizumab followed by surgery in patients with stage III nonsquamous non-small cell lung cancer: The Tokyo Cooperative Oncology Group trial (TCOG1002)** *Presenting Author: Toshihiko Iizasa, Chiba Cancer Center, Chiba, Japan*

**Background:** The clinical staging and treatment of locally advanced non-squamous non-small-cell lung cancer (NSCLC) remains controversial. We performed a phase II trial of induction chemotherapy with carboplatin, paclitaxel, and bevacizumab followed by surgery in patients with stage III non-squamous NSCLC. **Methods:** This study was a multicenter phase II trial (TCOG 1002). After staging N status by endobronchial ultrasonography or positron emission tomography, patients with stage III non-squamous NSCLC received induction chemotherapy with carboplatin (AUC6), paclitaxel (200mg/m$^2$), and bevacizumab (15mg/kg) twice every 3 weeks, followed by carboplatin (AUC6) and paclitaxel (200mg/m$^2$) 3 weeks later. Surgery was then performed. The primary endpoint was overall response rate. **Results:** Among 26 patients enrolled, 24 underwent surgery after induction chemotherapy. Their demographic characteristics were as follows: 12 men and 12 women, 42 to 73 years of age (mean 58.7 ± 8.3 years); 23 adenocarcinomas; stage IIIA, 22 patients and stage IIIB, 2 patients; performance status (PS) 0, 22 patients. Induction chemotherapy was completed according to the protocol in 21 (88%) of the 24 patients. The response rate was 62.5% (partial remission, 15 patients; stable disease, 9 patients). The most frequent grade 3-4 toxicities were neutropenia, 16 cases; leukopenia, 4 cases; liver dysfunction, 2 cases; hypertension 1 case; and febrile neutropenia, 1 case. Complete resection was performed in 20 (83%) of the 24 patients (17 lobectomies and 5 bilobectomies). There were no severe perioperative complications. The pathological response rate was 32% (complete response, 1; major response, 6; minor response, 15). Nodal downstaging was found in 6 patients (N0, 4; N1, 2). **Conclusions:** Induction chemotherapy with carboplatin, paclitaxel, and bevacizumab followed by surgery is safe and feasible in patients with stage III non-squamous NSCLC. Our results indicate that further studies are warranted to confirm the safety and efficacy ofthis treatment regimenin stage III non-squamous NSCLC. Clinical trial information: UMIN000004327.

**7543 General Poster Session (Board #151), Sat, 1:15 PM-5:00 PM**

**Stereotactic body radiotherapy versus lobectomy for operable clinical stage IA pulmonary adenocarcinoma: Comparison of prospective clinical trials with propensity score analysis (JCOG1313-A).** *Presenting Author: Junko Eba, Japan Clinical Oncology Group Operations Office, National Cancer Center, Tokyo, Japan*

**Background:** No randomized controlled trials comparing stereotactic body radiotherapy (SBRT) and lobectomy for operable early-stage non-small cell lung cancer have been successfully conducted. This study compared survival outcomes in two multi-institutional prospective clinical trials for SBRT (Japan Clinical Oncology Group [JCOG] 0403) and lobectomy (JCOG 0201). **Methods:** Inclusion criteria for this combined analysis consisted of: being operable, cT1N0M0, and adenocarcinoma diagnosed prior to treatment. Forty out of 169 patients enrolled in JCOG 0403 between 2004-2007, and 219 out of 811 patients enrolled in JCOG 0201 between 2002-2004 were included. The primary endpoint was overall survival adjusted with propensity score analysis. The patient selection factors included in the logistic model to estimate the propensity score were age, sex, and two findings on CT: tumor diameter and consolidation/tumor ratio (CTR). **Results:** The age distribution was quite different, with little overlap: the median was 79 (interquartile range (IQR): 74.5-83.5) in SBRT and 62 (IQR: 55-68) in lobectomy, although other factors were well balanced: males/females were 20/20 in SBRT and 108/111 in lobectomy; the median tumor diameter was 2.36 (IQR: 1.92-2.55) in SBRT and 2.20 (IQR: 1.90-2.70) cm in lobectomy; and the median CTR was 1.00 (IQR: 0.85-1.00) in SBRT and 1.00 (IQR: 0.68-1.00) in lobectomy. In propensity score matching analysis, 21 patients from each group were matched and the hazard ratio (HR) was 9.00 (95% CI: 1.14-71.04), favoring lobectomy. In the inverse probability of treatment weighting (IPTW) analysis, subjects were limited to those aged 75 or younger because JCOG0201 only included those 75 or younger. Thirteen patients for SBRT and 219 for lobectomy were compared and the HR was 1.19 (95% CI: 0.38-3.73), favoring lobectomy. **Conclusions:** Although all estimates tended to favor lobectomy over SBRT, no confirmatory conclusion was drawn due to the sample size for SBRT being too small. Further investigation with a larger sample size for a younger population with SBRT is needed to facilitate a valid comparison with surgery.

**7544 General Poster Session (Board #152), Sat, 1:15 PM-5:00 PM**

**Candidates for intensive local treatment in cIIIA-N2 NSCLC: Impact of mediastinal nodal extent and appearance.** *Presenting Author: Hidehito Horinouchi, Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan*

**Background:** Clinical stage IIIA non-small cell lung cancer (NSCLC) with N2 nodal involvements (cIIIA-N2) includes a broad spectrum of patients. Phase III trials examining higher radiotherapy dose and surgery after neoadjuvant therapy have failed to yield satisfactory results. **Methods:** Between 1997 and 2010, we analyzed consecutive NSCLC patients diagnosed as having cIIIA-N2 disease and received chemoradiotherapy (CRT). The appearance of the mediastinal lymph nodes (MLNs) was classified into discrete (D) or infiltrative (I) according to the criteria proposed by the ACCP (Silvestri et al., Chest 2013). The extent of MLN involvement (MLNI) was divided into limited (close to the primary tumor) or extended (including upper MLNI in the case of tumors in the lower lobes and vice versa). **Results:** A total of 148 patients with cIIIA-N2 NSCLC received CRT; male/female, 118/30; median age, 62 years. The disease characteristics were as follows; appearance of the involved MLNs (D/I), 83/63; extent of MLNI (limited [L]/extended [E]), 81/64; histology (squamous [sq] /non-squamous [non-sq]), 36/112. The median progression-free survival (PFS) and median overall survival (OS) (95% confidence interval) in the entire subject population were 9.9 (9.0-12.3) months and 34.7 (28.8-41.1) months, respectively. Discrete appearance, limited extent of MLNI and treatment initiation after 2005 contributed to a significantly better PFS and OS. The percentages of cases with local relapses within the irradiated field according to the disease characteristics were as follows; MLN appearance (D/I), 24.6/18.9%; MLNI (L/E), 25.9/17.9%; histology (sq/non-sq), 52.0/12.6%. **Conclusions:** Among patients with cIIIA-N2 NSCLC, those with a discrete appearance of the involved MLNs and a limited extent of MLNI could be a favorable subgroup. With regard to local relapses after CRT, development of a better strategy for local treatment in this population (especially patients with a sq histology) is warranted.

**7545 General Poster Session (Board #153), Sat, 1:15 PM-5:00 PM**

**A randomized phase III trial comparing triple weekly usage with weekly usage of paclitaxel in concurrent chemoradiotherapy for patients with locally advanced non-small cell lung cancer.** *Presenting Author: Guangying Zhu, Department of Radiation Oncology, Key laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing, China*

**Background:** Optimum management of clinically locally advanced non-small cell lung cancer (LANSCLC) presents challenges because of the high local recurrence rate. NCCN guidelines recommend concurrent chemoradiotherapy (CCRT) as the standard therapy for LANSCLC. A phase III study was performed to compare triple weekly usage (group 1) with weekly usage (group 2) of paclitaxel in concurrent chemoradiotherapy for patients with locally advanced non-small cell lung cancer. **Methods:** It is a multi-center, randomised, controlled, phase III trail. After 2 to 4 cycles of induction chemotherapy, patients with LANSCLC were randomly assigned to two groups. In group 1, chemotherapy consisted of paclitaxel (15 mg/m$^2$, 3times/week, 270 mg/m$^2$ over six weeks). In group 2, chemotherapy consisted of paclitaxel (45 mg/m$^2$, 1 time/week, 270 mg/m$^2$over six weeks). Radiotherapy consisted of 60-70Gy (2Gy per fraction and 5 fractions per week). **Results:** From March 2006 to February 2013, 115 patients were enrolled into the study. Sixty-three patients were enrolled in group 1, among which 3 patient had radiation esophagitis of Grade 3, 3 patients developed leucopenia of Grade 3, 12 patients had radiation pneumonitis of Grade 3, and 1 patient had radiation pneumonitis of Grade 5 and died of respiratory failure. Fifty-two patients were enrolled in group 2, 5 patient had radiation esophagitis of Grade 3, 15 patients developed leucopenia of Grade 3 or 4, 6 patients had radiation pneumonitis of Grade 3, and 2 patients had radiation pneumonitis of Grade 5 and died of respiratory failure. The response rate for the group 1 was significantly higher (87.3%) than that of the group 2 (57.7%) (p value 0.023), and the median PFS in the two groups were 11.0ms and 7.4ms (p value =0.039). **Conclusions:** The study results showed that triple weekly usage is more safe and effective than weekly usage of paclitaxel with CCRT for patients with LANSCLC. Clinical trial information: ChiCTR-TRC-10000786.

**7546 General Poster Session (Board #154), Sat, 1:15 PM-5:00 PM**

**Genetic features of pulmonary adenocarcinoma presenting with ground-glass nodules (GGN): Differences between those with growth potential and those without.** *Presenting Author: Yoshihisa Kobayashi, Department of Thoracic Surgery, Aichi Cancer Center Hospital, Nagoya, Japan*

**Background:** Some pulmonary GGNs become larger or increase solid component, whereas others, mainly pure GGNs, remain unchanged for years. We have previously reported that 3-year follow-up is a reasonable benchmark to distinguish GGNs with growth from those without growth, and that smoking history and larger diameter were associated with growth (Lung Cancer 83:61-66, 2014). However, genetic differences between them remain unclear. This study aimed to evaluate the genetic features of resected GGNs and clarify the differences. **Methods:** We examined 97 pulmonary nodules with ground-glass component ≥50% on CT in 90 patients that had been resected in 2012 and 2013. The tumors were evaluated for clinicopathologic features including lesion diameter, presence of invasion, and presence of EGFR/KRAS/ALK/HER2 mutations. **Results:** There were three atypical adenomatous hyperplasia (AAH), 17 adenocarcinoma in situ (AIS), 25 minimally invasive adenocarcinoma (MIA), and 52 invasive adenocarcinoma (IA). We identified mutations or rearrangements in 75 % (73/97): EGFR in 65% (63/97), KRAS in 4% (4/97), ALK in 5% (3/66), and HER2 in 7% (3/41). Smoking history, lesion diameter, solid component (mixed versus pure), tendency to grow, and pathological diagnoses (MIA/IA versus AAH/AIS) were significantly different (P <0.2) in tumors with any of driver oncogene mutation (mut+) as compared with those with no mutation (mut-), whereas age and gender were not (Table). In multivariate analyses, tendency to grow [Odds ratio (OR) 8.34, P <0.01], MIA/IA [OR 6.74, P = 0.01], and non-smoking history [OR 3.63, P = 0.02] were independent factors for mut+. **Conclusions:** Mut+ GGNs were associated with tendency to grow, MIA/IA, and non-smoking history. These results may suggest that mut- GGNs could remain unchanged and thus could be candidates for observation alone without surgical intervention.

| Variables | Mut+ (N=73) | Mut- (N=24) | p |
|---|---|---|---|
| **Age (mean)** | 62 | 62 | 0.95 |
| **Male** | 30 | 10 | 0.96 |
| **Nonsmoking** | 46 | 10 | 0.07 |
| **Lesion diameter ≥15mm** | 55 | 13 | 0.05 |
| **Mixed GGN** | 61 | 17 | 0.17 |
| **Tendency to grow** | 32 | 2 | <0.01 |
| **MIA/IA** | 64 | 13 | <0.01 |

**7547 General Poster Session (Board #155), Sat, 1:15 PM-5:00 PM**

**Early detection of lung cancer based on three-dimensional, morphometric analysis of cells from sputum.** *Presenting Author: Alan Nelson, Visiongate, Inc., Phoenix, AZ*

**Background:** Utilizing a new 3D morphometric analytical device called Cell-CT, we analyzed cells from sputum to detect lung cancer in patients with malignant nodules found using low-dose x-ray CT (LDCT). This study assesses the sensitivity and specificity of the Cell-CT analysis for lung cancer in this context. **Methods:** Case sensitivity was assessed by analyzing sputum from patients with biopsy-confirmed non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Spontaneously produced sputum was collected over three consecutive days and fixed. Specimens were then enriched for epithelial cells and stained with hematoxylin. These cells were imaged using VisionGate's Cell-CT system that computes 3D cell images with isometric, sub-micron resolution. Cell images were then automatically analyzed by a computer classifier to identify abnormal cells. Of the 800 measured features, the strongest 25 were used in the classifier. The diagnosis for these cells was computer-generated and manually confirmed by a cytotechnologist. Specificity was assessed by analyzing cells in sputum from normal patients who were at high risk for lung cancer. Bronchial epithelial cells were counted to determine specimen adequacy. **Results:** 26 NSCLC and 4 SCLC, or 30 total cases were processed that met the criteria for adequacy. Moderate/severe dysplasia or cancer cells were found in 28 of the 30 cases. In 26 of the 28 cases, cancer cells were present. Cancer and dysplastic cells were detected by the Cell-CT for an overall case sensitivity of 93.3%. 15 of 30 cases were either stage I or stage II lung cancer, and 14 of these 15 cases (or 93.3%) were detected. 5,146 sputum cells from 17 normal patients at high risk for lung cancer were processed with zero false positive indications. The lower 95% confidence bound for specificity is 99.8%. **Conclusions:** With a sensitivity of 93.3% to early stage lung cancers and a lower limit to specificity of 99.8% based on a non-invasive sputum analysis, the Cell-CT platform could be deployed to help eliminate false positives from LDCT. Further studies will establish the Cell-CT performance across a broader range of clinical conditions to evaluate the potential use of the Cell-CT as a primary screener for lung cancer.

**7548 General Poster Session (Board #156), Sat, 1:15 PM-5:00 PM**

**Computed tomography (CT) imaging features in early-stage lung adenocarcinoma differentiating exon 19 and exon 21 epidermal growth factor receptor (EGFR) mutated tumors.** *Presenting Author: Benjamin F. Chu, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, OH*

**Background:** Imaging studies provide essential clinical information for lung cancer diagnosis, treatment and management. Features such as ground glass opacity (GGO), while commonly seen in early stage lung cancer, have minimal clinical implication. We previously described a correlation between GGO and exon 21 mutation in a subset of our current cohort. Here, we report our analysis in a single institution confirming GGO component as an imaging characteristic differentiating exon 19 and exon 21 EGFR-mutated (MT) tumors. **Methods:** Since 2009, our institution has prospectively characterized the EGFR status of all non-squamous lung carcinomas. Our inclusion criteria included tumor size $< 3$ cm and positive EGFR mutation. We randomly selected wild type (WT) patients matched by age and tumor size. The CT imaging of these patients was evaluated by a single radiologist (EO). **Results:** Imaging features were extracted from 20 WT and 45 EGFR-MT tumors. Of the EGFR-MT tumors, 21 had the exon 21 point mutation and 24 had in-frame exon 19 deletion. There were 69% (31) solid nodules in EGFR-MT and 90% (18) in WT tumors. While solid nodule was the primary feature seen in both WT and EGFR-MT tumors, exon 21-MT tumors were associated with GGO component ($p = 0.006$). This tendency, however, is not present in the exon 19-MT tumors. Lack of pleural attachment is seen more frequently with exon 19-MT tumor as compared to WT tumors. Other imaging features such as internal air bronchogram, and spiculated/lobulated border did not differentiate between groups. **Conclusions:** Among these treatment-naive lung adenocarcinomas, we discovered a propensity for exon 21-MT tumor to develop GGO on CT imaging. While both exon 21 point mutation and exon 19 deletion are predictive of response to EGFR tyrosine kinase inhibition, they exhibited distinct radiological phenotypes suggesting a different underlying biology.

| | Exon 19 n=24 (%) | Exon 21 n=21 (%) | Exon 19 and 21 n=45 (%) | Wild type n=20 (%) |
|---|---|---|---|---|
| GGO | 3(12) | 11(52) | 14 (31) | 2(10) |
| Solid | 21(88) | 10(48 ) | 31(69) | 18(90) |
| p values | 1.000* | 0.009$^{\neq}$ 0.006# | 0.107& | |

* p value comparing WT and Exon 19. $^{\neq}$ Exon 19 and Exon 21. # WT and Exon 21. & WT and Exon 19 and 21.

**7549 General Poster Session (Board #157), Sat, 1:15 PM-5:00 PM**

**When should surgeons begin surveillance with CT scans after lobectomy for stage 1A non-small cell lung cancer?** *Presenting Author: Mohan K. Mallipeddi, Duke University Medical Center, Durham, NC*

**Background:** Guidelines for surveillance after resection of stage 1A non-small cell lung cancer (NSCLC) vary in terms of recommended modality and frequency. The purpose of this study was to assess the optimal time to start surveillance when using CT scans. **Methods:** All patients who underwent lobectomy from 1996 to 2010 for stage 1A NSCLC without induction or adjuvant therapy and who had CT surveillance that started within 15 months of resection were reviewed. Only patients followed for at least two years or until new or recurrent disease was discovered were included. Patients were grouped as "early CT" if their initial surveillance CT scan was $6\pm3$ months after lobectomy and "late CT" if their initial surveillance CT scan was $12\pm3$ months after lobectomy. Between the two groups, the incidence of new or recurrent disease on the initial CT scan was compared using Fisher's exact test and overall survival was compared using the log-rank test. **Results:** During the study period, 198 patients met inclusion criteria. There were 99 cases in both the early and late CT groups. Overall, 11% of patients (21/198; 8 local only, 13 distant) had recurrent disease and 16% of patients (31/198) were found to have new primaries over their follow up period. On average, recurrent disease was found $26\pm19.8$ months and new primaries were found $45.7\pm28.9$ months after resection ($p=0.009$). For the 31 patients with new primaries, 29 (94%) received some form of local therapy; surgery was used in 21 patients (68%). Repeat surgery was used in 3 of the 8 patients with local recurrence (37.5%), though 2 of these 3 developed contralateral lung metastases within 4 years of reoperation. In the early CT group, new or recurrent disease was found on the initial surveillance scan in 2% of patients (2/99) compared to 4% of patients (4/99) in the late CT group ($p=0.7$). The 5-year survival from initial resection of the two groups was not significantly different. **Conclusions:** Both recurrent disease and new primary cancers are relatively common after lobectomy for stage 1A NSCLC, but rarely are evident on CT scan within 15 months of surgery. Waiting to starting CT scan surveillance until 9 to 15 months after surgery is unlikely to miss clinically important findings.

**7550 General Poster Session (Board #158), Sat, 1:15 PM-5:00 PM**

**Serum biomarker analysis of WJOG4107: A randomized phase II trial of adjuvant chemotherapy with S-1 versus CDDP+S-1 for resected stage II-IIIA non-small cell lung cancer (NSCLC).** *Presenting Author: Tetsuya Mitsudomi, Department of Thoracic Surgery, Kinki University Faculty of Medicine, Osaka-Sayama, Japan*

**Background:** We conducted a randomized phase II trial for patients with resected stage II-IIIA NSCLC comparing postoperative long-term oral S-1 (80 mg/m2/day for consecutive 2 weeks q3w for 1 year) (S) ($N=100$) and cisplatin (CDDP) (60 mg/m2 day1) plus oral S-1, (80 mg/m2/day for 2 weeks) q3w for 4 cycles (CS) ($N=100$), and previously reported that the disease-free survival rate at 2 years (DFS@2yr), a primary endpoint, was 66 % (95%CI, 55-74%) for S and 58% (48-67%) for CS (Yoshioka et al., ESMO 2012). Here, we report the results of pre-planned serum biomarker analysis to identify biomarkers that are significantly associated with patient outcome. **Methods:** Serum samples were obtained from the 197/200 patients. Concentrations of 16 growth factors and 27 cytokines were measured by Luminex. Concentration of each protein was dichotomized at its median. **Results:** As is often the case with interaction test, a p-value of less than 0.10 was considered to be statistically significant and was used for this study. HGF, GCSF and leptin showed the moderate association with prognosis by multivariate Cox regression analysis considering treatment arm, age, sex, histology, smoking history, and stage with P for treatment-protein interaction $<0.10$ (HGF, $P=0.0576$; GCSF, $P=0.0579$; leptin, $P=0.0741$). Furthermore, patients with lower serum HGF level showed significantly favorable prognosis than those with higher serum HGF level in postoperative long-term S-1 therapy ($P=0.0072$ by the log-rank test). DFS@2yr for HGF low/S and HGF high/S were significantly different, 77% (95%confidence interval: 66-91%) and 56% (44-72%), respectively, while those of HGF low/CS and HGF high/CS were almost identical, 61% (48-77%) and 61 (48-78%), respectively. **Conclusions:** Low serum HGF level may define patient subset that would benefit from postoperative long-term S-1 therapy. It is possible to hypothesize that low HGF may enhance S-1- induced apoptosis through inhibition of angiogenesis, because HGF is a potent angiogenetic factor and S-1 acts on tumor angiogenesis (Cancer Lett., 2008, 267, 26). Indeed, NK4 (HGF/MET antagonist) reportedly enhances 5FU-induced apoptosis.

**7551 General Poster Session (Board #159), Sat, 1:15 PM-5:00 PM**

**The effect of institutional clinical trial enrollment volume on survival of patients with stage III non-small cell lung cancer treated with chemoradiation: A report of the Radiation Therapy Oncology Group (RTOG) 0617.** *Presenting Author: Bree Ruppert Eaton, Department of Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, GA*

**Background:** This analysis evaluates the potential association between institutional clinical trial accrual volume and the outcome of patients with locally advanced non-small cell lung cancer (LA-NSCLC) receiving chemoradiation therapy (CRT) on a phase III trial (RTOG 0617). **Methods:** Patients with LA-NSCLC were randomized to 60 Gy vs. 74 Gy with concurrent carboplatin and paclitaxel +/- cetuximab, with initial results reported at ASCO 2013 (abst # 7501) and IASLC 2013. Participating institutions were divided into tertiles based on accrual to RTOG 0617. Those within the two lowest accrual tertiles were categorized as low volume centers (LVC), and those within the highest accrual tertile were categorized as high volume centers (HVC). **Results:** Range of accrual for LVC ($n=195$) vs. HVC ($n=300$) was 1-3 vs. 4-18 patients. Patients treated at HVC were more likely to be treated with intensity modulated RT (54.0% vs. 39.5%, $p=0.002$), to have a lower mean esophageal RT dose (26.1 Gy vs. 28.0 Gy, $p=0.03$), and to have a lower heart RT dose (V5Gy 38.2% vs. 54.1%, $p<0.001$; and V50Gy 3.6% vs. 7.3%, $p<0.001$). All other clinical variables were similar between the two cohorts. Treatment at a HVC was associated with significantly better OS and PFS compared with treatment at a LVC, median OS: 26.2 months vs. 19.8 months (HR 0.7, 95% CI 0.56 – 0.88, $p=0.002$), and median PFS: 11.4 months vs. 9.7 months (HR 0.80, 95% CI 0.65 – 0.99, $p=0.04$). HVC remained favorably associated with both OS ($p=0.013$) and PFS ($p=0.028$) when accounting for other factors. Additional factors associated with better OS were 60 Gy dose level ($p=0.006$), low heart V5Gy ($p=0.003$), and upper lobe tumor location ($p=0.014$); and with better PFS were 60 Gy dose level ($p=0.006$) and low heart V5Gy ($p=0.004$). Patients treated at HVC had a lower incidence of grade 5 adverse events (AEs) (5.3% vs. 9.2%, $p=0.09$) and were less likely to have RT terminated due to AEs (1.3% vs. 4.1%, $p=0.07$) than those treated at LVC. **Conclusions:** Treatment at institutions with higher clinical trial accrual was associated with better OS and PFS among patients with LA-NSCLC participating in a phase III trial. Clinical trial information: NCT00533949.

**7552 General Poster Session (Board #160), Sat, 1:15 PM-5:00 PM**

**Nodal stage of surgically resected non-small cell carcinoma of the lung and its effect on recurrence pattern and survival.** *Presenting Author: Satvik Ramakrishna, Northwestern University, Chicago, IL*

**Background:** Current NCCN guidelines recommend post-operative radiotherapy (PORT) for patients with resected non-small cell lung cancer (NSCLC) with N2-involvement. We investigated the relationship between nodal-stage and local-regional recurrence (LR), distant recurrence (DR) and overall survival (OS) for patients having an R0 resection. **Methods:** A multi-institutional database of consecutive patients undergoing $R_0$resection for Stages I-IIIA NSCLC from 1998-2009 was used. Patients receiving any radiation therapy before relapse were excluded. Variables analyzed were age, sex, surgical procedure, extent of lymph node sampling, histology, LVI, tumor size, tumor grade, chemotherapy, nodal stage, and visceral pleural invasion. Cumulative incidence rates were calculated for LR and DR as first sites of failure and Kaplan-Meier estimates for OS. Competing-risk analysis was used to compare times to recurrence events. Multivariate Cox modeling was used to analyze OS. **Results:** 1,288, 210 and 78 patients were identified with N0, N1, and N2 involvement respectively. 161 patients received chemotherapy. Median follow-up was 28.7 months. Patients with N1 or N2 nodal stage had similar rates of LR as patients with N0 disease, but were both at significantly increased risk for DR (N1, HR = 1.77, p = 0.0012; N2, HR = 2.27, p <0.001) and death (N1, HR = 1.464, p =0.0004; N2, HR = 2.32, p <0.0001). LR was associated with squamous histology, visceral pleural involvement, tumor size and segmentectomy in the Cox model. **Conclusions:** The risk of LR did not vary substantially in relation to N-stage in our population, though DR did. Although the number of patients with N2 disease was small, these findings call into question the NCCN guidelines. Prospective studies of PORT after R0 resection are needed.

| | Cumulative Incidence rates (%) | | | | Kaplan-Meier estimates (%) | |
|---|---|---|---|---|---|---|
| | Local recurrence | | Distant recurrence | | Overall survival | |
| N-stage | 3-year | 5-year | 3-year | 5-year | 3-year | 5-year |
| N0 | 13 | 15 | 15 | 17 | 66 | 50 |
| N1 | 19 | 22 | 30 | 38 | 50 | 32 |
| N2 | 16 | 18 | 37 | 42 | 32 | 26 |

**7553 General Poster Session (Board #161), Sat, 1:15 PM-5:00 PM**

**Are the criteria indicating patients to be "medically inoperable" that are used in clinical trials on stereotactic body radiotherapy appropriate for patients with early-stage non-small cell lung cancer?** *Presenting Author: Kazuya Takamochi, General Thoracic Surgery, Juntendo University School of Medicine, Tokyo, Japan*

**Background:** The standard treatment for patients with early stage non-small cell lung cancer (NSCLC) is surgical resection. Stereotactic body radiotherapy (SBRT) has recently been investigated as an alternative treatment in place of surgery in clinical trials, especially for medically inoperable (MI) patients. However, no clear rationale for the criteria used to determine whether or not a patient is MI has yet been demonstrated. **Methods:** Between January 2004 and October 2012, 740 patients underwent surgical resection for clinical stage IA NSCLC. In the present study, MI was defined as patients with FEV1.0≤0.8L, %DLCO<40%, PaO2≤70mmHg, PaCO2>50mmHg, or three or more severe comorbidities, based on the criteria of MI that are frequently used in clinical trials in SBRT for NSCLC patients. The clinicopathological characteristics and surgical outcomes were compared between the MI patients (n = 91) and non-MI patients (n = 649). **Results:** The proportion of males ($P = 0.002$), elderly ($P < 0.001$), smokers ($P < 0.001$) and those with a non-adenocarcinoma histology ($P < 0.001$) were higher in MI patients than in non-MI patients. No statistical difference was observed in the proportion of pathological stage IA between the groups (69% in MI vs 77% in non-MI, $P = 0.09$). Limited operation (wedge lung resection or segmentectomy) was performed for 37 (41%) MI and 227 (35%) non-MI patients ($P = 0.3$). Mediastinal lymph node dissection was performed for 48 (53%) MI and 413 (64%) non-MI patients ($P = 0.05$). Although the rates of overall morbidity (39% in MI vs 23% in non-MI, $P = 0.002$) and 90-day mortality (3% in MI vs 0.5% in non-MI, $P = 0.03$) were higher in the MI patients, there were no statistical differences in 30-day mortality (1% in MI vs 0.2% in non-MI, $P = 0.2$), overall survival ($P = 0.2$) or cancer-specific survival ($P = 0.7$) between the groups. **Conclusions:** Surgical resection can be performed in MI patients with an equivalent survival to non-MI patients. The current criteria that are used to determine whether or not a patient is MI for clinical trials in SBRT for NSCLC patients are therefore not considered to be appropriate to evaluate the true operability.

**7554 General Poster Session (Board #162), Sat, 1:15 PM-5:00 PM**

**Clinical characteristics and outcomes of atypical carcinoid (AC) tumor of the lung: A Surveillance, Epidemiology, and End Results database analysis.** *Presenting Author: Conor Ernst Steuer, The Winship Cancer Institute of Emory University, Atlanta, GA*

**Background:** AC is a rare form of thoracic malignancy. The limited knowledge of the presentation and treatment of this tumor comes largely from small, single institution experiences. We analyzed the Surveillance, Epidemiology, and End Results database (SEER) to better understand the clinic characteristics of this disease. **Methods:** Demographic, treatment and outcome data on all patients with pulmonary AC was obtained from the SEER database with 18 reporting sites from 1973-2010 using SEER*Stat 8.1.2. All analyses were performed using SAS 9.3. **Results:** Out of 947,463 patients diagnosed with lung and bronchus tumors from 1985 to 2010, 441 patients with AC were identified. Demographic data and median overall survival (OS) for patient subgroups are presented in the table below. The median OS for all patients is 26 months. The 3-year survival rate (N=254) is 67%. The 3-year survival rate for distant (M1), regional (lymph node involvement), and localized (lung only) disease is 26%(13/50), 69%(50/72), and 85%(99/116) respectively. Older age, black race, and advanced disease are associated with a worse overall prognosis. Univariate analyses showed patients treated with surgery had reduced risk of death OS (HR .19, p <0.001) while radiation treatment was associated with increased risk of death (HR 2.45, p <0.001). **Conclusions:** Atypical carcinoid tumors are more frequent in women and present with early stage disease in nearly 80% of the patients. Patients who were able to undergo surgical resection had superior outcomes.

| Variable | Level | N (%) | Median OS (months) |
|---|---|---|---|
| Age | Median (range) | 65 (21 - 90) | |
| Race | | | |
| White | | 381 (87.19) | 28 |
| Black | | 37 (8.47) | 14 |
| Other | | 19 (4.35) | |
| Sex | | | |
| Male | | 138 (31.29) | 27.5 |
| Female | | 303 (68.71) | 26 |
| Summary stage | | | |
| Distant | | 83 (19.9) | 13 |
| Regional | | 131 (31.41) | 28 |
| Localized | | 203 (48.68) | 35 |
| Radiation | | | |
| Yes | | 54 (12.5) | 19 |
| No | | 378 (87.5) | 28 |
| Surgery of primary site | | | |
| Yes | | 341 (77.5) | 32 |
| No | | 99 (22.5) | 13 |

Total N=441. Data are presented as number of patients (%) or median (range).

**7555 General Poster Session (Board #163), Sat, 1:15 PM-5:00 PM**

**Lobectomy, sublobar resection, and stereotactic radiation for early-stage non-small cell lung cancers in the elderly.** *Presenting Author: Shervin Mohajer Shirvani, Banner MD Anderson Cancer Center, Gilbert, AZ*

**Background**: Early-stage non-small cell lung cancers (NSCLC) among the elderly are expected to rise dramatically due to demographic trends and CT screening. However, no modern trials have compared the most commonly delivered treatments. Therefore, we determined clinical characteristics and outcomes associated with three definitive therapies for early-stage NSCLC in the elderly population. **Methods***:* The SEER–Medicare database was used to compare the outcomes of 9,093 patients with early-stage, node-negative NSCLC who underwent treatment with lobectomy, sublobar resection, or stereotactic ablative radiation (SABR) between 2003 and 2009. Overall survival and lung-cancer specific survival were compared using Medicare claims through December 2012. Proportional hazards regression and propensity score matching (PSM) were used to adjust outcomes for key patient, tumor, and practice environment factors. **Results**: Median age was 75 years, and treatment distribution was as follows: Lobectomy (79.4%), sublobar resection (16.5%), and SABR (4.2%). Unadjusted 90-day mortality was highest for lobectomy (4.0%) followed by sublobar resection (3.7%, P=0.79) and SABR (1.3%, P=0.008). At three years, unadjusted mortality was lowest for lobectomy (25.0%), followed by sublobar resection (35.3%, P<0.001) and SABR (45.1%, P<0.001). Proportional hazards regression demonstrated that sublobar resection was associated with worse overall survival (Hazard ratio [HR] 1.32; 95%CI 1.20-1.44) and lung-cancer specific survival (HR 1.50; 95%CI 1.29-1.75) compared to lobectomy. PSM analysis reiterated these findings. In proportional hazards regression, SABR was associated with better overall survival than lobectomy in the first 6 months after diagnosis (HR 0.45; 95%CI 0.27-0.75), but worse survival thereafter (HR 1.66; 95%CI 1.39-1.99). PSM analysis of well-matched SABR and lobectomy cohorts demonstrated similar overall survival (HR 1.01; 95%CI 0.74-1.38). **Conclusions**: Lobectomy was associated with better outcomes than sublobar resection in elderly patients with early-stage NSCLC. PSM analysis suggests that SABR may be a good option for those with very advanced age and multiple comorbidities.

**7556 General Poster Session (Board #164), Sat, 1:15 PM-5:00 PM**

**Computed tomographic window setting for predicting invasive adenocarcinomas in pulmonary nonsolid tumors.** *Presenting Author: Takashi Eguchi, Shinshu University, Matsumoto, Japan*

**Background:** Nonsolid pulmonary tumors are occasionally diagnosed as invasive adenocarcinomas. Preoperatively distinguishing adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA) from invasive adenocarcinoma is essential for treatment decision making. However, this distinction is potentially difficult to make using the conventional computed tomographic (CT) settings, that is, the lung and mediastinal windows. This study aimed to evaluate novel CT window settings for preoperative detection of invasive adenocarcinomas. **Methods:** We retrospectively evaluated 101 nonsolid tumors resected between July 2006 and November 2013. In the preoperative CT procedures performed, the predictive invasion diameter was determined as the maximum diameter of the residual tumors under the window level/window width settings as follows: −600/0, −550/0, −500/0, −450/0, −400/0, −350/0, and −300/0. Correlation analyses were used to verify whether each viewing condition could be useful for predicting pathological invasion. Then, a receiver operating characteristic (ROC) curve analysis was performed to evaluate the usefulness of the predictive invasion diameter for predicting pathological invasive adenocarcinomas that have a maximum invasion diameter of more than 5 mm. **Results:** Thepathological classification of the lesions was AIS for 47 lesions, MIA for 30 lesions, and invasive adenocarcinoma for 24 lesions (lepidic, 10 lesions; papillary, 8 lesions; and acinar, 6 lesions). The mean pathological invasion diameter was 2.9 ± 3.7 mm. The correlation coefficients between the pathological and predictive invasion diameters under the −600/0, −550/0, −500/0, −450/0, −400/0, −350/0, and −300/0 settings were 0.60, 0.61, 0.64, 0.66, 0.57, 0.47, and 0.41, respectively. In the ROC analysis, the sensitivity and specificity for predicting invasive adenocarcinomas in the window setting of −450/0 was 91.7% and 81.5%, respectively. For this, the cutoff predictive invasion diameter was set at 5.3 mm, and the area under the curve was 0.91. **Conclusions:** The window level/window width setting of −450/0 might be useful for predicting invasive adenocarcinomas in pulmonary nonsolid tumors.

**7557 General Poster Session (Board #165), Sat, 1:15 PM-5:00 PM**

**A randomized phase II trial of concurrent chemoradiation of oral vinorelbine and two doses of radiotherapy, 60 and 66 Gy, in local-regionally advanced non-small cell lung cancer (LA-NSCLC).** *Presenting Author: Olfred Hansen, Odense University Hospital, Odense, Denmark*

**Background:** A high rate of isolated loco-regional failure is a problem in RT of LA-NSCLC. This study tested two doses of radiotherapy (RT), 60 Gy/ 30 F (A) and 66Gy/ 33 F (B), 5 F W, concurrent with oral Vinorelbine (Nav) 50 mg q 3 wk. **Methods:** The primary endpoint was local progression failure free survival (LPFS) 9 months (m) after start of RT. Secondary endpoints included overall survival (OS) and safety. The results were compared with a historical cohort (CTRL) of pts, stage 2B-3B and PS 0-1 treated with same induction chemotherapy as in the study and 1 cycle of Ca-Nav during RT 66 Gy/33 F. Main inclusion criteria were histological/cytological proven stage 2B-3B NSCLC, PS 0-1. Prior to randomization the pts received induction chemotherapy, and the pts had to be proven able to receive 66 Gy/33F. No elective nodes were treated. Follow up with CT was every 3 m from RT start. At 9 m. a FDG-PET-CT scan was applied. The LPFS was calculated as the time of randomization to the date of the scan demonstrating local or distant failure. From Jul 2009-Aug 2013, 121 pts were randomized from 5 centers. All together, 117 pts were eligible. By Jan 2014, 102 pts had +10 m. follow-up forming the basis of this preliminary analysis. The final analysis is expected in May 2014. **Results:** The LPFS at 9 m. was arm A: 46% (95% CI: 40%; 53%), and in B: 56% (95% CI: 40%; 63%), and 76% (95% CI 67%; 82%) in CTRL. The overall survival in A, B, and CTRL were similar. No hematological G4 side effects were observed. Dysphagia and dyspnoe tended to be higher in B. One G4 pneumonitis was observed in Arm and 1 G5 in Arm B, and 1 G5 in CTRL. **Conclusions:** Both regimens were well tolerated, but neither of the arms met the phase II criteria. OS was comparable to CTRL. This suggests that the inferior local control observed at 9 m was due to the use of FGD-PET-CT, but omission of platin-chemotherapy during RT may have influenced the results. Clinical trial information: NCT 00887783.

**7558 General Poster Session (Board #166), Sat, 1:15 PM-5:00 PM**

**The impact of *EGFR* mutation on definitive concurrent chemoradiation therapy for inoperable stage III lung adenocarcinoma.** *Presenting Author: Kosuke Tanaka, Department of Thoracic Oncology, Aichi Cancer Center Hospital, Nagoya, Japan*

**Background:** Concurrent chemoradiation therapy (CRT) is the current standard of care for patients with locally advanced lung adenocarcinoma, however little has been reported about the impact of *EGFR* mutation to CRT efficacy. **Methods:** From 2005-2012, we retrospectively screened 73 unresectable stage III adenocarcinoma patients who were examined *EGFR* mutation status and received definitive concurrent CRT consisting of platinum doublet in first-line setting, and compared the clinical outcomes and recurrence patterns according to mutation status. **Results:** Among 73 patients, *EGFR* mutation was detected in 21 (28.8%). Overall response rate did not differ between *EGFR*-mutant and wild-type patients (66.7% vs. 74.0%, $p$=0.362). Median recurrence-free survival (RFS) in concurrent CRT was significantly shorter in *EGFR*-mutated patients than wild-type patients (8.7 [95%CI: 6.7-10.8] vs. 13.5 [95%CI: 11.0-18.3] months, $p$=0.022). The 2 year recurrence-free survival rate was 5.6% and 23.8% in *EGFR*-mutant and wild-type patients, respectively ($p$=0.090). Distant metastases were more frequently identified as the first recurrence site in *EGFR* mutant patients than in wild-type patients (81.0% vs. 38.5%, $p$<0.001). The brain was the most affected site in *EGFR*-mutant patients (8/17; 47.1%). None of the *EGFR*-mutant patients relapsed with primary lesions, whereas 11 wild-type patients showed primary lesion recurrence (0% vs. 21.2%, $p$=0.017). Overall survival did not differ according to *EGFR* mutation status (51.1 months vs. not reached, $p$=0.186). **Conclusions:** Concurrent CRT gave shorter RFS in *EGFR*-mutated stage III adenocarcinoma patients compared with wild-type patients, mainly due to distant metastasis relapse, regardless of better local control. Because of these distinct biological features, we will need different strategies against *EGFR*-mutant, locally advanced, adenocarcinoma patients.

**7559 General Poster Session (Board #167), Sat, 1:15 PM-5:00 PM**

**MiRNA profiling by NGS in resectable non-small cell lung cancer: Prognostic implications.** *Presenting Author: Sandra Gallach, Fundación para la Investigación del Hospital General Universitario de Valencia, Valencia, Spain*

**Background:** MicroRNAs (miRNA) regulate gene expression, and are implicated in several processes like tumorogenesis. Here, we applied a multiplexed NGS approach to study differentially expressed miRNAs (tumor/ normal) in a cohort of resectable NSCLC patients and its correlation with clinical outcome. **Methods:** RNA was isolated from frozen lung specimens (tumor/ normal) from 33 patients. High-quality samples were analyzed and enriched in the miRNA fraction. Libraries were prepared according to manufactured instruction (SOLID), and miRNAs were sequenced. Data analysis was carried out using CLCbio software. First, raw data were annotated using miRBase and normalized by total reads followed by differential expression analysis. Results validation were performed by RTqPCR in an independent cohort (n= 195). Functional studies of differentially expressed miRNAS were done using in silico tools. Statistical significance was considered at p<0.05. **Results:** 28 miRNAs were significantly up-regulated and 11 were down-regulated in tumor samples compared with normal lung. Most of them were validated by RTqPCR in an independent cohort of samples obtaining the same results (Wilcoxon test). Survival analysis were done for those validated miRNAs. We found that patients with overexpression (2.0X tumor/ normal) of miR21, miR196b and miR188-5p had worse clinical outcome (Table). In silico functional studies showed several GO terms and KEGG pathways related to cell cycle, apoptosis, angiogenesis, among others, that were significantly overrepresented among the miRNAs differentially expressed in NSCLC. **Conclusions:** 25 miRNAs were found differentially expressed and validated in NSCLC. These miRNAs were found to regulate important KEGG and GO process involved in carcinogenesis. Prognostic analysis showed that higher levels of miR21, miR196b and miR188-5p were related to shorter PFS and OS in our cohort of resectable NSCLC.

| | PFS | | OS | |
|---|---|---|---|---|
| | Median Survival (months) | p | Median Survival (months) | p |
| **miR188-5p (high vs low)** | 22.1 - 81.2 | 0.005 | 42.6 - NR | 0.015 |
| **miR196b (high vs low)** | 25.6 - NR | 0.031 | 42.6 - NR | 0.006 |
| **miR21 (high vs low)** | 37.9 - NR | 0.015 | 81.2 - NR | 0.023 |

**7560 General Poster Session (Board #168), Sat, 1:15 PM-5:00 PM**

**Breath analysis as a noninvasive biomarker for early detection of lung cancer.** *Presenting Author: Nir Peled, Thoracic Cancer Unit, Davidoff Cancer Center, Rabin Medical Center, Petach Tikwa, Israel*

**Background**: The search for non-invasive diagnostic methods of lung cancer (LC) has led to new avenues of research, including the exploration of the exhaled breath. Previous studies have shown that LC can be detected through exhaled-breath analysis. This study evaluated the potential of exhaled-breath analysis for the distinction of early and advanced LC and for control (COPD) and lung cancer patients in an international setting. **Methods**: Breath samples were taken from untreated lung cancer patients and matching COPD controls. Patients were enrolled in Israel, Colorado and Florida. All samples were analyzed in a central lab (Technion Institute; Haifa, Israel). Analysis was performed by both gold nanoparticle-based Artificial Olfactory System (NaNose) and gas-chromatography linked with mass-spectrometry (GC-MS). Pattern recognition methods were used to analyze the results obtained from GC-MS and NaNose to correlate the results with the clinical data. **Results**: A total of 358 subjects were enrolled in this study (Israel: 174; Denver: 111; Florida: 73). 213 patients had lung cancer, among 62 early disease and 143 were at advanced stage. 145 patients did not have cancer. In our preliminary sub-analysis, of 80 cancer patients (64 advanced stage) and 31 COPDs subjects: discriminant function analysis of the signals of the sensor array distinguished significantly between control versus early LC ($p < 0.0001$; accuracy 85.11%), between control and advanced LC ($p < 0.0001$; 82.11%) and between early and advanced LC ($p< 0.0001$; 78.75%). **Conclusions**: In this multi-national pilot study, breath analysis discriminated malignant disease from benign conditions in a high-risk cohort based on LC-related volatile organic compound profiles. Furthermore, it discriminated between early versus advanced disease. These achievements stand in consistency with the requirements of society for rapid and early diagnosis of diseases as a part of therapeutic approach and facilitating rapid treatment. Clinical trial information: NCT01386203.

**7561 General Poster Session (Board #169), Sat, 1:15 PM-5:00 PM**

**Treatment-related deaths after concurrent chemoradiotherapy in locally advanced non-small cell lung cancer: A meta-analysis of randomized studies.** *Presenting Author: Jing Zhao, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, GRU Cancer Center/Medical College of Georgia, Georgia Regents University, Augusta, GA*

**Background:** Treatment related deaths (TRDs), defined as grade 5 events that were not explained by tumor progression, may occur after concurrent chemoradiotherapy (cCRT) in patients with locally advanced non-small cell lung cancer (NSCLC). The purpose of this study is to 1) compare the TRDs rates between patients treated with cCRT and non-cCRT (sequential chemoradiotherapy or radiotherapy alone); 2) determine whether radiation dose and chemotherapy regimens were independent risk factors associated with TRDs after cCRT. **Methods:** Eligible studies include randomized controlled trials for locally advanced NSCLC patients with any treatment arms of cCRT and TRDs data reported between January 1, 1999 and November 30, 2013. The log-rank test was used to calculate pooled hazard ratios (HRs), with a fixed effect model. $X^2$ tests and $I^2$ were used to study heterogeneity between trials. **Results:** Twenty-eight studies (5897 patients) were eligible. The TRD rates were 3.0%, and 3.7% for cCRT and non-cCRT, respectively ($P = 0.313$). In univariate analysis, radiation dose ($> 60$ Gy), number of drugs for cCRT (above one), regimens for cCRT (other than etopside + cisplatin) or consolidation chemotherapy were not significantly correlated with TRDs. In 9 trials available for comparing TRD between cCRT and non-cCRT, the HR of TRD for two groups was 1.22 (95% CI: 0.72-2.06; $P = 0.455$). The test for heterogeneity was not significant ($X^2 = 9.62$, $P = 0.38$, $I^2 = 6\%$). Four of 28 trials were included in the analysis of correlation between TRDs and dose fractionated methods. After pooling the data, no significant difference was found in TRDs treated between standard-fractionated radiation and hyper-fractionated radiation (HR = 0.99, 95% CI: 0.46-2.13, $P= 0.977$). Choice of chemotherapy agent (3rd generation chemotherapy regimens or other regiments) and consolidation versus no-consolidation, each available in 4 trails, did not significantly impact TRD rates. **Conclusions:** Compared to sequential chemoradiotherapy or radiotherapy alone, cCRT did not significantly increase the TRD. Neither radiation dose nor chemotherapy regimens increases the treatment mortality.

**7562 General Poster Session (Board #170), Sat, 1:15 PM-5:00 PM**

**Tumor expression levels of CSC markers in resectable non-small cell lung cancer.** *Presenting Author: Silvia Calabuig, General University Hospital Research Foundation, Valencia, Spain*

**Background:** Cancer stem cells (CSCs) have been proposed as the driving force of tumorigenesis and the seeds of metastases. However, their existence and role remain a topic of intense debate. The purpose of this study is to analyze differentially expressed CSC genes from a large cohort of resectable NSCLC patients and its prognostic implications. **Methods:** mRNA was isolated from 188 frozen samples from resectable NSCLC patients (tumor and normal lung). The mRNA expression of *OCT4, NANOG, SOX2, CD44, CD133,* was analyzed by RTqPCR using hydrolysis probes. Relative expression levels were obtained using *GUSB* as endogenous gene and Pfaffl formulae. Statistical significance was considered at $p<0.05$. **Results:** Patient's median age was 64 years [26-85], 87.8 % were males and 66 % presented PS= 0. Squamous histology represented a 45.9%. There were positive correlations (Spearman test) between the expression levels of the CD44 and OCT4 ($p=0.002$), OCT4 and NANOG ($p<0.001$) whereas no correlation were found between CD133 and the other CSC markers studied. Correlation analysis of gene expression values and clinico-pathologic characteristics of the cohort showed that the higher levels of CD44, OCT4 and NANOG were associated with poor differentiation grade ($p=0.003$, $p=0.05$, $p=0.007$). Clinico-pathological variables such as histology, PS, stage or smoking status show no association with the levels of expression of the analyzed genes. Kaplan-Meier curves show no statistical differences between groups (median as cut-off) for CD133, NANOG and OCT-4. Interestingly, higher levels of CD44 correlates with increased overall survival in our cohort of resected NSCLC patients (median 42.90 months vs NR, $p=0.013$). **Conclusions:** CD44 may play a role as prognostic biomarker in NSCLC. Our results are in concordance with recent findings regarding the relationship between increased levels of expression of CD44 and better overall survival for patients with resectable NSCLC. Therefore, further investigations of the role of CD44 in CSC maintenance and regulation are still needed. Supported in part by ISCIII grants PI12/02838, RD12/0036/0025, SEOM grant 2012.

**7563 General Poster Session (Board #171), Sat, 1:15 PM-5:00 PM**

**A comparative study of blood-based *KRAS* mutation analysis in circulating tumor cells versus circulating plasma DNA to predict primary tumor mutations in lung cancer.** *Presenting Author: Eric Kian Saik Lim, Royal Brompton Hospital, London, United Kingdom*

**Background:** Biopsy of the primary tumour for predictive testing is not always convenient nor possible and may incur both delays and complications. In a move towards blood based predictive testing for personalised medicine, we sought to determine the test performance of circulating tumour cell (CTC) versus circulating tumour DNA (ctDNA) as a surrogate of the underlying tumour mutations using *KRAS* (a common mutation) as a prototype. **Methods:** *KRAS* mutation status in primary tumours were analysed using cobas4800 (Roche) allele-specific PCR. From 9ml of blood, ScreenCell MB devices were used to capture CTCs and the DNA was extracted from CTC and matched plasma using QIAamp DNA kits (QIAGEN). *KRAS* mutation detection was undertaken using custom-designed high-resolution melting assay and confirmed by pyrosequencing using *therascreen* kit (QIAGEN). **Results:** From January 2012 to 2013 the peripheral blood of 92 patients who underwent surgery for lung cancer at The Royal Brompton Hospital were analysed for mutations in codons 12/13 of *KRAS* gene. The total number of patients with *KRAS* mutations in FFPE tumour tissue was 18 (19.6%), the ctDNA was 17 (20%) and CTC DNA was 47 (58.8%). In total 9 primary tumours identified as "wild-type" in FFPE tissue appeared mutant in ctDNA. After 7 FFPE samples were re-tested by pyrosequencing, 6 previously undetected KRAS mutations were revealed. After re-testing FFPE tissue, the final concordance between primary tumours and ctDNA was 92% and concordance between CTC DNA was 52%. The sensitivity and specificity for blood based predictive *KRAS* testing was 81% (95% CI 58%-96%) and 97% (87%-100%) for ctDNA and 86% (61%-98%) and 38% (23%-56%) for CTC DNA. **Conclusions:** Blood based mutation testing is feasible and FFPE tumour biopsies cannot always be considered to be the "reference" as *KRAS* mutations not initially detected in the tumour were detected in the blood. ctDNA may be more reflective of the global tumour burden and is more closely indicative of underlying tumour mutation compared to CTC DNA due to tumour heterogeneity.

**7564 General Poster Session (Board #172), Sat, 1:15 PM-5:00 PM**

**Cisplatin and etoposide versus carboplatin and paclitaxel with concurrent radiation for stage III non-small cell lung cancer: An analysis of Veterans Health Administration data.** *Presenting Author: Rafael Santana-Davila, Medical College of Wisconsin, Milwaukee, WI*

**Background:** For the definitive treatment of stage III NSCLC, the optimal chemotherapy regimen to use with radiation is not clearly defined. Using a large cohort of patients treated across the entire VHA system, we compared the outcome of patents treated with EP vs. those treated with CP. **Methods:** Using the VA Central Cancer Registry, patients with stage III NSCLC diagnosed between 2001 and 2008 were identified. For analysis, patients were included if concurrent chemoradiotherapy was initiated within 4 months of diagnosis and excluded if treated with surgery or sequential chemoradiotherapy (i.e. chemotherapy was not started within 7 days of the start of radiotherapy). **Results:** Out of 13,572 pts identified, 1435 pts were eligible for analysis of which 26% (n=380) received EP. In multivariable analysis, the use of EP was not associated with any survival advantage (HR 0.94, 95% CI 0.81-1.09, p=0.41). In a propensity score analysis that matched 292 pts treated with EP with the same number of patients treated with CP, there was no survival advantage for EP (HR 1.01, 95% CI 0.86-1.2, p=0.87). Subsequently, a multivariate model weighted on the inverse propensity for being treated with EP was fitted and similarly showed no survival advantage for EP (HR 0.93, 95% CI, 0.80-1.07, p=0.32). Finally, an instrumental variable analysis was used to compare matched patients between eight VHAs that were "EP-encouraged" (i.e. >50% received EP, mean 71.1%) with 12 VHAs that were "EP-discouraged" (i.e. <10% received EP, mean 2.8%). This analysis found no survival advantage for EP (HR 1.02, 95% CI, 0.71-1.45, p=0.93). When adverse events were compared to CP, patients treated with EP had increased hospitalization (2.6 vs. 1.7, p<0.01), outpatient visits (16.4 vs. 12.2, p<0.01), infectious complications (48.9% vs. 39.3%, p<0.01), acute renal failure (48.9 vs. 18.6%, p<0.01), and mucositis/esophagitis (20.8 vs. 14.9%, p<0.001). **Conclusions:** After accounting for various prognostic variables, matched cohorts, and regional differences, there was no difference in survival between patients treated with EP and CP, however EP was associated with increased morbidity.

**7565 General Poster Session (Board #173), Sat, 1:15 PM-5:00 PM**

**Significance of the estrogen signaling pathway in *EGFR* wild-type lung adenocarcinoma.** *Presenting Author: Kazumi Tanaka, Division of Thoracic and Visceral Organ Surgery, Gunma University Graduate School of Medicine, Maebashi, Japan*

**Background**: Estrogen and growth factor pathways are potential targets for novel preventative and treatment strategies of lung adenocarcinoma. The purpose of this study is to examine the correlation among estrogen receptor (ER), aromatase expression, and other prognostic factors including epidermal growth factor receptor (*EGFR*) mutation in lung adenocarcinoma. **Methods**: We evaluated 150 resected primary lung adenocarcinoma specimens. Expression of aromatase, ER$\alpha$, ER$\beta$, progesterone receptor (PR), and HER2 was evaluated with immunostaining. Aromatase expression was scored from 0 to 3+ according to immunoreactive intensity. *EGFR* mutation was evaluated with SmartAmp2 method. Overall survival (OS) and recurrence free survival (RFS) was calculated by Kaplan-Meier method, and differences in survival were determined by log-rank test. Cox proportional hazards model was used to evaluate independent prognostic factors. **Results**: Expression of aromatase, ER$\alpha$, ER$\beta$, PR, and HER2 were detected in 79.3%, 1.3%, 88.0%, 2.7%, 39.3% of all patients, respectively. In all patients, high aromatase expression (2+, 3+) was an independent predictor of poor OS (Hazard Ratio [HR]=2.3; 95% confidential interval [CI], 1.2-4.4; *P*= .017), while no prognostic significance was seen in RFS. ER$\beta$ was not an independent predictor of OS and RFS. In patients with wild-type *EGFR*, high aromatase expression was an independent predictor of poor OS (HR=2.6; 95%CI, 1.2-5.9; *P*= .019) and RFS (HR=2.5; 95%CI, 1.2-5.4; *P*= .020). Positive ER$\beta$ was also an independent predictor of poor RFS (HR=4.0; 95%CI, 1.2-13.2; *P*= .022). Furthermore, high aromatase expression was a significant predictor of poor survival only in women (OS, *P*= .010; RFS, *P*= .007), while positive ER$\beta$ was a significant predictor of poor survival only in men (OS, *P*= .073; RFS, *P*= .051). No prognostic significance was seen in patients with *EGFR* mutations. **Conclusions:** Aromatase and ER$\beta$ expression were independent negative prognostic factors in *EGFR* wild-type adenocarcinoma. We further showed that in patients with wild-type *EGFR*, high aromatase expression was a significant predictor of poor survival only in women, while ER$\beta$ expression was a significant predictor of poor survival only in men.

**7566 General Poster Session (Board #174), Sat, 1:15 PM-5:00 PM**

**Evaluation of a lung cancer RNA expression subtyping panel and comparison with histologic diagnosis in lung tumor samples from multiple data sets including The Cancer Genome Atlas (TCGA).** *Presenting Author: Mark Robert Miglarese, GeneCentric Diagnostics, Durham, NC*

**Background:** Lung cancer subtypes are described by morphological and molecular characteristics. Differentiation between various subtypes is important for guiding patient management. Variability in morphology, limited tissue, and the need for performing a growing number of genomic tests pose challenges to the current diagnostic standard. **Methods:** The Lung Subtype Panel (LSP), a previously published 57 gene expression panel for prediction of lung tumor morphologic class (Wilkerson *et al*.JMD 2013), was investigated using 2,168 lung cancer samples from multiple publically available data sets (TCGA, NCI, UNC, Duke, Expo, Seoul, Tokyo, and France). Data sets with both gene expression data and morphologic classification were selected. Three platforms for gene expression were represented: Affymetrix U133+2 (n=883), Agilent 44K (n=334), and Illumina RNA-seq (n=951). A centroid predictor was used to assign an expression-defined histologic class. Predicted results were compared with tumor morphologic classification and percent agreement was calculated. **Results:** Ten lung tumor RNA expression datasets were combined into three platform specific data sets comprised of a diverse patient population, including smokers and nonsmokers with Stage I – Stage IV disease. Using the centroid predictor for two classes only (adenocarcinoma or squamous cell carcinoma), the agreement of the predictor with morphologic classification ranged from 79%-94% across the 3 data sets. Analysis of the 4-class predictor is underway and will be reported. To estimate an error rate in morphologic classification, a subset of tumors were reviewed by multiple pathologists, which showed an agreement rate of 65% (CI 49%-73%). **Conclusions:** In multiple datasets with over two thousand lung cancer samples, molecular profiling using the Lung Subtype Panel compared favorably to light microscopic derived diagnoses, and showed a higher level of agreement than seen by reassessment by multiple pathologists. RNA-based tumor subtyping can provide valuable information, especially when tissue is limiting and the overall morphologic diagnosis remains unclear.

**7567 General Poster Session (Board #175), Sat, 1:15 PM-5:00 PM**

**Clinical characteristics and molecular profile in patients with non-small cell lung cancer harboring *CRKL* amplification.** *Presenting Author: Hirotsugu Kenmotsu, Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan*

**Background:** It has been reported that *CRKL* amplification, associated with overexpression, has induced cell transformation as well as resistance to EGFR inhibitors. We analyzed *CRKL*amplification in archived genomic DNA samples from the Shizuoka Lung Cancer Mutation Study. **Methods:** To identify *CRKL* amplification, we performed copy number analysis using the real-time PCR system. The standard curve was generated by PCR of serially diluted plasmid clones of *CRKL* and a reference gene. Triplicate reactions were performed using 2 ng of genomic DNA extracted from surgically resected tissues and tumor biopsies from non-small cell lung cancer (NSCLC) patients. Biopsy samples were obtained from NSCLC patients with EGFR mutations. In surgically resected tissues, TruSeq amplicon cancer panel was used for the detection of somatic mutations in 48 cancer related genes followed by ultra-deep sequencing (Illumina) at an average coverage of approximately 3,400x. *ALK*, *ROS1* and *RET* translocations and *EGFR, MET, PIK3CA, FGFR1* and *FGFR2* amplifications were also detected by multiplex RT-PCR and quantitative PCR, respectively. **Results:** Between July 2011 and March 2013, 268 NSCLC patients treated with surgical resection, and 40 NSCLC patients with *EGFR* mutations, were enrolled in this study. Patient characteristics (treated with surgical resection) were as follows: median age (range) 69 (38-92) years; female 35%; never-smoker 27%; histology adenocarcinoma/squamous cell carcinoma/others 74/23/3 %; and differentiation well/moderate/poor 21/53/23 %. We detected *CRKL* amplification in 7.5% of 268 NSCLC patients treated with surgical resection. Frequencies of *CRKL* amplification in patients with gene alterations were as follows: 7.5 % of 93 *EGFR*; none of 38 *KRAS*, 8.7% of 23 *PIK3CA*; 8.8% of 91 *TP53*, none of 4 *EML4-ALK*, and 50% of 4 *KIF5B-RET*. 18% of 40 patients with *EGFR* mutations showed *CRKL* amplification before EGFR-TKI treatment. **Conclusions:** C*RKL* amplification was identified in 7.5% of NSCLC patients. These results suggest that *CRKL* amplification may be mutually exclusive with mutations in *KRAS*, and frequently observed in those with *KIF5B-RET*.

**7568 General Poster Session (Board #176), Sat, 1:15 PM-5:00 PM**

**Association between metformin (M) use and survival among non-small cell lung cancer (NSCLC) patients (pts).** *Presenting Author: Alice K Fortune-Greeley, Center for Health Services Research & Development, Durham VA Medical Center, Durham, NC*

**Background:** The antidiabetic drug M may improve cancer-specific survival; however, little is known about the association between M use and survival among NSCLC pts. **Methods:** We retrospectively identified pts diagnosed with stage I-IV NSCLC from the Veterans Affairs Central Cancer Registry. A diagnosis of type 2 diabetes (DM) within 6 months of diagnosis was obtained from VA administrative data. Anti-DM medication (med) use, including M, was identified using VA pharmacy data. We used Cox proportional hazards regression controlling for age, race, BMI, stage, co-morbidities, HbA1C, and NSCLC treatment to estimate adjusted hazard ratios (AHR) to compare mortality risk among (1) DM pts with M use (2) DM pts with non-M anti-DM med use (3) DM pts with no anti-DM med use and (4) non-DM pts. **Results:** Between 2001-2008, 51,824 pts were diagnosed with NSCLC, 19% (n=9,982) of whom had a diagnosis of DM. Of the DM pts, 33% (n=3,309) were treated with M, 41.2% (n=4,113) were treated with non-M anti-DM meds, and 26% (n=2,560) were not treated with any anti-DM meds. When compared to non-DM pts, DM pts treated with M had similar survival [AHR: 0.99; 95% CI: (0.96, 1.03)] while DM patients treated with non-M anti-DM meds [AHR: 1.14; 95% CI: (1.10, 1.18)] or who received no anti-DM meds [AHR: 1.10; 95% CI: (1.05, 1.15)] were associated with poorer survival. DM pts treated with M were associated with improved survival compared to DM pts treated with non-M anti-DM [AHR: 0.86; 95% CI: (0.82, 0.91)]. DM pts treated with M had a similar improved survival relative to DM pts treated with non-M anti-DM meds across all stage groups [stage I/II: AHR 0.85; 95% CI: (0.77-0.93), stage III: AHR 0.88; 95% CI: (0.81-0.97), stage IV: AHR 0.86; 95% CI: (0.80-0.99)], including stage IA [AHR 0.83; 95% CI: (0.75-0.93)]. **Conclusions:** M use in NSCLC pts with DM is associated with (1) similar survival to non-DM pts, and (2) improved survival among DM NSCLC pts. These associations were observed regardless of stage, suggesting a broad anti-NSCLC effect of M or an unidentified confounding factor.

**7569 General Poster Session (Board #177), Sat, 1:15 PM-5:00 PM**

**Concordance of PD-L1 expression by different immunohistochemistry (IHC) definitions and in situ hybridization (ISH) in squamous cell carcinoma (SCC) of the lung.** *Presenting Author: Alex Martinez Marti, Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain*

**Background:** Recent clinical trials have shown that immune-checkpoint blockade can result in striking and durable responses in advanced non-small cell lung cancer. Preliminary data suggest a relationship between PD-L1 expression by IHC and objective response. No consensus about PD-L1 positivity expression exists. The aim of this study is to compare different IHC definitions and to explore the value of ISH for PD-L1 expression. **Methods:** Formalin-fixed paraffin-embedded tumor tissue samples from SCC were included. Clinical characteristics were analyzed. PD-L1 protein expression was evaluated by IHC using a mouse monoclonal antibody (clone h5H1). Three definitions for IHC positivity were applied: IHC 1 ≥5% of tumor cells exhibiting cell-surface staining; IHC 2 ≥1% of tumor cells exhibiting cell-surface staining; IHC 3 H-score, cut off: negative (0), positive (1-300). PD-L1 gene expression was evaluated by ISH with RNA Scope probe (Advanced Cell Diagnostics). For ISH, cut off: negative (<1), positive ( ≥1). Comparisons were made using *kappa*(k) correlation index. **Results:** 114 SCC tumors were included, median age 68.5 years, males 90.4%, current/former smokers 99.1%. By stage: IA 9.6%, IB 20.2%, IIA 16.7%, IIB 18.4%, IIIA 28.1%, IIIB 2.6%, and IV 4.3%. IHC and ISH results (see Table). According to IHC 3 20 (20.6%) SCC were positive for PD-L1. No differences by age, sex, smoking or stage were found. Median OS was 67.3 months (m), being of 58.7m for PD-L1 negative patients and of 81.5m for PD-L1 positive patients (p=0.598). A higher percentage of tumors resulted positive by ISH (29.4%), mainly due to a 13% of tumors that persistently remain negative by any IHC. K correlation index between IHC 1 versus (vs) IHC 2, IHC 1 vs IHC 3 and IHC 2 vs IHC 3 were of 0.94, 0.96 and 0.98, respectively. K correlation index for IHC3 vs ISH was 0.44. **Conclusions:** Our data suggests that the accuracy of different IHC definitions for PD-L1 expression have a high concordance. Results of ISH gene expression for PD-L1 warrant further investigation and can detect a subset of patients with PD-L1 pathway activation that remains negative by IHC.

| | PD-L1 + | PD-L1 - | Nonevaluable |
|---|---|---|---|
| **IHC 1** | 18 | 79 | 17 |
| **IHC 2** | 20 | 78 | 16 |
| **IHC 3** | 20 | 77 | 17 |
| **ISH** | 30 | 72 | 12 |

**7570 General Poster Session (Board #178), Sat, 1:15 PM-5:00 PM**

**Clinicopathologic characteristics and prognostic impact of MET receptor overexpression in patients with stage I-IIIA squamous cell lung carcinomas (SQCLCs).** *Presenting Author: Matthew David Hellmann, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** MET is an oncogenic driver involved in cellular proliferation, survival, and invasion (Rong et al, PNAS 1994) and has been identified as a therapeutic target in some patients with lung cancers (Dziadziuszko et al, J Thorac Oncol 2012; Spigel et al, J Clin Oncol 2013). The clinicopathologic features and outcomes of patients with stage I-IIIA SQCLCs with MET receptor overexpression have not previously been described. **Methods:** A cohort of histopathologically-defined completely resected SQCLCs were tested for membranous MET receptor expression using IHC (Ventana, SP44) and assessed by two thoracic pathologists independently (TA, NR). Expression was scored using the METmAb scoring system, in which "MET+" tumors had moderate/strong intensity expression (i.e., ≥2+) in ≥50% of tumor cell membranes. Associations between MET status and clinical features, DFS, and OS were assessed using the Fisher's exact, unpaired T-, log-rank tests and Kaplan-Meier methods. Multivariate DFS and OS analyses were performed using Cox regression. **Results:** 17 of 62 stage I-IIIA SQCLCs were MET+ (27%, 95% CI 18-40%). There were no differences in age (p=0.31), gender (p=1.0), or tobacco exposure (p=0.78) between pts with MET+ and MET- SQCLCs. Median DFS and OS were significantly inferior in pts with MET+ vs MET- SQCLCs (15 vs 37 mo, p=0.01; 32 vs 54 mo, p=0.04, respectively). In this cohort, age or KPS were not associated with OS or DFS. In multivariate analyses including stage, gender, and MET status, outcomes of pts with MET+ SQCLC remained significantly inferior (HR for recurrence=4.1, 95% CI 1.6-10; HR for survival=2.2, 95% CI 1.0-4.7). **Conclusions:** More than a quarter of pts with stage I-IIIA SQCLCs are characterized by MET receptor overexpression. DFS and OS are significantly shorter in pts with MET+ SQCLCs. Pts with MET+ SQCLCs represent an oncogene-defined subgroup and should be considered for enrollment in clinical trials of agents targeting the MET pathway in this illness.

| | MET+ (n=17) | MET- (n=45) |
|---|---|---|
| **Median DFS** | 15 mo | 37 mo |
| **p-value** | 0.01 | |
| **Multivariate HR for recurrence (95% CI)** | 4.1 (1.6-10) | |
| **Median OS** | 32 mo | 54 mo |
| **p-value** | 0.04 | |
| **Multivariate HR for survival (95% CI)** | 2.2 (1.0-4.7) | |

**7571 General Poster Session (Board #179), Sat, 1:15 PM-5:00 PM**

**The impact of a novel lung gross dissection protocol on intrapulmonary lymph node (LN) retrieval from lung cancer (LC) resection specimens.** *Presenting Author: Raymond U. Osarogiagbon, Boston Baskin Cancer Foundation, Baptist Cancer Center, Memphis, TN*

**Background:** Although thorough pathologic LN staging provides the greatest prognostic information in patients with potentially curable non-small cell LC, N1 nodal metastases are frequently missed. We tested the impact of corrective intervention with a novel gross dissection protocol on intrapulmonary LN retrieval. **Methods:** Retrospective review of consecutive lobectomy, or greater, LC specimens over a period of 15 months before and 15 months after training pathology technicians on the novel dissection protocol. **Results:** N= 152 specimens before, and 110 after introduction of the novel dissection protocol. The median number of intrapulmonary LN retrieved increased from 2 to 5 (p<.0001), and the 75th – 100th percentile range of detected intrapulmonary LN metastasis increased from 0 – 5 to 0 – 17 (p=.0003). In multivariate analysis (table), the extent of resection, examination period (pre- / post-intervention), and pathologic N1 (vs. N0) status were most strongly associated with increased intrapulmonary LN retrieval. **Conclusions:** A novel pathology dissection protocol is a feasible and effective means of improving intrapulmonary LN retrieval for examination. Dissemination and implementation studies of this novel pathology dissection protocol are warranted.

| | LN examined | | | |
|---|---|---|---|---|
| | All N1 LN | | Intrapulmonary LN | |
| **Variables** | **RR (95% C.I)** | **p-value** | **RR (95% C.I)** | **p-value** |
| **Intervention period** | 1.00 | - | 1.00 | - |
| Before | 2.27 (2.09 – 2.46) | < 0.0001 | 2.52 (2.32 – 2.75) | < 0.0001 |
| After | | | | |
| **Age Category** | 1.00 | - | 1.00 | - |
| < 65 | 1.00 (0.89 – 1.11) | 0.922 | 0.91 (0.84 – 0.99) | 0.030 |
| 65-74 | 1.06 (0.87 – 1.29) | 0.558 | 0.93 (0.80 – 1.09) | 0.373 |
| >74 | | | | |
| **Race** | 1.00 | - | 1.00 | - |
| White | 0.84 (0.60 – 1.17) | 0.307 | 0.72 (0.50 – 1.03) | 0.072 |
| Black | | | | |
| **Sex** | 1.00 | - | 1.00 | - |
| Female | 1.22 (1.09 – 1.36) | 0.001 | 1.34 (1.14 – 1.59) | 0.001 |
| Male | | | | |
| **Histology** | 1.00 | - | 1.00 | - |
| Non-adeno | 0.92 (0.81 – 1.04) | 0.177 | 0.87 (0.79 – 0.95) | 0.002 |
| Adeno | | | | |
| **N-category** | 1.00 | - | 1.00 | - |
| N0 | 1.80 (1.40 – 2.32) | < 0.0001 | 2.15 (1.57 – 2.93) | < 0.0001 |
| N1 | 1.10 (0.88 – 1.38) | 0.419 | 0.97 (0.72 – 1.30) | < 0.0001 |
| N2 | | | | |
| **T-category** | 1.00 | - | 1.00 | - |
| 1 (Ref) | 0.90 (0.80 – 1.01) | 0.084 | 0.92 (0.074 – 1.14) | 0.418 |
| 2 | 1.34 (1.12 – 1.58) | 0.001 | 1.25 (1.01 – 1.55) | 0.041 |
| 3 | | | | |
| **Extent of resection** | 1.00 | - | 1.00 | - |
| Greater than lobectomy | 0.74 (0.66 – 0.83) | < 0.0001 | 0.58 (0.51 – 0.65) | < 0.0001 |
| Lobectomy | | | | |

**7572 General Poster Session (Board #180), Sat, 1:15 PM-5:00 PM**

**Phase II study of biomarker guided neoadjuvant treatment strategy for IIIA-N2 non-small cell lung cancer based on EGFR-mutation status.** *Presenting Author: Wenzhao Zhong, Guangdong Lung Cancer Institute, Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China*

**Background:** Neoadjuvant EGFR-TKI therapy and customized adjuvant therapy are appealing but controversial strategy in patients with IIIA-N2 NSCLC. The purpose of this study was to evaluate the role of biomarker guided neo-adjuvant treatment strategy in patients with IIIA-N2 non-small cell lung cancer (NSCLC) stratified by epidermal growth factor receptor (EGFR) mutation status. **Methods:** Patients with resectable histologically documented stage IIIA-N2 NSCLC were assigned to either a neoadjuvant erlotinib arm or a gemcitabine/carboplatin (GC) arm based on EGFR mutation status (NCT00600587). The primary endpoint of this phase II study was response rate (RR). The secondary endpoints were progression-free survival (PFS) and overall survival (OS). **Results:** Twenty-four patients with IIIA-N2 NSCLC were enrolled in the trial from January 2008 until May 2011. The overall RR was 42%, and 58.3% (7/12) for the erlotinib arm with mutant EGFR, 25.0% (4/12) for the GC arm with wild-type EGFR ($P = 0.18$). Six cases in the erlotinib arm and seven cases in the GC arm received surgical resection. Median PFS was 6.9 months for the erlotinib arm and 9.0 months for the GC arm ($P = 0.071$). Median OS was 14.5 months for the erlotinib arm and 29.3 monthsfor the GC arm ($P = 0.304$). The median OS of the resected patients was 28.9 months for the erlotinib arm and 55.8 months for the GC arm ($P = 0.218$). In the overall population, the PFS and OS were 7.9 and 24.1 months, respectively. In addition, all six cases in the erlotinib arm that underwent resection gained partial response to tyrosine kinase inhibitor (TKI) re-treatment after progression, with a 2nd median PFS of 11 months. **Conclusions:** Biomarker guided neo-adjuvant treatment strategy in patients with IIIA-N2 NSCLC is feasible. Erlotinib had a tendency to improve the response, while the benefit did not transfer to better PFS or OS in this subgroup. Further randomized controlled studies of neoadjuvant combined with adjuvant EGFR-TKI are required to establish the role of perioperative TKI therapy in patients with IIIA-N2 NSCLC. Clinical trial information: NCT00600587.

**7573 General Poster Session (Board #181), Sat, 1:15 PM-5:00 PM**

**Role for surgical resection in the multidisciplinary treatment of stage IIIB non-small cell lung cancer (NSCLC).** *Presenting Author: Matthew Bott, Washington University School of Medicine in St. Louis, St. Louis, MO*

**Background:** The role of multi-modality therapy in stage IIIB NSCLC remains inadequately studied. Although chemoradiation is currently the mainstay of treatment, randomized trials evaluating the efficacy of surgical resection are lacking and surgery is offered selectively. **Methods:** Data of clinical stage IIIB NSCLC patients undergoing multimodality therapy were obtained from the National Cancer Database (NCDB). Information on patient- and tumor-related variables, therapy modalities, and outcomes was abstracted. Multivariable Cox regression models were fitted to evaluate variables influencing overall survival (OS). **Results:** From 1998-2010, 7,662 clinical stage IIIB NSCLC patients were treated with chemoradiation ($\leq$ 60 Gy radiation dose) (CR group), while 1,715 patients were treated with chemotherapy, radiation, and surgery in any order (CRS group). CRS patients were more likely to be younger, Caucasian, receive treatment at academic centers, and have slightly smaller tumors (all $p < 0.01$). There was no difference in Charlson Comorbidity Index (CCI) between the groups ($p = 0.5$). In the CRS group, 55% of patients received preoperative chemoradiation, 5% preoperative chemotherapy, and 3% preoperative radiation. The remaining CRS patients received adjuvant therapy (chemoradiation 30%, radiation 7%). Thirty-day surgical mortality was 3%. Factors associated with improved OS in multivariate analysis included younger age, female gender, decreased CCI, smaller tumor size and surgical resection (HR 0.57, 95% CI 0.52-0.63). Among patients treated with surgery, incomplete resection was associated with decreased OS (HR 1.52, 95% CI 1.20-1.92). Median OS was longer in CRS patients (25.9 months vs. 16.3 months, $p<0.001$). In a subset analysis of patients with N3 disease, median OS was longer in CRS patients (48.2 months vs. 26.5 months $p<0.001$) with 5-year OS of 26.3% after surgery. **Conclusions:** Surgical resection as a part of multimodality therapy is associated with improved overall survival in carefully selected patients with stage IIIB NSCLC. Multidisciplinary evaluation of these patients is critical.

**7574 General Poster Session (Board #182), Sat, 1:15 PM-5:00 PM**

**Role of PET scan in predicting response to neoadjuvant chemotherapy and long-term outcomes for stage II lung cancer.** *Presenting Author: Ankit Bharat, Feinberg School of Medicine, Northwestern University, Chicago, IL*

**Background**: While the role of neo-adjuvant chemotherapy (NAT) in stage IIIA non-small cell lung cancer (NSCLC) is well established, its efficacy in stage II is unclear. We evaluated the role of PET scan in predicting long-term outcomes in patients with stage II NSCLC undergoing surgical resection following NAT. **Methods**: Clinical stage II NSCLC (7th ed. AJCC) patients that underwent NAT between 1995 and 2010 were identified using a prospectively maintained database. All patients underwent clinical staging using CT scan and PET scan, with or without invasive lymph node staging. Chemotherapy regimen was unchanged during the study period. **Results**: Fifty-five patients with clinical stage II were identified who received NAT prior to surgery. The mean age was 63.1±10.2. Patients were predominantly white (69%) and female (53%). Most tumors were adenocarcinomas (70%), and most patients underwent a lobectomy (87%). Seventeen patients (30%) developed temporary interruption due to side effects from NAT. The 30-day perioperative mortality was 0%. Overall five-year and recurrence free survival were 65% and 70%, respectively. Mean preoperative PET SUV was 13.4±8.9 that decreased to 4.7±3.2 after NAT ($p<0.01$). Twenty-six (47%) patients had a greater than 50% reduction (PETc) while 15 (27%) did not (PETu) and 10 (18%) did not have restaging PET. There was no difference in invasive lymph node staging performed between PETu and PETc (30% vs 36%, $p=0.8$). The mean preoperative tumor size was no different (PETu 4.1 vs PETc 5.0). On final path the mean tumor size reduced 24% for PETc in contrast to 2% for PETu although this was not statistically significant. There was a 19% incidence of nodal metastasis in PETc group compared to 13% in PETu ($p=0.07$). PETc demonstrated a significantly improved survival compared to PETu (82.1% vs 40.8%, $p=0.04$). **Conclusions**: In patients with clinical stage II NSCLC, surgery after NAT was associated with low perioperative mortality and good long-term survival. Patients with a >50% reduction of SUV had a significant improvement in long-term survival.

**7575 General Poster Session (Board #183), Sat, 1:15 PM-5:00 PM**

**Diffusion of stereotactic body radiotherapy (SBRT) for early-stage non-small cell lung cancer (NSCLC) in the Medicare population, 2007-2009.** *Presenting Author: James B. Yu, Yale School of Medicine, New Haven, CT*

**Background:** Although the standard of care for early stage NSCLC is surgery, SBRT has emerged as an alternative for elderly patients who refuse surgery or are medically inoperable. As patterns of care may evolved since the introduction of SBRT for NSCLC in 2003, we investigated the adoption of SBRT vs. surgery in the Surveillance, Epidemiology, and End Results (SEER)– Medicare database in the years 2007-2009. **Methods:** We identified patients age > 67 who were diagnosed with stage I NSCLC from 2007 through 2009 and had undergone SBRT or surgery based on Medicare claims. Patient and hospital referral region (HRR) characteristics were recorded. Disability status (DS), a validated claims-based proxy for poor performance status, Elixhauser comorbidity index, and life expectancy (LE) were calculated using Medicare claims 12 months prior to diagnosis. The trend in receipt of SBRT was assessed for different categories of age, DS, and LE for patients whom SBRT was available in their HRR of residence. **Results:** There were 383 SBRT patients and 3,852 surgery patients. The proportion of patients undergoing SBRT rose from 4.4% in 2007 to 12.7% of treated patients in 2009 ($p<.001$). Patients who were older (Age 85-94; Odds Ratio (OR) vs. age 66-69: 5.98 [95% CI 3.34-8.08] , $p<.001$), female (OR 1.49 [95% CI 1.16-1.91], $p=.002$), with higher comorbidity (3+ conditions vs. 1: OR 4.23 [95% CI 2.97-6.02], $p<.001$) or disability status (Highest DS quartile vs. lowest OR 1.96 [95% CI 1.41-2.72],$p<.001$) were significantly more likely to undergo SBRT. The proportion of patients receiving SBRT (vs. surgery) increased in particular for patients with a shorter LE: SBRT use among patients with LE < 5 years from 11.8% in 2007 to 35.0% in 2009. In comparison, SBRT use for LE ≥ 5 years increased from 3.9% to 10.6% in the same period. **Conclusions:** The use of SBRT has disseminated rapidly into the care of older persons with early localized lung cancer, particularly those shorter life expectancies. Prospective studies are needed to identify patient and treatment factors associated with optimal outcomes.

**7576 General Poster Session (Board #184), Sat, 1:15 PM-5:00 PM**

**A phase II study of S-1 and concurrent thoracic radiotherapy (TRT) for elderly pts with locally advanced non-small cell lung cancer (LA-NSCLC): Okayama Lung Cancer Study Group trial 0801.** *Presenting Author: Yoshiro Fujiwara, Department of Respiratory Medicine, Okayama University Hospital, Tsuyama, Japan*

**Background:** Although thoracic irradiation is one of the standard therapies in elderly pts with LA-NSCLC, its treatment outcome is still poor. We previously reported safety profiles of S-1, an oral fluoropyrimidine possessing a radio-sensitizing effect, and concurrent TRT in such population [Lung Cancer 2011]. The objective of this study was to assess the efficacy and safety of S-1 with concurrent TRT for elderly pts with LA-NSCLC. **Methods:** Pts with stage III, aged ≥76 years and PS 0-1, and without any prior chemotherapy were eligible for this study. ps were treated with S-1 (40 mg/m²/dose b.i.d. on days 1-14 and 29-42) and TRT (60 Gy/30 fr over 6 weeks starting on day 1). Primary endpoint was response rate (RR), and required sample size was 30 pts, with a rate of 50% would be the lower limit of interest, with $\alpha = 0.05$ and $\beta = 0.20$. **Results:** Between 2007 and 2012, 30 pts were enrolled (24 men; median age, 79 years; PS 0, 15; IIIA, 20; Sq, 12). Median Charlson score was 1 ranging from 0 to 3. The proportion of actual dose schedule relative to the planned one of S-1 and TRT was 95 and 98%, respectively. Partial response was observed in 19 pts (63%; 95% confidence interval: 45-82%), which did not meet the endpoint. At the time of this analysis, 26 pts recurred at the local and distant sites in 18 and 10 pts, respectively. At a median follow-up of 23.7 months, median progression-free survival and MST were 13.0 months and 65.2 months, respectively. No difference in efficacy (response and survivals) was observed stratified by histology (sq vs. non-sq). Toxicities were generally mild, including G3/4 neutropenia (13%), G3 febrile neutropenia (7%) and G3 pneumonitis (10%). No one developed Gr3/4 esophagitis. No toxic deaths occurred. **Conclusions:** Although this study did not meet the primary endpoint, concurrent S-1 and radiotherapy yielded a favorable survival data. Also, it was well-tolerated in elderly pts with LA-NSCLC. Clinical trial information: UMIN000013077.

**7577 General Poster Session (Board #185), Sat, 1:15 PM-5:00 PM**

**Increasing ER stress response in pemetrexed-resistant mesothelioma cells.** *Presenting Author: Yuying Luo, New York University Langone Medical Center, New York, NY*

**Background:** Clinically silent progression and extraordinary resistance to therapy dictate poor survival for malignant pleural mesothelioma (MPM) patients. Current standard therapies such as antifolate (pemetrexed) treatment only minimally increase patient survival. Induction of ER-stress is a desired response of tumor cells to chemotherapy. We tested the hypothesis that butein (3,4,2',4'-tetrahydroxychalcone), a naturally occurring compound shown to counteract pemetrexed resistance in vitro and in vivo, may function by enhancing the ER-stress response of pemetrexed-treated MPM cells. **Methods:** MPM and benign mesothelial cells were treated with vehicle or butein, alone or in combination with pemetrexed. Levels of known ER-stress markers were evaluated by western blotting. The splicing of XBP-1, a transcription factor activated by ER-stress, was evaluated by PCR. Induction of CHOP, a main effector of ER-stress induced apoptosis was visualized and quantified by a CHOP-mCherry reporter and measured at the endogenous level by RT-qPCR. Established ER-stress inducing agents served as positive controls. Viability (vital cell count) and clonogenicity assays were used to evaluate the in vitroeffect of butein and butein + pemetrexed treatment. **Results:** MPM cells were resistant to pemetrexed treatment. MPM cells treated with butein demonstrated increased levels of ER-stress markers (BiP, CHOP, spliced XBP-1) as well as increased CHOP mRNA levels and promoter activation (fig.1). Moreover, butein was a stronger ER-stress inducer than pemetrexed. In line with this, viability and cytotoxicity assays revealed the potential for butein to strongly enhance the sensitivity of the mesothelioma cells to pemetrexed. Interestingly, butein treatment alone did not affect the viability of pemetrexed-sensitive hTERT transformed normal mesothelial cells (LP9). **Conclusions:** Butein triggers ER stress in MPM cells and may potentiate the ER-stress response of pemetrexed-treated cells. This may be one underlying mechanism for the anticancer effects of butein. Given its lack of effects on untransformed mesothelial cells, we propose that butein may be tested as an addition to the current clinically limited therapies for MPM.

**7578 General Poster Session (Board #186), Sat, 1:15 PM-5:00 PM**

**Malignant pleural mesothelioma: A 21-year single-center experience.** *Presenting Author: Mathieu D. Saint-Pierre, University of Ottawa, Ottawa, ON, Canada*

**Background:** Malignant pleural mesothelioma (MPM) is associated with a poor prognosis as most patients (pts) have advanced disease at diagnosis. Commonly used palliative chemotherapy (CT) is platinum based, and since 2004 the partner drug is usually a folate antimetabolite, either pemetrexed or raltitrexed. Selected pts presenting with early stage disease are considered for extrapleural pneumonectomy (EPP), although this approach remains controversial. We performed a single institution chart review investigating efficacy of EPP, and outcomes from CT pre- and post-2004. **Methods:** With ethics approval, all MPM pts from 1991 to June 2012 were identified. Data collected included age, gender, asbestos exposure, presenting symptoms, performance status (PS), histology, stage, bloodwork, treatment modalities, and date of death or last follow-up. Primary endpoint was overall survival (OS). Cox models were applied to determine variables associated with OS. **Results:** Of 245 identified pts, 87% were male, mean age 68 (range 21 to 88). Histology was epithelioid (63%), sarcomatoid (14%), mixed (11%) or unknown (12%). Common presentations were dyspnea (76%) and effusion (73%). Median OS for all pts was 9.4 months (mo). In univariate analysis, factors associated with shorter survival were: increasing age, poor PS, stage, sarcomatoid histology, weight loss >5%, leucocytosis (≥8.7) and thrombophilia (>400). In multivariate analysis PS, stage, histology, leucocytosis and thrombophilia remained independently associated with shorter OS. Among all pts who received CT (n=139), there was no difference in OS between the periods 1991-2004 (pre-pemetrexed) and 2004-2012 (pemetrexed era); 14.2 vs 13.2 mo (p=0.35). 20 pts underwent EPP, of which 11 had trimodality therapy with induction CT and post-op radiation. Their median OS was 24.7 vs 9.1 mo in non-EPP pts (p=0.0001). However, after multivariate analysis, the benefit of EPP was no longer statistically significant; HR 1.57, 95% CI 0.80-3.08 (p=0.19). **Conclusions:** In this review we did not observe an incremental improvement in survival after pemetrexed became available. Secondly, the longer OS seen in EPP pts is likely secondary to pt selection, rather than the intervention. The role of EPP remains unclear.

**7579 General Poster Session (Board #187), Sat, 1:15 PM-5:00 PM**

**A phase II trial of prolonged, continuous infusion of low-dose gemcitabine plus cisplatin in patients with advanced malignant pleural mesothelioma.** *Presenting Author: Oscar Rodriguez, Instituto Nacional de Cancerología, Mexico City, Mexico*

**Background:** Low-dose, prolonged infusion of gemcitabine has effects similar to standard doses in several cancers. We evaluated the toxicity and efficacy of low-dose gemcitabine in prolonged infusion plus cisplatin in patients with advanced pleural mesothelioma. **Methods:** Patients with mesothelioma received gemcitabine (250 mg/m$^2$) in a 6-h infusion plus cisplatin (35 mg/m$^2$) on days 1 and 8 every three weeks. We used the modified Response Evaluation Criteria In Solid Tumors. This study is registered in Clinical Trials (NCT01869023). **Results:** We included 44 patients; 82.1% were low risk according to the European Organisation for Research and Treatment of Cancer prognostic group. 39 patients had an objective evaluable response; partial response was observed in 53.8% (21/39), stable disease in 33.3% (13/39) and progression in 12.8% (5/39). The median progression free survival was 6.9 months (95% IC 3.2-10.6 months) and the associated factors were the EORTC risk and histology. The median overall survival was 20.7 months (95% IC 10.7-30.8 months). The functional, physical and emotional roles and dyspnoea, insomnia and pain symptom scales improved. The most commonly graded 3/4 side effects were neutropenia (24.4%), lymphopenia (14.6%), thrombocytopenia (14.7%) and anaemia (12.2%). **Conclusions:** Low-dose, prolonged gemcitabine infusion plus cisplatin has acceptable toxicity and high efficacy with improved quality of life, representing an affordable regimen for the low-income population. Clinical trial information: NCT01869023.

**Efficacy data.**

| Best tumor response | n = 39* | % |
|---|---|---|
| Complete response | 0 | 0 |
| Partial response | 21 | 53.8 |
| Stable disease | 13 | 33.3 |
| Progression | 5 | 12.8 |
| Global response | 21 | 53.8 |
| Disease control rate (CR + PR + SD) | 34 | 87.1 |

Abbreviations: CR, complete response; PR, partial response; SD, stable disease.
*39/44 patients with objective evaluable response.

**7580 General Poster Session (Board #188), Sat, 1:15 PM-5:00 PM**

**Prognostic significance of circulating secreted protein acidic and rich in cysteine (SPARC) in malignant pleural mesothelioma (MPM).** *Presenting Author: Steven Chuan-Hao Kao, Chris O'Brien Lifehouse, Sydney, Australia*

**Background:** Supervised proteomic analyses (discovery with isobaric tag for relative and absolute quantitation [iTRAQ] and validation with enzyme-linked immunosorbent assay [ELISA]) using 12 MPM patients from two phase II studies identified circulating SPARC as a promising prognostic marker, with high SPARC level associated with poor survival ($p<0.01$). We aimed to determine the independent prognostic significance of circulating SPARC in an independent cohort of MPM patients. **Methods:** Serum samples from MPM patients treated at the Netherlands Cancer Institute between 1995 and 2011 were included in this validation study. The samples were collected at the time of diagnosis and stored at -80°C, with clinical data collected prospectively. SPARC concentration was measured using the SEA791Hu ELISA kit (USCN Life Science Inc) according to the manufacturer's instruction. The primary end point of the study was overall survival (OS) from the date of sample collection, determined by the Kaplan-Meier method. The independent prognostic value of SPARC (categorised into high vs. low according to median concentration) was examined using Cox regression analysis, incorporating known prognostic factors in a multivariate model, including age (<60 vs. ≥60 years), gender (male vs. female), stage (I-II vs. III-IV) and histological subtype (epithelial vs. non-epithelial). **Results:** A total of 97 patients were included: median age 60 years; 85% male; 50% stage I-II; and 75% epithelial subtype. Treatment received included: 67% chemotherapy; 22% radical surgery; and 18% supportive care alone. The median OS was 13.5 months (92 patients deceased). The median SPARC concentration was 1745$\mu$g/ml. In the multivariate analyses, male gender (median OS: 10.8 vs. 22.4 months; $p=0.05$), stage III-IV (median OS: 10.1 vs. 17 months; $p=0.05$) and high SPARC level (median OS: 9.3 vs.19 months; $p=0.05$) were independently associated with poor OS. **Conclusions:** This validation study is the first to demonstrate the prognostic role of circulating SPARC in MPM, with high SPARC level being an independent predictor of poor OS.

**7581 General Poster Session (Board #189), Sat, 1:15 PM-5:00 PM**

**A multicenter phase II toxicity study of lung-sparing intensity modulated radiation therapy (IMRT) for malignant pleural mesothelioma (MPM).** *Presenting Author: Marjorie Glass Zauderer, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Given the trend away from extrapleural pneumonectomy (EPP) towards pleurectomy/decortication (P/D), we are developing a technique to deliver radiation to the pleura in patients with two intact lungs. In our initial experience with 36 patients (20 post P/D), 20% had grade ≥ 3 pneumonitis, most treated effectively with steroids, and survival was promising (Rosenzweig 2012). We now report our prospective, multicenter, phase II study of the safety and efficacy of pleural IMRT as part of a multimodality, lung-sparing, treatment approach. **Methods:** Patients with stage I-IV MPM received <4 cycles of pemetrexed and platinum chemotherapy. If feasible, P/D was performed. IMRT was delivered to the pleura (goal of 50.4 Gy, 28 fractions). The primary endpoint was the incidence of ≥ grade 3 radiation pneumonitis (RP); those who received any IMRT were considered evaluable. A Simon two-stage design was used: among the initial 9 patients, one case of grade 3 reversible RP occurred, so the cohort expanded to 28. **Results:** 39 patients are enrolled: 23 evaluable, 5 to receive IMRT, and 11 off-study before IMRT (7 due to disease progression, 3 were poor IMRT candidates at the time of simulation, and 1 withdrew consent). Demographics are in Table 1. 21 patients completed IMRT: 4 had grade 2 RP and 1 had grade 3 RP and was weaned from oxygen after a course of steroids. No grade 4 or 5 radiation-related toxicities were observed. Follow-up PFTs demonstrated an average decrease in DLCO of 18% (range 6-34%) from baseline. **Conclusions:** Pleural IMRT for MPM is safe with an acceptable rate of RP and feasible in a multicenter setting. The incorporation of IMRT with chemotherapy and P/D could form a new treatment paradigm for locally advanced MPM. In order to increase the number of patients able to complete all therapy and to improve local control in areas of bulkier disease, we plan a follow up study with upfront P/D, followed by chemotherapy and then radiation with dose-painting techniques. Clinical trial information: NCT00715611.

| | All N=39 (%) |
|---|---|
| **Age, median (range)** | 68 (38-75) |
| **Gender M/F** | 35 (90)/4 (10) |
| **Stage** | |
| **I** | 2 (5) |
| **II** | 10 (26) |
| **III** | 14 (36) |
| **IV** | 13 (33) |
| **Histology** | |
| **Epithelioid** | 32 (82) |
| **Sarcomatoid** | 3 (8) |
| **Biphasic** | 4 (10) |
| **Surgery** | |
| **P/D** | 21 (54) |
| **Unresectable** | 18 (46) |

**7582 General Poster Session (Board #190), Sat, 1:15 PM-5:00 PM**

**Blood tests in malignant pleural mesothelioma (MPM).** *Presenting Author: Kazue Yoneda, Second Department of Surgery, University of Occupational and Environmental Health, Kitakyushu, Japan*

**Background:** Serum mesothelin is the best available blood test for diagnosing MPM, but provides a poor sensitivity (J Clin Oncol 2012). We previously showed that two blood tests, a test for circulating tumor cell (CTC) and a test for endothelial cell (CEC), provided significant diagnostic and prognostic performance (ASCO 2011 and 2012), and we compared these blood tests in the present study. **Methods:** A total of 140 patients, who present at Hyogo College of Medicine Hospital with suspicion of MPM, were enrolled; the final pathological diagnosis was MPM in 107 patients and non-malignant diseases in 33 patients. CTC-count in 7.5mL of peripheral blood and CEC-count in 4.0ml of peripheral blood were quantitatively evaluated with the "CellSearch" system. The MESOMARK ELISA kit was sued for measurement of serum soluble mesothelin-related peptides (SMRP). **Results:** A receiver-operating characteristic (ROC) curve analysis showed each test provided a significant diagnostic performance; at the cut-off value of 1/7.5mL (for CTC-test), 70/4.0mL (for CEC-test), and 2nmol/L (for SMRP-test), each test provided a high specificity (over 90%) but a poor sensitivity (28%-44%) (Table). When these tests were combined and a patient with positive result in any test (CTC≥1, or CEC≥70, or SMRP≥2) was judged to have MPM, the diagnostic performance improved with the sensitivity of 79% (specificity, 76%). In addition, patients with positive-CTC (CTC≥1) or higher-CEC (CEC≥70) showed a significantly poor prognosis (median survival time, 11 months vs 23months; $p<0.001$). **Conclusions:** Novel blood tests (CTC-test and CEC-test) improved a diagnostic performance of SMRP-test, and provided a significant prognostic value in MPM.

**Diagnostic performance of blood tests.**

| | CTC | CEC | SMRP |
|---|---|---|---|
| **AUC-ROC** | 0.619 | 0.725 | 0.703 |
| **P-value** | 0.039 | <0.001 | 0.009 |
| **Cut-off** | 1cell/7.5mL | 70cells/4.0mL | 2 nmol/L |
| **Sensitivity** | 28% | 44% | 33% |
| **Specificity** | 95% | 91% | 91% |

**7583 General Poster Session (Board #191), Sat, 1:15 PM-5:00 PM**

**Dendritic cell vaccination in malignant pleural mesothelioma: A phase I/II study.** *Presenting Author: Zwi N. Berneman, University of Antwerp, Antwerp, Belgium*

**Background:** The prognosis of malignant pleural mesothelioma (MPM) is dismal, with a median overall survival from diagnosis of 12 months. New therapeutic approaches are needed. We evaluated the feasibility, safety, immunogenicity and clinical efficacy of consolidative treatment with autologous dendritic cells (DC) electroporated with mRNA encoding the MPM-associated Wilms' tumor 1 (WT1) antigen. **Methods:** Ten patients (median age 62 [range: 53-73]) with unresectable MPM and non-progressive disease after platinum/pemetrexed-based chemotherapy underwent leukapheresis. CD14+ monocytes were isolated, cultured into mature DC according to our clinical-grade protocol (Van Tendeloo et al. PNAS 2010) and electroporated with mRNA derived from a codon-optimized *WT1* construct with a sig-LAMP sequence and a deletion of the nuclear localization signal. Biweekly intradermal vaccinations were administered for an intended period of 6 months, followed by monthly or bimonthly injections. Delayed type hypersensitivity (DTH) was tested, in order to assay in vivo T-cell responsiveness to the DC vaccine. Overall survival was measured from entry into trial. **Results:** Leukapheresis was successful in all patients, with a mean number of 19.4 ± 6.9 DC vaccines produced (range: 7-29); 3 patients underwent an additional leukapheresis. A mean number of 18.4 ± 10.7 vaccines were administered (range: 5-44). DC vaccination was well-tolerated; no systemic toxicity was recorded; local reactions at the injections sites occurred in all patients, but were mild and self-limiting. At a median follow-up of 22.7 months, 6 patients are alive, 4 have died and median survival has not yet been reached. The 6-, 12- and 18-month survival rates were 100%, 90% and 75%, respectively. Significant DTH responses (i.e. ≥ 10 mm² induration [Disis et al. Clin Cancer Res 2000]) were elicited in all patients except UPN006, who had the lowest survival (7.3 months). **Conclusions:** WT1-targeted DC vaccination is feasible and well-tolerated in MPM patients. In vivo evidence of vaccine-elicited immunity to the DC vaccine administered was obtained in 9/10 patients. Overall survival data suggest that adjuvant DC-based immunotherapy provides a clinical benefit for patients with MPM. Clinical trial information: NCT01291420.

**7584 General Poster Session (Board #192), Sat, 1:15 PM-5:00 PM**

**Impact of treatment-free interval (TFI) and disease control rate (DCR) on survival outcome in relapsed malignant pleural mesothelioma (MPM).** *Presenting Author: Vanesa Gregorc, Department of Oncology, Istituto Scientifico San Raffaele, Milan, Italy*

**Background:** Both TFI (the time elapsing from end of first line to start of second line therapy) and DCR (the nonprogression rate at first tumor evaluation) have been found to predict overall survival (OS) in some tumor types. **Methods:** The impact of TFI and DCR on the outcome of relapsed MPM patients who had failed a pemetrexed-based regimen was tested in an individual patient data pooled analysis. Second line therapy (n=450) was single agent NGR-hTNF (n=50, ph 2 trial) or chemotherapy (gemcitabine, vinorelbine or doxorubicin) plus NGR-hTNF/placebo (n=400; ph 3 trial). In both trials, tumor evaluation was done every 6 weeks by MPM-modified RECIST. OS was computed from second line therapy and median follow-up time was 19.3 months. TFI data were treated as a continuous or dichotomous variable using the median value as cutpoint (4.6 months; 95% CI 4.0-5.0). In multivariable models, hazard ratios (HR) for OS were derived from Cox models adjusted for baseline factors: age (median, 66 years), sex (men, 75%), PS (1-2, 66%), histology (nonepithelial, 19%), EORTC score ($\geq$ 1.27, 35%), best response to first line therapy (DCR, 74%), neutrophil to lymphocyte ratio (NLR; median, 4). **Results:** TFI data individually predicted for OS when tested as continuous (HR=1.02; p=0.005) or median value (HR=1.35; p=0.005). A TFI shorter than 4.6 months remained independent predictor of poor OS on multivariate analysis (HR=1.38; p=0.01) along with male sex (1.70; 0.001), PS of 1-2 (1.48; 0.004), nonepithelioid histology (1.77; 0.002), EORTC score $\geq$ 1.27 (1.36; 0.05) and NLR $\geq$ 4 (2.1; <0.0001). A short TFI was also related to worse progression free survival (adjusted HR=1.36; p=0.009) and DCR (adjusted odds ratio=0.62; p=0.02). After second line therapy, the 6-week DCR was 54%, while 46% of cases had early progression or were unevaluable. Using DCR at 6 weeks as a time dependent covariate, the nonprogression rate was univariately associated with OS improvement (HR=0.58; p<0.0001), which persisted after adjusting for baseline risk factors (HR=0.61; p<0.0001). **Conclusions:** In relapsed MPM, a prior short TFI is an independent predictor of poor prognosis and the 6-week DCR can be used as early surrogate endpoint for survival. Clinical trial information: NCT00484276-NCT01098266.

**7585 General Poster Session (Board #193), Sat, 1:15 PM-5:00 PM**

**Association of activation of mTOR and MAPK signal pathway with prolonged survival in patients with malignant pleural mesothelioma.** *Presenting Author: Ayumi Kuroda, Hyogo College of Medicine, Department of Thoracic Surgery, Nishinomiya, Japan*

**Background:** Malignant Pleural Mesothelioma (MPM) is a rare disease with poor prognosis. The combination chemotherapy with cisplatin and pemetrexed is the first line of MPM. The AKT/mTOR (Mammalian Target of Rapamycin) pathways and Ras/Raf/MEK/ERK (MAPK) pathway are known to be activated in some kind of cancer. The purpose of this study is to evaluate the correlation between the activation of these pathways and prognosis of MPM patients. **Methods:** 46 patients with MPM underwent a multimodality therapy including extrapleural pneumonectomy (EPP) at Hyogo College of Medicine, Nishinomiya, Japan from April 2004 to October 2012. These 46 cases consisited of 35 males (76.0%) and 11 females (23.9%) with median ages of 59.8 years (ranged from 37 to 71 years). Histologic subtype was 43 epithelial type (93.4%), 2 biphasic type (4.3%), 1 desmoplastic type (2.1%). Paraffin embedded surgical sample was used for immunohistochemistry to evaluate the expression of phospho-AKT, phospho- mTOR (p-mTOR), phospho-S6 Ribosomal Protein (p-S6RP), phospho-4EBP-1, phospho-mitogen-activated protein kinase kinase(p-MEK) and phospho-extracellular signal-regulated kinase(p-ERK) . Overall survival (OS) from the time of surgery was determined by Kaplan-Meier method and results were compared by log-rank test. **Results:** OS was significantly better in phospho-S6RP positive patients (32/46) in comparison with phosphor-S6RP negative patients (14/46) (43.6 months vs. 14.4 months, P=0.03). OS was significantly better in phospho-mTOR positive patients (18/46) in comparative with phosphor-mTOR negative patients (28/46) (37.1 months vs. 14.4 months, P=0.08).OS was significantly better in phospho-MEK negative patients (6/46) in comparative with phosphor-MEK positive patients (40/46) (31.7 months vs. 17.4 months, P=0.08). **Conclusions:** In MPM patients, high phospho-S6RP expression was predictive of improved OS. And this study support that the AKT/mTOR and MAPK pathways is promising candidate of molecular target therapy for MPM.

**7586 General Poster Session (Board #194), Sat, 1:15 PM-5:00 PM**

**Old and new prognostic factors in a series of 910 patients with malignant pleural mesothelioma (MPM).** *Presenting Author: Anthony Linton, Asbestos Diseases Research Institute, Sydney, Australia*

**Background:** Whilst the prognosis of most MPM patients is poor, a small proportion demonstrate long term survival. We investigate patient and treatment factors associated with survival and the impact of chemotherapy (CT) and surgery in a large patient series. **Methods:** Data sets of patients registered with the NSW Dust Diseases Board (2002-2009) were reviewed and prognostic factors such as age, gender, histological subtype and stage evaluated using Kaplan-Meier and Cox regression analysis. The impact of treatment, smoking and asbestos exposure were evaluated and subgroup analyses explored long(er) (>20 months) vs. short(er) (< 20 months) survivors. **Results:** We identified 910 patients: 90% male; median age 72 yrs; histological subtype (epithelioid 60%; biphasic 13%; sarcomatoid 17%; unknown 10%); stage (Tx-I-II 48%; III-IV 52%); calretinin expression (74.8%). Treatment: CT 41%, extrapleural pneumonectomy (EPP) 6%. Median age of first occupational asbestos exposure was 18 yrs; cumulative exposure 24 yrs. Median overall survival (OS) was 10.1 mo. Longer OS (p<0.001) was associated with: age <70yrs (13.5 vs. 8.5 mo.); female gender (12.0 vs. 9.9 mo.); epithelioid subtype (13.4 vs. 6.2 mo.); calretinin expression (11.0 vs. 5.5 mo.); NLR (neutrophil lymphocyte ratio) <5 (12.0 vs. 7.5 mo.); platelets <400 (11.6 vs. 7.1 mo.); and normal hemoglobin (16.6 vs 8.8). Patients undergoing CT (15.6 vs. 6.6 months; p<0.001) and EPP (24.8 vs. 9.5 months; p<0.001) had improved survival. Smoking history and cumulative asbestos exposure did not affect survival. On multivariate analysis, all variables remained significant, including EPP and CT use (time dependent analysis). 24% of patients survived >20 months: 16% underwent EPP, 61% received CT; but 31% received neither. Epithelioid histology, calretinin expression, age, stage and hemoglobin levels were independently associated with survival >20 months. **Conclusions:** In this large, population-based series, we validated calretinin expression, age, gender, histological subtype, stage and NLR as significant prognostic factors. Patients undergoing EPP/CT demonstrated better survival but 84% and 39% of long survivors respectively did not receive EPP or chemotherapy.

**7587 General Poster Session (Board #195), Sat, 1:15 PM-5:00 PM**

**Metabolomic analysis of pegylated arginine deiminase treatment in patients with malignant pleural mesothelioma.** *Presenting Author: Essam Ahmed Ghazaly, Centre for Haemato-Oncology, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom*

**Background:** Arginine is a key amino acid for tumorigenesis modulating a diverse array of metabolic pathways, from synthesis of proteins, NO and polyamines to nucleotide turnover and mTOR signalling. Tumors deficient in the urea cycle enzyme, argininosuccinate synthetase 1 (ASS1), are especially sensitive to deprivation of exogenous arginine using the drug pegylated arginine deiminase (ADI-PEG20, Polaris Group, US). Previously, we have reported the metabolic changes induced by ADI treatment in a panel of ASS1-deficient bladder cancer and malignant pleural mesothelioma (MPM) cell lines. Here, we examined the metabolic effects in plasma of patients with MPM treated with ADI [ClinicalTrials.gov NCT01279967]. **Methods:** MPM plasma samples (29 patients treated with ADI-PEG20 and 6 control patients over a 9 wk period) were analysed by ultra performance liquid chromatography-mass spectrometry (UPLC-MS) for untargeted identification and quantitation of the metabolomic changes. The top metabolic changes were then assessed by targeted UPLC-MS/MS. **Results:** ADI-PEG20 induced marked changes in plasma, which clearly discriminated treated from untreated patients using partial least squares discriminant analysis (PLS-DA), a multivariate statistical approach. As expected, the plasma [arginine] decreased (126$\pm$15$\mu$M wk 0 vs 3.2$\pm$2.5 $\mu$M wk3) with a reciprocal increase in the plasma [citrulline] (56$\pm$6$\mu$M wk 0 vs 879$\pm$113 $\mu$M wk3) in ADI-PEG20 treated patients only. In addition, ADI-PEG20 treatment triggered the following novel plasma metabolite changes: increased [thymine] (3.0$\pm$0.4 $\mu$M week 0 vs 11.5$\pm$1.5 $\mu$M wk 3), [carnitine] (43$\pm$5 $\mu$M week 0 vs 96$\pm$7 $\mu$M wk 3) and [proline] (147$\pm$18 $\mu$M wk 0 vs 246$\pm$37 $\mu$M wk 3), while decreasing [isoleucine] (53$\pm$11 $\mu$M week 0 vs 17$\pm$4 $\mu$M wk 3). A 2-fold increase in plasma [glutamine] and [glutamate] was detected in non-responder patients as assessed by PET-CT, reaching a maximum by wk 5 of ADI-PEG20 treatment. **Conclusions:** This study has identified several metabolic changes in plasma that may be employed as potential biomarkers for optimizing the efficacy of ADI-PEG20 in the treatment of MPM and other arginine-dependent cancers. Clinical trial information: NCT01279967.

**7588 General Poster Session (Board #196), Sat, 1:15 PM-5:00 PM**

**Enhancing accurate prediction of survival outcomes and aiding decision making in malignant pleural mesothelioma (MPM) using a three-item index from the LCSS-meso PRO measure: Results from a randomized 444 patient (pt) prospective trial.** *Presenting Author: James Thomas Symanowski, Levine Cancer Institute, Carolinas Healthcare System, Charlotte, NC*

**Background:** Accurate prediction of survival of patient groups is required for appropriate trial design, while attention to the effect of treatment on PROs can help guide individual patient management. No pt reported factor is routinely used for these purposes, as performance status (PS) is not pt rated; nor is PS change known to guide accurately treatment changes. **Methods:** This study analyzes data from the prospective MPM EMPHACIS study comparing pemetrexed + cisplatin with cisplatin in 444 pts. LCSS-meso was given to all pts. An index of the 3 global LCSS items (symptom distress, activity level, quality of life) was correlated with survival outcomes. **Results:** Baseline and 6 week LCSS results and survival data were available for 83% of pts. Survival results were analyzed for differences for those scoring less than or greater than the median for each LCSS symptom and global factor. Unlike individual symptoms which are found only in subsets of pts, the 3 LCSS pt reported global items each apply to all pts. Median survival differences above (positive factor) or below (negative factor) medians for each global item varied by $< 6$ months. An index was created using the number of negative factors, 0 to 3, based on scoring less than the median for each of these 3 factors; see the Table. A landmark survival analysis was done comparing survival of those with a total LCSS 3-item score at 6 weeks which had fallen by $> 20\%$ since baseline vs all other pts. Median survivals = 7.8 months vs 13.3 months (HR 1.91, p <.001). **Conclusions:** This 3-item index, based entirely on PROs, has strong predictive properties. It can help improve trial design and analysis. For all patients, a fall by $> 20\%$ in the total 3-item score after just 2 cycles of chemotherapy allows rapid, convenient and inexpensive identification of a large group of patients (28%) with poorer survival on their current chemotherapy, which can assist in clinical decision making.

| # of negative PRO factors | % of pts (N = 444) | Median survival: mos. | Survival: 1 year | HR* |
|---|---|---|---|---|
| **0** | 35% | 14.6 | 61% | 0.371 (p<.001) |
| **1,2** | 33% | 10.8 | 45% | 0.616 (p<.001) |
| **3** | 32% | 7.4 | 26% | -- |

*Reference group is 3 negative PRO factors.

**7589 General Poster Session (Board #197), Sat, 1:15 PM-5:00 PM**

**T-cell inflamed phenotype and PDL1 expression in malignant mesothelioma.** *Presenting Author: Hedy Lee Kindler, The University of Chicago, Chicago, IL*

**Background:** Malignant mesothelioma (MM), a universally lethal disease caused principally by asbestos exposure, develops in the pleura, peritoneum, pericardium and tunica vaginalis. MM is commonly associated with a prominent inflammatory reaction, though it remains unknown whether this relates primarily to asbestos-induced chronic inflammation or an anti-tumor immune response. We therefore evaluated markers of an anti-tumor immune response established for melanoma in MM. **Methods:** We analyzed gene expression data on 44 MM (Gordon et al 2005), applied a melanoma-derived signature of T-cell inflammation (Harlin 2009), and analyzed other immune response related genes. We also evaluated 8 MM tumors (7 epithelioid, 1 biphasic; 7 pleural, 1 peritoneal) by multi-color immunohistochemistry (IHC), staining for CD68 (macrophages), CD8 (tumor infiltrating lymphocytes), and PDL1 (immune checkpoint). **Results:** 14/44 (32%) of MM showed high CD8 gene expression; 11% demonstrated a T-cell inflamed phenotype similar to that observed for melanoma. IHC revealed prominent CD68 infiltration in all tumors. CD8 tumor infiltrating lymphocytes (TILs) were present in all epithelial tumors; the biphasic tumor was negative. Germinal centers surrounding and within the tumor were rich in CD8+ cells; 1 tumor showed accumulation of CD8+ lymphocytes along the tumor invasive front. Two patterns of PDL1 expression were observed: 1) PDL1 expression occurred in 6 MM tumor samples, which was 2-3+ in 3 tumors, and 1+ in 3 tumors; 2) Patchy higher level PDL1 expression was observed in stromal or CD68 cells located close to CD8+ cells in the germinal center or the invasive tumor front in 6 tumor samples (2+ in 4 samples; 1+ in 2 samples). **Conclusions**: Mesothelioma is an 'inflammatory' tumor, with prominent infiltration with CD68+ cells (macrophages). We describe the presence CD8+ tumor infiltrating lymphocytes and a T-cell inflamed expression pattern in a fraction of MM, characteristic of the T-cell inflamed phenotype found in other tumors such as melanoma that benefit from immune checkpoint blockade. These preliminary data suggest that agents that target PDL1 may be appropriate to evaluate in MM. Ongoing work will further characterize immune checkpoints in MM.

**7590 General Poster Session (Board #198), Sat, 1:15 PM-5:00 PM**

**Clinical and molecular profiling of surgically resected small-cell lung cancer: Intergroup study with FIGHT002 and HOT1301.** *Presenting Author: Hiroshi Yokouchi, Department of Pulmonary Medicine, Fukushima Medical University, Fukushima, Japan*

**Background:** NCCN and Japanese guidelines suggest surgery for patients with c-stage I small-cell lung cancer (SCLC). However, the clinical impact of surgery with other variables on patients with early-stage SCLC has yet to be determined. Thus clarification of the clinical and molecular profile of SCLC is required. **Methods:** We reviewed the clinical courses of 149 patients with SCLC who had undergone surgery at 16 institutes from January, 2003 through January, 2013. Eighty-nine paraffin-embedded tissue samples were subjected to immunohistochemistry using 8 antibodies, and to next-generation sequencing system (NGS) using MiSeq and TruSight Tumor Panel (Illumina) loading 26 genes (UMIN registration No. 000010116/10117). **Results:** Median relapse-free survival (RFS) and overall survival (OS) were 16.6 (95%CI=7.1-26.2), and 36.7 (17.3-56.2) months, respectively. Multivariate analysis revealed that OS was longer in patients without interstitial pneumonitis (IP) (HR=0.372, 95%CI=0.181-0.767, p=0.007), without history of malignancy (HR=0.446, 0.229-0.868, p=0.017), with preoperative diagnosis (HR=0.401, 0.210-0.767, p=0.006), with c-stage II and under (HR=0.204, 0.065-0.640, p=0.006), and with p-stage IA (HR=0.294, 0.142-0.605, p=0.001). Of the 89 patients whose samples were available, MED12 and TGF-$\beta$RII were highly expressed in nucleus and cytoplasm, respectively in 92% and 61%. Multivariate analysis demonstrated that high expression of either c-Kit or HER2 in tumors is an independent factor for longer OS (HR=0.396, 95%CI=0.209-0.752, p=0.005). None of the tumors expressed ALK. There was no relationship between the expression of c-Met, EGFR, and VEGFRII and either of RFS or OS. Thirty-five samples were subjected to NGS so far. However, no druggable mutations of *BRAF, EGFR, ERBB2, KRAS, KIT, PDGFRA, PIK3CA, FOXL2, GNAQ, GNAS*, and *FGFR2* were found. **Conclusions:** These results indicate that i) complication of IP and history of malignancy might be major decision factors of surgery, and: ii) patients with c-stage II should be considered for surgery in a prospective trial. Immunohistochemistry results assist us in gaining a better understanding of the biology of SCLC.

**7591 General Poster Session (Board #199), Sat, 1:15 PM-5:00 PM**

**Retrospective evaluation of prophylactic cranial irradiation in patients with limited-stage small cell lung cancer with stereotactic radiotherapy: A multi-institutional study.** *Presenting Author: Yuichi Ozawa, Department of Respiratory Medicine, Respiratory Disease Center, Seirei Mikatahara General Hospital, Hamamatsu, Japan*

**Background:** The benefits of prophylactic cranial irradiation (PCI) on survival time have been repeatedly reported especially in patients with limited stage small cell lung cancer (LS-SCLC). However, almost all such studies were performed decades ago and whether PCI is still beneficial in conjunction with pre-symptomatic brain screening and stereotactic radiotherapy (SRT) in patients with brain metastasis (BM) remains unknown. **Methods:** The data of all patients with pathologically proven SCLC from 1/1/2006 to 6/31/2013 were collected from 4 designated cancer care hospitals in Japan, all of which were equipped with or had access to SRT, and thoroughly reviewed. LS disease at diagnosis and who were estimated as CR or good PR after the first treatment were enrolled. All possible patients were periodically screened for BM by CT or MRI and patients with BM were preferentially considered for SRT. The effects of PCI and SRT were analyzed by Kaplan-Meier method and Cox proportional hazards model. **Results:** Of all 418 patients with SCLC, 124 matched our criteria. The 124 patients were divided into a PCI (P) group ($n$=29) and non-PCI (NP) group ($n$=95). Patient backgrounds were similar with the exception of median age (65 *v* 73; p<0.001) and stage (1/2/3) at diagnosis (1/4/24 *v* 31/15/49; p=0.001). Neither the cumulative occurrence of BM at 2 years (COB) (45.5 *v* 29.9%; p=0.250) nor the median survival time (MST) (25.5 *v* 34.5 months (m); p=0.312) showed statistically significant differences between the two groups. Even when only stage 3 cases were analyzed, no statistically significant differences in COB or MST were found between the two groups (43.1 *v* 53.7%; p=0.437, 25.5 *v* 26.5 m, p=0.546, respectively). 10 patients in P group and 25 in NP group developed BM. Survival time after BM detection was significantly longer in NP group (8.0 *v* 20.2 m, p=0.050). Furthermore, SRT was significantly associated with longer survival after BM detection when adjusted for age and stage (hazard ratio; 0.468, p=0.045). **Conclusions:** PCI does not benefit patients with LS-SCLC in conjunction with periodical brain screening and SRT. A prospective study is currently underway.

**7592 General Poster Session (Board #200), Sat, 1:15 PM-5:00 PM**

**Multiplex testing of potentially 'actionable' alterations in small cell lung cancer (SCLC).** *Presenting Author: Shirish M. Gadgeel, Karmanos Cancer Institute, Wayne State University, Detroit, MI*

**Background:** Therapy and outcomes of SCLC patients have not changed for many years. Recently, driver mutations have been identified in many cancers and targeting these mutations can provide clinical benefit. Recent data from whole genome sequencing suggest that driver mutations may exist in SCLCs. We conducted multiplex testing of SCLCs to identify mutations potentially predictive of response to novel and established therapeutics. **Methods:** We identified tumor tissues of 30 SCLC patients collected as part of two different institutional review board approved studies. Using the Sequenom MassArray system and a multiplexed panel, we analyzed tumor DNA for 214 mutations in 26 genes associated with the pathogenesis of lung cancer. Gene copy number analysis utilized a 180K oligonucleotide microarray and comparative genomic hybridization assay. **Results:** The median age at diagnosis of patients was 63 years; 66 % of were males; 23% were African-Americans; 57% patients had extensive stage SCLC at diagnosis. Point mutations were identified in 5 (17%) patients, 2 patients had p53 mutations, 1 each had PI3K, EGFR and Kras mutation. Of the 21 tumors for which gene copy number analysis has been completed, the median number of genes, listed in the Sanger Institute Cancer gene census, that were altered was 135 (range 0-299). Only 1 tumor had no gene copy number alterations. Of the genes that are targets for novel anticancer agents, PI3K (76%) and DDR2 (48%) amplifications were the most frequent alterations. Among the 21 tumors analyzed for both point mutations and gene copy number variations, one or more potentially actionable alterations were identified in 19 (90%) tumors. **Conclusions:** Our analysis indicates that potentially "actionable" genome alterations can be identified in a high proportion of SCLCs by conducting point mutation and gene copy number variation analyses. We plan to initiate a clinical trial with prospective analyses of tumors of SCLC patients to identify "actionable" mutations and assess the clinical benefit of therapy based on these genome alterations.

**7593 General Poster Session (Board #201), Sat, 1:15 PM-5:00 PM**

**Pharmacokinetics (PK) and exposure-response (ER) of rilotumumab (Rmab) in patients (pts) with small-cell lung cancer (SCLC).** *Presenting Author: Yilong Zhang, Amgen, Inc., Thousand Oaks, CA*

**Background:** Rmab is a fully human monoclonal antibody against hepatocyte growth factor that was evaluated as a first-line treatment for extensive-stage SCLC in a phase 1b/2 trial (*J Thorac Oncol*. 2013;8(S2):021.05). That trial did not show meaningful improvements in progression-free survival (PFS) or overall survival (OS). We characterized Rmab PK in pts with SCLC and performed an ER analysis that related PK to tumor size (TS), PFS, and OS. **Methods:** Rmab population PK (PPK) and ER were assessed in 132 pts with SCLC who were randomized 1:1 to receive either Rmab (15 mg/kg) or placebo, with etoposide plus carboplatin/cisplatin every 3 weeks (Q3W). A PPK model was developed using data from phase 1 and earlier phase 2 studies. TS vs time was characterized using a tumor dynamic model, and time to tumor growth (TTG) and TS ratios (the ratios of TS at 6, 9, or 12 weeks to TS at baseline) were derived from this model. The relationships between PFS/OS and baseline pt characteristics, exposure metrics, and tumor response metrics were evaluated using Cox proportional hazards and parametric survival models. Pts were divided into high- and low-exposure groups based on median Rmab trough concentration at steady state (Cminss). Survival analyses were performed with R, and PPK and tumor dynamic analyses were performed with NONMEM. **Results:** Rmab PK was well characterized by a two-compartment PK model. Body weight (WT) affected clearance (CL) and central volume of distribution (Vc): a 10% increase in WT increased CL by 6% and Vc by 7%. Chemotherapy reduced TS, but Rmab did not have an additional effect on TS. OS was best described by a log-logistic distribution. Rmab improved OS relative to placebo in the high-exposure group (Cminss $>$ 155 mg/mL) but not in the low-exposure group (Cminss $\leq$ 155 mg/mL). Univariate analysis suggested that favorable predictive factors of OS included higher Rmab exposure, female sex, and longer TTG. There was no apparent PK-PFS relationship. **Conclusions:** High Rmab exposure was associated with improved OS in this ER analysis, but further studies will be needed to determine whether this association is causative and whether a combination of chemotherapy and Rmab at a dose $>$ 15 mg/kg Q3W leads to improved OS.

**7594 General Poster Session (Board #202), Sat, 1:15 PM-5:00 PM**

**Final results of a phase I study of amrubicin and cyclophosphamide in patients with advanced solid organ malignancies: HOG LUN 07-130.** *Presenting Author: Shadia Ibrahim Jalal, Indiana University School of Medicine, Indianapolis, IN*

**Background:** Relapsed small cell lung cancer (SCLC) has limited treatment options. Anthracyclines and cyclophosphamide have shown synergy in a wide variety of tumors. Amrubicin (AMR) and cyclosphosphamide both have single agent activity in SCLC. This phase I trial evaluated the combination of AMR and cyclophosphamide in refractory solid organ malignancies and in relapsed SCLC. **Methods:** Eligible patients (pts) had refractory solid organ malignancies, PS 0-1, and adequate organ function. The primary endpoint was MTD and dose limiting toxicities (DLTs). Secondary endpoint was to assess response. Pts were enrolled in sequential dose escalation cohorts in a standard 3+3 design. Treatment consisted of cyclophosphamide IV at 500mg/m$^2$ on day 1 with escalating doses of AMR IV on days 1-3 (25-40mg/m$^2$ with increments of 5mg/m$^2$ per cohort).Cycles were repeated every 21 days. **Results:** Thirty six patients (pts) were enrolled on the dose escalation portion with 18 patients with SCLC as the primary diagnosis. Remaining patients had NSCLC, extrathoracic small cell carcinoma or other malignancies. The median number of cycles was 4 (range 1-6). MTD was determined to be dose level 2 (cyclophosphamide 500mg/m$^2$, AMR 30mg/m$^2$) due to grade 4 thrombocytopenia. Incidence of grade 3-4 neutropenia, anemia, thrombocytopenia and febrile neutropenia was 33.3%, 19.4%, 25% and 5.56% respectively. Other grade 3-4 toxicities included nausea, vomiting, hyponatremia, hypokalemia and fatigue. Partial responses were only noted in patients with SCLC or extrathoracic small cell with PR noted in 7 pts, SD in 5 pts and PD in 7 pts. Of the pts achieving PRs on our study, 4 were platinum sensitive, 3 were refractory. The median duration of response was 4 months, median progression free survival was 3.06 months and the median overall survival was 9.1 months. Ten additional pts with relapsed SCLC were treated at the MTD on a compassionate cohort and 9 were evaluable for response. In this cohort SD was noted in 3 pts, PD in 6 pts with median OS of 6 months. **Conclusions:** AMR and cyclophosphamide can be safely combined with activity observed in a heavily pretreated SCLC population. Clinical trial information: NCT00890955.

**7595 General Poster Session (Board #203), Sat, 1:15 PM-5:00 PM**

**A randomized, multicenter phase III study of lobaplatin/etoposide versus cisplatin/etoposide as first-line therapy in patients with extensive-stage small-cell lung cancer and circulating tumor cells (CTCs) as an exploratory biomarker.** *Presenting Author: Ying Cheng, Jilin Provincial Cancer Hospital-(JPCH), Changchun, China*

**Background:** Cisplatin plus etoposide (EP) is conventional regimen to treat small cell lung cancer (SCLC), however the toxicities of cisplatin limited its efficacy. Here, we showed the results of a phase III clinical trial using lobaplatin, a third-generation platinum compounds, in combination with etoposide (EL) in comparison to EP for extensive SCLC (ES-SCLC). **Methods:** A total 234 Chinese patients with newly diagnosed ES-SCLC were randomized into two groups: (1) the EL Group (n=122): 6 cycles of lobaplatin (30 mg/m$^2$/day on day 1) and etoposide (100 mg/m$^2$/day on days 1-3, every 21 days) and (2) EP Group (n=112): 6 cycles of cisplatin (80 mg/m$^2$/day on day 1) and etoposide. The primary end point was progression-free survival (PFS); secondary end points included toxicity, QOL and overall survival (OS). Eighty five ES-SCLC patients were tested for circulating tumor cells (CTCs) (CELLSEARCHÒ) prior to treatment, at 2 cycles after therapy and disease progression. **Results:** For EL and EP group, the median PFS and the disease control rate (DCR) was 5.37 versus 5.99 months ($P$=0.1638), and 82.64% versus 83.78% ($P$=0.8618), respectively. In terms of toxicities, the incidence of nephrotoxicity in the EL group was significantly lower than that in the EP group (2.48% vs 11.71%, $P$=0.0079), as well as incidences of nausea and vomiting (22.31% vs 36.04%, $P$=0.0292, and 14.05% vs 25.23%, P=0.0453, respectively). At baseline as well as 2 cycles after chemotherapy, the median OS was significantly lower in patients with $\geq$5 CTCs than those with $<$5 CTCs (baseline: 23 months vs $>$26 months, $P<0.0028$ and 2 cycles: 23 months vs $>$26 months, $P<0.0124$). **Conclusions:** EL regimen is not inferiority to EP regimen in terms of PFS. The tolerance and QOL with EL regimen are better than that with EP regimen. Thus EL regimen provides an alternatively new choice for first-line ES-SCLC treatment in China. The study is the first worldwidely prospective clinical study using CTCs as a biomarker monitoring SCLC therapeutic effects. Clinical trial information: ChiCTR-TRC-10001047.

**7596 General Poster Session (Board #204), Sat, 1:15 PM-5:00 PM**

**Comparison of cisplatin- versus carboplatin-based concurrent chemoradiation for limited-stage small cell lung cancer using SEER-Medicare data.** *Presenting Author: Ellen Kim, Case Western Reserve University School of Medicine, Cleveland, OH*

**Background:** Small cell lung cancer (SCLC) accounts for 14% of lung cancers. Current standard therapy for limited stage (AJCC stages I-III) SCLC is concurrent chemoradiation (CCRT) with cisplatin/etoposide but carboplatin/etoposide is often used for patients with poor tolerance or contraindication to cisplatin. The aim of this retrospective cohort study is to compare survival of cisplatin (cis) and carboplatin (carb) based CCRT in limited stage SCLC. **Methods:** Cases were selected from the population-based SEER-Medicare lung cancer database if the patient's first cancer was limited stage SCLC diagnosed at age 66-80 in 1992-2007. CCRT was defined with radiation starting within 60 days of the start of the first cycle of cis/carb. Study endpoints were overall survival (OS, time from diagnosis until death) and cause specific survival (CSS, time from diagnosis until death from lung cancer). SAS v9.3 was used to select cases, and R v3.0.2 was used to calculate Kaplan-Meier survival analysis and log-rank tests for significance. **Results:** Study sample meeting inclusion criteria included 1603 patients, with median age 72 (66-81) and gender ratio 1.1. Majority were stage III (n=1342, 84%), with some stage I (11%) and II (5%). Cis was used in 617 cases (38%) while carb was used in 986 cases (62%). On average, cis group was younger ($p<0.001$). Median (OS, CSS) were (1.20, 1.34) and (1.17, 1.33) years for cis and carb groups, respectively. Five-year (OS, CSS) for cis and carb were (13.7%, 24.4%) and (11.1%, 20.5%), respectively. There was no statistically significant difference in OS ($p=0.163$) or CSS ($p=0.683$) between the groups. **Conclusions:** Cis vs carb based CCRT had comparable OS and CSS, even though cis group was younger. This suggests that if carb is better tolerated, it should be preferred for limited stage SCLC, though randomized trials are needed.

**7597 General Poster Session (Board #205), Sat, 1:15 PM-5:00 PM**

**Clinical outcomes of patients with recurrent small cell lung cancer receiving third-line chemotherapy.** *Presenting Author: Koichi Saruwatari, National Cancer Center Hospital East, Kashiwa, Japan*

**Background:** Patients with small-cell lung cancer (SCLC) that progress after first-line therapy have a dismal prognosis. Second-line chemotherapy is effective for some patients, but there is little evidence for third-line chemotherapy. The purpose of this study is to evaluate the efficacy of third-line chemotherapy and clarify prognostic factors for patients receiving it. **Methods:** Between November 2001 and October 2011, 202 of 648 patients who were consecutively diagnosed with SCLC at the National Cancer Center Hospital East received third-line chemotherapy. We performed multivariate Cox regression analysis to identify the prognostic factors of overall survival after third-line chemotherapy (OS). **Results:** At the start of third-line chemotherapy, median age was 66 years (range 38-83), male/ female: 168/34, ECOG performance status (PS) 0/1/2/3: 22/122/49/9, stage at diagnosis LD/ED: 88/114, response to second-line chemotherapy CR/PR/SD/PD: 3/95/56/48, and median progression free survival after second-line chemotherapy (PFS2) : 4.4 months. 155 and 47 patients received single-agent and platinum-based regimen, respectively. Overall response rate was 17.8%, which was significantly associated with response (CR/PR) to second-line chemotherapy (23.5% vs. 12.5%, $p=0.042$) and PFS2 (25.6% vs. 7.4%, $p=0.024$). Median PFS and OS from third-line chemotherapy were 2.7 months and 5.1 months, respectively. Multivariate Cox analysis identified PS 0-1 (hazard ratio [HR], 0.38; 95% confidence interval [CI], 0.27-0.55; $p < 0.001$) and PFS2 $\geq$5 months (HR, 0.59; 95%CI, 0.42-0.81; $p=0.001$) were the independent prognostic factors indicating better OS. An optimal threshold of 5 months of PFS2 ($\geq$5/<5 months: 82/120) was selected based on the concordance index adjusted by PS. **Conclusions:** PS 0-1 and PFS2 $\geq$5 months were associated with favorable prognosis among SCLC patients receiving third-line chemotherapy. These two factors would be worth considering as stratification factors when conducting future clinical trials.

**7598 General Poster Session (Board #206), Sat, 1:15 PM-5:00 PM**

**Limited-stage small cell lung cancer treated with cisplatin/irinotecan and concurrent thoracic radiation therapy.** *Presenting Author: Salini Sathya Naidu, Leo Jenkins Cancer Center, Brody School of Medicine at East Carolina University, Greenville, NC*

**Background:** Concurrent chemotherapy and radiation therapy (CRT) is a curative option for limited-stage small cell lung cancer (SCLC). The standard of care in the United States is concurrent etoposide-platinum CRT. In Asia, CRT with irinotecan and cisplatin has been shown to be an effective and tolerable regimen. (Han et al J Clin Oncol 2005 and Jeong et al Lung Cancer 2006) Irinotecan is a potent radiosensitizing agent (Tamura et al Jpn J Cancer Res 1997). Patients with limited-stage SCLC treated with irinotecan-platinum concurrent CRT were identified from our institutional thoracic oncology program database. **Methods:** 36 patients with limited stage SCLC from 2006-2013 were identified from our database. Ages 49-85. 17 females and 27 males. All patients were treated with cisplatin 30mg/m2 and irinotecan 65mg/m2 on day 1 and 8 every 21 days for a total of 4 cycles, along with concurrent radiation therapy commensurate with cycle 2. 29 patients received BID concurrent radiation therapy (45Gy), and 7 patients received daily dosing (54Gy). 25 patients received prophylactic cranial irradiation. Median follow-up two years; 22 patients followed for over 3 years. **Results:** Overall radiographic response rate 67% (18 CR, 8 PR). Median overall survival 19 months. 1 year survival 60%: 2 year survival 44%; 3 year survival 30%. No symptomatic pneumonitis with 13% of patients developing symptomatic esophagitis. **Conclusions:** Irinotecan and cisplatin with concurrent CRT achieved a 30% 3-year overall survival in an American patient population with limited stage SCLC.

**7599 General Poster Session (Board #207), Sat, 1:15 PM-5:00 PM**

**Trends in small cell lung cancer (SCLC) survival: Predictors and impact of systemic therapy.** *Presenting Author: Madhusmita Behera, The Winship Cancer Institute of Emory University, Atlanta, GA*

**Background**: The last 2 decades witnessed limited therapeutic advances in SCLC management. We evaluated trends in the use of systemic therapies and the impact on outcome in the US. **Methods**: We employed data from the SEER-MEDICARE database for SCLC patients diagnosed between 1985 and 2005. The 1985-1990 period served as a baseline for a temporal survival analysis conducted at 5-year intervals (1985-1990, 1991-1995, 1996-2000 & 2001-2005). Predictors of chemotherapy use were identified by logistic regression model with a backward variable selection method. Cox proportional hazards models were employed to estimate the effect of chemotherapy on survival by time of diagnosis with adjustment for significant predictors of chemotherapy use. **Results**: There were 47,351 eligible patients; M/F (52%/48%); median age (71 years); ethnicity (Whites-87%; Blacks- 7%; Hispanic: <0.4%; Asians: 1.4%; Others-2.8%); median OS overall, with and without chemotherapy (7.2, 9.6 and 3.6 months). Rate of chemotherapy use was very low but showed a significant increase over time (38, 55, 50, 53%, $p<0.001$). Females (51%), Asians (53%) and rural residents (60%) were more likely to receive chemotherapy. Race, comorbidity, year, age and location at diagnosis significantly predicted chemotherapy use. Linear trend analyses across the defined 5-year intervals showed improved survival in patients treated with chemotherapy over untreated patients (HR: 0.70; 0.66, 0.67, 0.64; $p<0.001$) after adjusting for significant predictors of chemotherapy use. While survival did not significantly change over time among patients treated with chemotherapy (HR: 1.0, 1.014, 1.035,1.033; $p=0.337$) it became worse in untreated patients (HR: 1.0, 1.047, 1.057, 1.071; $p=0.002$). Treatment with >1 type of chemotherapy was associated with improved survival (HR: 1.315; 0.941; 0.858; 0.827; $p<0.001$). Analysis in propensity score matched patients showed no survival difference between carboplatin and cisplatin (HR: 0.906 (0.761-1.078); $p=0.267$) or platinum doublet and CAV regimen (HR: 0.929 (0.847-1.019); $p=0.118$). **Conclusions**: Chemotherapy use was associated with an incremental survival benefit in MEDICARE-eligible SCLC patients treated in the real-world setting.

**7600 General Poster Session (Board #208), Sat, 1:15 PM-5:00 PM**

**Final outcome results of platinum-sensitive small cell lung cancer (SCLC) patients treated with platinum-based chemotherapy rechallenge: A multi-institutional retrospective analysis.** *Presenting Author: Giovenzio Genestreti, Medical Oncology Department, Bellaria-Maggiore Hospital, Azienda USL of Bologna - IRCCS Institute of Neurological Sciences, Bologna, Italy*

**Background:** Rechallenge might be used as rescue therapy in progressing platinum-sensitiveSmall Cell Lung Cancer (SCLC). This international multicenter retrospective analysis evaluates the clinical outcomes of SCLC patients treated with this strategy. **Methods:** We retrospectively collect each institutional data warehouse of platinum-sensitive SCLC treated with platinum/etoposide rechallenge. Primary endpoint was overall survival (OS) from diagnosis and from the rechallenge of chemotherapy (PPS). Secondary endpoints were response rate (RR) and Progression-Free Survival2 (PFS2) yielded by rechallenge. **Results:** We reviewed 2000 SCLC patients from 9 institutions. One hundred twelve (5.6%) with sensitive SCLC were treated with first-line platinum/etoposide rechallenge. There were 72 (64%) males and 40 (36%) females with a median age of 64 years (range 40–83). At diagnosis, 49 (44%) patients had limited disease (LD) whereas 63 (56%) had extensive disease (ED). ECOG Performance Score (PS) was $<1$ and $>1$ in 87% and 13% of patients, respectively. First-line chemotherapy yielded: 14 % complete response (CR), 84% partial response (PR) and 2% stable disease (SD). Mean number of cycles of rechallenging chemotherapy was 3.6 (range 1-7). Carboplatin and cisplatin were administered in 96 (86%) and 16 (14%) of the patients, respectively. There were 3% CR, 42% PR, 19% SD, 27% progressive disease and 9% not evaluable yielding a median PFS2 of 5.5 months (95% CI 4.4-6.3). Median OS and PPS were 21.4 months (95% CI 19.8-24.1) and 7.9 months (95% CI 6.9-9.7), respectively. Forty (36%) patients received further chemotherapy. At the multivariate analysis stage at diagnosis, PS and platinum (carboplatin or cisplatin) used in rechallenge were not prognostic factors, while time from diagnosis to first progression disease (PFS1) $>$ 150 days ($p<0.0001$) was. **Conclusions:** Rechallenge may be an efficacy option in patients with platinum sensitive disease with a PFS1 $>$ 150 days.

**7601 General Poster Session (Board #209), Sat, 1:15 PM-5:00 PM**

**Phase 1b of anticancer stem cell antibody OMP-59R5 (anti-Notch2/3) in combination with etoposide and cisplatin (EP) in patients (pts) with untreated extensive-stage small-cell lung cancer (ED-SCLC).** *Presenting Author: David R. Spigel, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN*

**Background:** The Notch pathway plays a central role in embryonic development, the regulation of stem and progenitor cells, and is implicated centrally in many human cancers, including SCLC. OMP-59R5, a fully human IgG2 antibody, inhibits signaling of Notch2 and 3 receptors. Anti-tumor activity was noted in 7 of 8 pt-derived SCLC xenografts expressing Notch 2 and 3 with OMP-59R5 treatment. The maximum tolerated dose (MTD) of single agent OMP-59R5 was 7.5mg/kg IV every 3 weeks (Smith, EORTC 2012); the main dose-limiting toxicity (DLT) was Grade 3 diarrhea. This study is to determine the MTD, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of OMP-59R5 in combination with EP in ED-SCLC. **Methods:** Cohorts of 3 to 6 pts were treated at each dose level of OMP-59R5. OMP-59R5 was given IV on Day 1 of each 21 day cycle along with etoposide 100 mg/m$^2$ on Days 1, 2, and 3 and cisplatin 80 mg/m$^2$ on Day 1. After 6 cycles, pts continued OMP-59R5 alone every 21 days in the absence of disease progression or unacceptable toxicities. **Results:** By Jan 17, 2014, 8 pts were treated. No DLTs have occurred. Frequently reported (>25%) adverse events (all grades, G) regardless of relationship were: fatigue(62.5%), nausea(62.5%), anemia(50%), diarrhea(50%), peripheral edema(50%), alopecia(37.5%), blood creatinine increase(37.5%), decreased appetite(37.5%), neutropenia(37.5%), and weight loss(37.5%); Of these, fatigue(50%), anemia(37.5%), diarrhea(37.5%), nausea(37.5%), alopecia(25%), decreased appetite(25%), and weight loss(25%) were considered related to OMP-59R5-treatment. The events were mostly G 1 or 2, and managed with supportive care. Additional data are below (see Table). **Conclusions:** OMP-59R5 with EP is well tolerated. The MTD has not been reached. Encouraging anti-tumor activity is observed. Updated Safety, PK/PD, and efficacy data will be presented. Clinical trial information: NCT01859741.

| OMP-59R5 Dose (mg/kg) | | 5 (n=3) | 7.5 (n=3) | 10 (n=2) |
|---|---|---|---|---|
| Etoposide (mg/m$^2$) | | | 100 | |
| Cisplatin (mg/m$^2$) | | | 80 | |
| DLT evaluable | | 3 | 3 | 2 |
| incidence | | - | - | - |
| RECIST 1.1 evaluable | | 3 | 3 | -- |
| Best response | PR | 3 | - | 2 |
| | SD | - | 3 | - |
| | PD | - | - | - |
| mPFS (days) | | 175 | - | - |
| Pts still on treatment | | 1 | 3 | 2 |

**7602 General Poster Session (Board #210), Sat, 1:15 PM-5:00 PM**

**Phase I trial of the hedgehog (Hh) inhibitor, LDE225, in combination with etoposide and cisplatin (EP) for initial treatment of extensive stage small cell lung cancer (ES-SCLC).** *Presenting Author: Maria Catherine Pietanza, Memorial Sloan-Kettering Cancer Center, New York, NY*

**Background:** SCLC relies on the Hh developmental pathway for tumor initiation and progression. Pharmacologic blockade with Hh inhibitors blocks these processes. We performed a phase I study to determine the maximum tolerated dose (MTD) of LDE225, a selective, oral smoothened antagonist, in combination with EP in newly diagnosed ES-SCLC patients. **Methods:** Untreated patients with measurable disease, Karnofsky performance status ≥70, and asymptomatic brain metastases were eligible. All patients received 4 to 6 21-day cycles of EP (E, 120mg/m2 D1-3; P, 60mg/m2 D1) with daily LDE225. Patients with response or stable disease were continued on LDE225 until disease progression or unacceptable toxicity. Prophylactic cranial irradiation was performed after EP + LDE225, and LDE225 was held during that therapy. Two dose levels of LDE225 were planned: 400mg and 800mg daily, with 200mg daily de-escalation if necessary. Circulating tumor cells were quantified by Veridex Cell Search Platform at baseline and with disease evaluation. **Results:** 14 patients with ES-SCLC were enrolled (median age 56 (range, 46-68); 57% male). Patients were treated as follows: 200mg (n=2); 400mg (n=7); 800mg (n=5). The first 3 patients were enrolled at 400mg, and 2 experienced a dose limiting toxicity (DLT) (nausea, n=1; febrile neutropenia (FN), n=1), leading to dose de-escalation (200mg). The definition of DLT was changed to exclude FN. The 400mg dose level was expanded with 4 additional patients without any further DLTs. 800mg has been established as the recommended phase II dose in combination with EP. Toxicity led to removal of one patient from study (grade 3 colitis and acute kidney injury). Grade 3 toxicities included: anemia (n=1), thrombocytopenia (n=1), CPK elevation (n=1), fatigue (n=2), and fever (n=1). 3 patients had grade 4 neutropenia. One patient died of an unrelated myocardial infarction. 5 patients actively are being treated. Partial responses were confirmed in 50% (7/14; 95% CI: 27-73%); 3 received maintenance LDE225 ≥4 months. **Conclusions:** LDE225 800mg daily was the MTD when administered with EP. The phase II dose expansion of this regimen is underway. Clinical trial information: NCT01579929.

**7603 General Poster Session (Board #211), Sat, 1:15 PM-5:00 PM**

**Clinical characteristics and outcomes for patients with thymic carcinoma: Evaluation of Masaoka staging.** *Presenting Author: Anna Maria Litvak, Memorial Sloan Kettering Cancer Center, New York City, NY*

**Background:** Thymic carcinomas (TC) are rare cancers with limited data regarding outcomes, particularly for those patients (pts) with advanced disease. **Methods:** We identified pts with TC diagnosed between 1993-2012. Pt characteristics, recurrence free survival (RFS) from date of resection, and overall survival (OS) from date of diagnosis were analyzed. Pts were followed until death or last follow up. Time-to-event outcomes were determined using the Kaplan-Meier method. **Results:** 121 pts with TC were identified with 7 pts (6%) with Masaoka stage I, 13 (11%) with stage II, 25 (21%) with stage III, 13 (11%) with stage IVA, 61 (51%) with stage IVB, and 2 (2%) with unclear staging. Higher Masaoka stage was associated with worse OS and RFS (5-yr OS of 100%, 81%, 51%, 24%, and 17% for stage I, II, III, IV respectively, $p<0.001$ and 5-yr RFS of 80%, 28%, and 7% for stage I/II, III, and IV respectively, $p<0.001$). Stage IVB pts with lymph node involvement had a better 5-year OS as compared to stage IVB pts with distant metastasis (24% vs. 7%, $p=0.025$). Of the 61 pts with stage IVB disease, 22/29 pts (76%) with lymph node involvement underwent curative intent resection vs. 3/32 pts (9%) with visceral metastasis. Of the 29 stage IVB pts with lymph node involvement treated with surgery, chemotherapy, and radiation, 3 (10%) are currently free of disease with long-term follow-up (range: 3.4 years to 6.8 years). **Conclusions:** This is the largest review of the clinical features of pts with TC in North America. Stage IVB pts with lymph node positive disease have significantly better OS as compared to Stage IVB pts with distant metastasis. Stage IVB pts with lymph node positive disease treated with multi-modality therapies can have long term recurrence free survival. If validated, these data would support a revised Masaoka staging system with subclassification of stage IVB disease into two groups.

**7604 General Poster Session (Board #212), Sat, 1:15 PM-5:00 PM**

**Outcomes of thymic neoplasms after the 1999 WHO classification.** *Presenting Author: Yousif Yonan, Penn State College of Medicine, Hershey, PA*

**Background:** In 1999 the World Health Organization (WHO) published a histologic sub-typing system for thymoma that divided it in to six classes, which included one category for thymic carcinoma (WHO C, Group 1) and five categories of invasive thymoma (WHO A, AB, B1, B2 and B3, Group 2). **Methods:** The SEER database was used to retrospectively identify thymic neoplasms from 2000-2010 using the six-tier classification system. Only those patients having thymic neoplasia as their only cancer and undergoing complete ($R_0$) resection were included in the analysis. Overall survival (OS) and thymic-specific survival (TSS) were evaluated by Kaplan-Meier methods. Multivariate analysis(MVA) was performed including group, age, race, Masaoka stage, gender, and adjuvant radiation therapy as key variables. **Results:** 505 thymic neoplasms were identified including 96 (19%) in group 1 and 409 (81%) in group 2. Median follow-up was 38 months. For patients with early Stage(I/II) group 1 and group 2 tumors, OS at 2, 3, and 5 years was 90.5, 90.5, 67.9% for Group 1 and 98.2, 95.8, 95.8 for Group 2 respectively. Group 1 classication ($p<0.0001$, HR 1.82), advancing age ($p=0.003$, HR 1.03) and increasing stage ($p=0.04$, HR 1.37) were significant predictors of worse OS. TSS was excellent in the overall group with thymus-related death listed as cause of death in only 35 (6.9%) of patients. Any Group 1 and Stage III/IV Group 2 tumors had significantly worse TSS. Histologic sub-typing within Group 2 was not associated with OS, TSS or high-risk of lymph node involvement (all<5%). In early-stage Group 1 patients, 15/34 (44%) did not have a nodal exam and 6/19 (32%) had positive nodes. **Conclusions:** Early-stage Group 2 patients have an excellent OS and TSS may not benefit from adjuvant therapy. Trials of adjuvant therapy should be considered for advanced-stage Group 2 patients and all Group 1 patients. Thymic carcinomas may be understaged due to lack of lymph node examination and the high percentage with involved nodes.

**7605 General Poster Session (Board #213), Sat, 1:15 PM-5:00 PM**

**National multidisciplinary tumor board (MTB): Report of the first 526 questions raised within RYTHMIC, the network for thymic malignancies in France.** *Presenting Author: Benjamin Besse, Gustave Roussy, Villejuif, France*

**Background:** RYTHMIC (Réseau tumeurs THYMiques et Cancer) is a nationwide network for thymic malignancies, which was funded in 2012 by the French National Cancer Institute. The objectives of the network include a territorial coverage by regional expert centers, elaboration of recommendations, dissemination of knowledge and promotion of collaborative research. All patients diagnosed with thymic malignancy in France have to be discussed on a real-time basis at a reference web-based national MTB or regional MTB. Patient's data from the MTB were prospectively entered in a database. **Methods:** We report the patient's and tumor's characteristics and treatment modalities of the patients included during the first 2 years of MTB. Questions raised during the MTB were reviewed. **Results:** From January to December 2013, 383 patients were included in the RYTHMIC database. There were 197 (51%) men and 186 (49%) women. Among 304 cases, histology was thymoma for 198 (65%) patients (16 (5%) type A, 31 (10%) type AB, 38 (12%) type B1, 46 (15%) type B2, 35 (12%) type B3, 38 (12%) mixed type, 4 unknown), and thymic carcinoma for 34 (11%) patients, 7 (2%) carcinoïds; other histologies were diagnosed for 65 (21%) patients. Among 206 cases, Masaoka-Koga stage was I, IIA, IIB, III, IVA, and IVB in 46 (22%), 33 (16%), 28 (13%), 37 (18%), 44 (21%), and 18 (9%) patients, respectively. 71 (18%) patients presented with autoimmune disorder, consisting of myasthenia gravis in 60% of the cases. Surgery was performed for 229 patients, mostly using a median sternotomy approach (52% of cases), video-assisted surgery accounted for 9% of the cases. Among the 526 questions addressed during the MTB, the most frequent were the indication of post-operative radiotherapy (29%), recurrence management (18%) and indication of surgery of a mediastinal lesion (17%). **Conclusions:** The RYTHMIC prospective cohort demonstrates the feasibility of a national MTB for thymic malignancies. It provides with a comprehensive tool to monitor dedicated actions to improve the management of patients in the future, increase the quality-of-care (mostly regarding locoregional treatment), and screen patients for future clinical trials.

**7606 General Poster Session (Board #214), Sat, 1:15 PM-5:00 PM**

**Programmed death receptor ligand-1 (PD-L1) expression in a thymoma (T) tissue microarray (TMA).** *Presenting Author: Sukhmani Kaur Padda, Department of Medicine, Division of Oncology, Stanford Cancer Institute/ Stanford University School of Medicine, Stanford, CA*

**Background:** Thymomas (T) contain lymphocytic infiltrates, and as they arise from an immune organ confer a unique tumor microenvironment. Tumor expression of the immune checkpoint ligand, PD-L1, is a known mechanism for immune evasion. Here, we evaluated T expression of PD-L1. **Methods:** A TMA was constructed from 69 Ts, with 15 thymic controls (C) (including 8 paired normal thymuses adjacent to tumor), at Stanford University. The pathologist was blinded to clinical data and sample identity. The TMA was stained with a monoclonal antibody (clone 15, Sino Biological) to human PD-L1 using human placenta for staining titration. To distinguish PD-L1 expression on epithelial cells from that on lymphocytes, a CK5/6 cytokeratin stain was used. An intensity scale of 0, 1, 2, and 3 representing no, equivocal, weak, and intermediate-strong staining, respectively, was used. Positive PD-L1 expression was defined as ≥2 staining intensity on thymic epithelial cells. A two-sample Wilcoxon rank sum test was used to compare the average intensity between Ts and Cs, and a Kruskal-Wallis rank test was used to compare the average intensity between type A, B, and AB histologies. A two-sided p-value ≤0.05 was considered statistically significant. **Results:** Characteristics for 69 patients: 36M/33F; mean age 54 years (2-86); WHO histology: 7 A, 17 AB, 8 B unspecified, 9 B1, 18 B2, 4 B3, 3 C, and 3 NOS. There were no PD-L1 intensity scores of 0 or 1 in either Ts or Cs. The majority of lymphocytic infiltrates did not stain for PD-L1. Ts had a higher frequency of more intense PD-L1 staining compared to Cs [T: 22.4% (2)/77.6% (3) v. C: 58.1% (2)/41.9% (3); $p=0.007$]. PD-L1 staining intensity also varied between histologic subtypes: B>AB>A ($p=0.0002$). The difference between A v. B was the most striking [A: 66.7% (2)/33.3% (3) v. B: 9.2% (2)/90.8% (3); $p=0.0001$]. **Conclusions:** To our knowledge, Ts have not been previously examined for PD-L1 expression. Although both Ts and Cs expressed PD-L1, Ts generally stained more intensely than Cs. There was also higher PD-L1 staining intensity in lymphocyte dominant histologies (i.e. type B). This finding is highly translatable as several PD-1 and PD-L1 inhibitors are in clinical trials.

**7607 General Poster Session (Board #215), Sat, 1:15 PM-5:00 PM**

**Mesothelin expression in thymic epithelial tumors (TETs).** *Presenting Author: Yuanbin Chen, National Cancer Institute at the National Institutes of Health, Bethesda, MD*

**Background:** Mesothelin (meso) is overexpressed in many solid tumors and has been used as a target for anticancer therapy. Limited data is available on meso expression in TETs and its clinical correlates. Standard treatments have limited efficacy for patients with advanced TETs, especially thymic carcinoma (TC) after failure of platinum-based chemotherapy. There is an urgent need to identify novel therapeutic targets. In view of early results demonstrating benefit in therapeutic targeting of meso, we characterized meso expression in TETs. **Methods:** Patients with histologically confirmed thymoma (T) or TC and available tumor tissue who were enrolled in clinical trials at the National Cancer Institute between December 2007 and December 2013 were included. Meso expression was assessed by immunohistochemistry (IHC) using monoclonal antibody 5B2 (Novocastra/Leica, Bannockburn, IL) by a pathologist who was blinded to histological subcategory (T vs. TC) and clinical outcome. IHC staining of > 50% was labeled as positive and ≤ 50% was considered negative. Associations between meso expression and patient characteristics were assessed. **Results:** 71 cases (42 TC; 29 T consisting of 3 WHO subtype AB, 2 B1, 13 B2 and 11 B3) were included in this series. Meso expression localized to tumor cell membrane was observed in 19 (45%) TC and 1 (3%) T. Median age and gender distribution of meso-positive vs. meso-negative TC was: 55 (21-73) vs. 50 (20-74) years and 11M/8F vs. 10M/5F respectively. Meso-expressing TC included 12 of 16 (75%) poorly differentiated carcinomas, 3 of 11 (27%) squamous cell carcinomas, 1 of 2 (50%) basaloid cancers and 0 of 8 neuroendocrine tumors (including atypical carcinoids). Median overall survival was significantly higher in meso-positive TC compared to meso-negative TC (not reached vs. 48 months; $p=0.03$). Extra-thoracic metastases were present in 13 of 19 (68%) meso-positive TC and 17 of 23 (74%) meso-negative TC. **Conclusions:** This is the largest series of meso expression in TC. Meso expression was detected in 45% of TC and associated with a significantly higher overall survival. Further studies are needed to assess the role of meso as a potential therapeutic target in TC.

**TPS7608 General Poster Session (Board #216A), Sat, 1:15 PM-5:00 PM**

**START2: Tecemotide in unresectable stage III NSCLC after first-line concurrent chemoradiotherapy.** *Presenting Author: Suresh S. Ramalingam, Emory University Winship Cancer Institute, Atlanta, GA*

**Background:** Tecemotide is an antigen-specific cancer immunotherapy targeting the mucinous glycoprotein MUC1, which is overexpressed and aberrantly glycosylated in a number of cancers including non-small cell lung cancer (NSCLC). The START study evaluated tecemotide after first-line concurrent or sequential chemoradiotherapy (CRT) for unresectable stage III NSCLC (Butts et al, *Lancet Oncol* 2013). Though the primary endpoint was not achieved for the overall patient population, the predefined subset of 806 patients treated with concurrent CRT showed improved overall survival (OS; adjusted HR 0.78, 95% CI 0.64–0.95; p=0.016). The pivotal phase III study START2 intends to confirm these results in patients having had initial concurrent CRT. **Methods:** START2 is a global, randomized, double-blind placebo-controlled phase III trial investigating tecemotide in patients with unresectable stage III NSCLC with stable disease or objective response after first-line concurrent CRT completed 4–12 weeks before randomization. Concurrent CRT is defined as ≥2 cycles of platinum-based chemotherapy that overlaps with radiotherapy (total tumor dose ≥60 Gy, single fraction dose ≥1.8 Gy); any other therapy for NSCLC constitutes an exclusion criterion. Patients will be stratified by response to CRT (stable disease or objective response) and region (North America and Australia; Western Europe; Rest of World), and randomized (1:1) to tecemotide (806 $\mu$g lipopeptide) or placebo. One low dose of i.v. cyclophosphamide (300 mg/m$^2$) or saline will be given 3 days prior to the first dose of tecemotide or placebo, respectively. Eight weekly subcutaneous injections will be given initially, followed by 6-weekly injections until disease progression or discontinuation. The primary endpoint is OS time. Secondary endpoints are: time to symptom progression (Lung Cancer Symptom Scale), progression-free survival, time to progression, and safety. Approximately 1002 patients will be enrolled. Sample size was calculated for a hazard ratio of 0.77 corresponding to an increase in median OS from 20 to 26 months in the placebo/tecemotide arm, respectively, a power of 90%, and 1-sided significance level of 2.5%. Clinical trial information: NCT02049151.

**TPS7609^ General Poster Session (Board #216B), Sat, 1:15 PM-5:00 PM**

**Randomized, double-blind, placebo-controlled study of tremelimumab for second- and third-line treatment of unresectable pleural or peritoneal mesothelioma.** *Presenting Author: Michele Maio, University Hospital of Siena, Siena, Italy*

**Background**: Mesothelioma is an uncommon cancer principally caused by asbestos exposure. After 1st-line pemetrexed/platinum, there are no approved or active agents. Novel approaches are clearly needed. Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) is expressed upon T-cell activation, modulating and eventually inhibiting the T-cell immune response. Tremelimumab is a fully human anti-CTLA-4 antibody that has been investigated in more than 1000 patients (pts) with various tumor types. A single-center, single-arm phase 2 trial of tremelimumab in 29 mesothelioma pts who progressed on 1 prior line of platinum-based therapy demonstrated encouraging activity, including durable partial responses lasting 6 and 18 mos, disease control in 31% of pts, median overall survival (OS) of 10.7 mos, and 1- and 2-y survival rates of 48% and 37%, respectively (Maio, *Lancet Oncol* 2013). **Methods**: This multicenter, international, phase 2b, randomized, double-blind, placebo-controlled study (NCT01843374) enrolls pts with unresectable pleural or peritoneal mesothelioma who progressed after 1–2 lines of treatment that must have included a prior anti-folate-platinum-based regimen. Pts, stratified by EORTC status (low vs. high risk), line of therapy (2nd vs. 3rd), and anatomical site (pleural vs. peritoneal) are randomized 2:1 to tremelimumab or placebo. The primary endpoint is OS; secondary efficacy end points include OS rate at 18 mos, patient-reported outcomes, disease control rate (DCR), progression-free survival (PFS), overall response rate (ORR), and duration of response, based on modified RECIST criteria for pleural mesothelioma and RECIST criteria v1.1 for peritoneal mesothelioma. Exploratory objectives include clinical outcomes (DCR, PFS, ORR, and duration of response) based on immune-related response criteria; health-related quality of life, disease-related symptoms, pain, and health status in pts with durable clinical activity; and biomarkers (cellular, protein, and nucleic acid) and their association with tremelimumab treatment and clinical outcome. Recruitment is ongoing to a total of 564 pts at approximately180 centers globally. Clinical trial information: NCT01843374.

**TPS7610 General Poster Session (Board #217A), Sat, 1:15 PM-5:00 PM**

**Phase I-Ib trial of tivantinib in combination with carboplatin and pemetrexed as first-line treatment in patients (pts) with advanced nonsquamous NSCLC or malignant pleural mesothelioma (MPM).** *Presenting Author: Paolo A. Zucali, Humanitas Cancer Center, Rozzano, Italy*

**Background:** Dysregulation of MET signalling has been reported as a key event in several malignancies and has been identified as a promising therapeutic target. Strong preclinical data on MPM and NSCLC showed that MET inhibition blocks tumor cell growth and migration (Jagadeeswaran et al, Cancer Res 2006; MA et al, Cancer Res 2005). Tivantinib (T) is a selective non-ATP competitive oral inhibitor of MET receptor. In a randomized phase III trial, the combination of T plus erlotinib improved overall survival in a subset of pts with non-squamous NSCLC and high MET expression (Scagliotti G, ESMO/ECCO 2013 abst. n°:3410). Adding T to first-line chemotherapy (CT) may improve efficacy. **Methods:** This Phase I-Ib study is designed to assess the maximum tolerated dose (MTD), pharmacokinetics, pharmacodynamics and preliminary anti-tumor activity of escalating doses of T in combination with fixed doses of carboplatin (AUC 5 i.v. d1-q21) and pemetrexed (500 mg/m$^2$ i.v. d1-q21) as first line treatment for pts with advanced MPM or non-squamous NSCLC. Eligible pts must be CT naïve with ECOG Performance Status <2 and adequate bone marrow, liver and kidney functions. Sequential cohorts of 3 pts per dose level are recruited according to a standard 3 + 3 dose-escalation design starting from level 0 (T 240 mg BID). In case of DLTs in the first 3 pts, a dose level -1 (T 120 mg BID) will be investigated; in absence of DLTs, dose escalation will continue at dose level +1 (T 360 mg BID). The MTD is defined as the highest dose level at which no more than 1 of 6 pts experiences a DLT during the first cycle. If the frequency of DLTs encountered at dose-level +1 will not fulfil the MTD definition it will be accepted as the recommended dose for phase II trials. Additional pts (in order to reach 13 pts with MPM and 18 with NSCLC) will be enrolled at the MTD in an expansion cohort, to evaluate the preliminary anti-tumor activity in terms of 3-month PFS% for MPM pts and 5-month PFS% for NSCLC pts. Enrollment has begun in October 2013. The first dose level has been completed without DLTs and the first pt at dose level + 1 started treatment in January 2014. Clinical trial information: NCT02049060.

**TPS7611 General Poster Session (Board #217B), Sat, 1:15 PM-5:00 PM**

**COMMAND: A phase II randomized, double-blind, placebo-controlled, multicenter study of defactinib as maintenance therapy in subjects with malignant pleural mesothelioma that has not progressed on at least four cycles of pemetrexed/platinum therapy.** *Presenting Author: Dean Anthony Fennell, University of Leicester, Leicester, United Kingdom*

**Background:** Malignant pleural mesothelioma (MPM) is an aggressive tumor in the pleural lining of the lung usually caused by asbestos exposure. Median OS following frontline chemotherapy with pemetrexed/cisplatin (pem/cis) is ~12 months. There is no established second line therapy. 40-50% of MPM tumors exhibit disruption of the NF2 tumor suppressor gene by mutation and/or deletion resulting in lack of expression of functional merlin protein. Mesothelioma cell lines that lack merlin are more sensitive to focal adhesion kinase (FAK) inhibitors than those with wild type merlin. Furthermore, pem/cis enrich cancer stem cells (CSCs) in tumors, while FAK inhibitors have been found to decrease CSCs in mesothelioma models. Given the sensitivity of mesothelioma cells lacking merlin and the effect on CSCs, the use of a FAK inhibitor in a maintenance setting after first line chemotherapy may be an attractive strategy to extend survival of MPM patients. Defactinib (VS-6063) is an oral inhibitor of FAK. **Methods:** A multinational, randomized, double-blind, placebo controlled, clinical trial will determine if defactinib provides superior clinical benefit compared with placebo as a maintenance treatment in patients with MPM following frontline therapy with pem/platinum therapy. Approximately 370 eligible patients with PR or SD following at least 4 cycles of pem/cis or pem/carboplatin will be enrolled. Patients will receive defactinib 400mg BID or matched placebo (1:1). Patients will continue treatment until disease progression. Randomization will be stratified by merlin status (high vs low) as determined by immunohistochemistry on archival tumor tissue. Primary endpoints will include OS and PFS. An adaptive enrichment design at the interim analysis may restrict patients to those with low merlin protein expression if benefit is observed among the subpopulation. Secondary endpoints include patient-reported outcomes, objective response and safety and tolerability. Twenty-eight sites are actively recruiting patients across 8 countries. Clinical trial: NCT01870609.

**TPS7612 General Poster Session (Board #218A), Sat, 1:15 PM-5:00 PM**

**Nintedanib plus pemetrexed/cisplatin followed by maintenance nintedanib for unresectable malignant pleural mesothelioma (MPM): An international, multicenter, randomized, double-blind, placebo-controlled phase II study.**

*Presenting Author: Giorgio V. Scagliotti, Department of Clinical and Biological Sciences, University of Turin, S. Luigi Hospital, Torino, Italy*

**Background:** MPM is a rare cancer originating from multipotent mesothelial cells capable of differentiating into epithelial, sarcomatoid, or biphasic (mixed) neoplasms. The only approved 1st-line chemotherapeutic regimen for unresectable MPM, combination pemetrexed/cisplatin extends OS to only approximately one year, illustrating a need for improved treatment strategies. In the present trial, we are investigating the efficacy and safety of nintedanib (BIBF 1120) combined with pemetrexed/cisplatin for the treatment of unresectable MPM. Nintedanib is an oral, twice-daily, angiokinase inhibitor targeting most prominently vascular endothelial growth factor receptors 1–3, platelet-derived growth factor receptors $\alpha/\beta$, and fibroblast growth factor receptors 1–3, as well as Src and Abl kinase signaling, which are involved in regulating tumor angiogenesis, growth, and metastasis of MPM. These signaling pathways are also implicated in the pathogenesis and maintenance of MPM. In previous studies, we demonstrated that nintedanib can be co-administered with various anti-cancer drugs to safely and significantly increase survival in patients (pts) with non-small cell lung cancer. **Methods:** A total of 86 pts—at least 18 years of age and with ECOG score of 0 or 1 and histologically confirmed epithelioid or biphasic MPM—will be randomized in a 1:1 ratio to receive either up to 6 cycles of 1st-line combination pemetrexed (500 mg/m$^2$)/cisplatin (75 mg/m$^2$) on day one administered along with nintedanib (200 mg bid) or placebo from days two to 21. Pts who do not develop progressive disease (PD) will continue to receive maintenance treatment with either nintedanib or placebo until PD. The primary endpoint is PFS. Secondary endpoints are OS and baseline change in forced vital capacity as a measure of pulmonary function. Frequency and severity of adverse events will also be evaluated as a measure of safety. All pts will attend an end-of-trial visit when they discontinue study treatment permanently, and return for follow-up visits until the end of trial, death, or loss to follow-up. Clinical trial information: NCT01907100.

**8000 Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Onartuzumab plus erlotinib versus erlotinib in previously treated stage IIIb or IV NSCLC: Results from the pivotal phase III randomized, multicenter, placebo-controlled METLung (OAM4971g) global trial.** *Presenting Author: David R. Spigel, Sarah Cannon Research Institute, Nashville, TN*

**Background:** A placebo-controlled, phase II trial of erlotinib + onartuzumab, a humanized monovalent antibody to the MET receptor, demonstrated a benefit in progression-free survival (PFS) when compared with erlotinib in patients with MET-positive NSCLC (JCO 2013;31;4105). The aim of the METLung trial was to confirm the efficacy and safety of onartuzumab + erlotinib in MET-positive NSCLC. **Methods:** This prospective, randomized, double-blind, placebo-controlled trial enrolled patients with previously treated MET-positive stage IIIb/IV NSCLC. MET diagnostic status was determined by an immunohistochemistry (IHC) assay using the CONFIRM anti-total MET SP44 monoclonal antibody (Ventana). Eligibility criteria included: ECOG PS 0–1, 1–2 prior lines of chemotherapy, and normal organ function. Stratification factors: *EGFR* mutation status (activating mutation vs negative; cobas® *EGFR* assay), MET IHC (2+ vs 3+), number of prior treatments (1 vs 2), and histology (squamous vs non-squamous). Patients were randomized (1:1) to receive erlotinib 150mg PO daily + placebo or onartuzumab 15mg/kg IV every 21 days. Tumor assessments occurred every 6 weeks. The primary endpoint was overall survival (OS). The sample size (n=490) was based on the assumption that adding onartuzumab to erlotinib would improve OS by 41% with 90% power (one-sided alpha 0.025). An interim analysis was planned when 67% (244 events) of the final events were reached. **Results**: 499 patients were enrolled between Jan 2012 and Aug 2013. An independent data review committee recommended to stop the trial for futility, as the addition of onartuzumab to erlotinib did not improve OS (HR 1.27, p=0.068; median OS 6.8 mos vs 9.1 mos), PFS (HR 0.99, p=0.92; median PFS 2.7 mos vs 2.6 mos), or overall response rate (8.4% vs 9.6%; p=0.63). The most frequent adverse events that were higher in the combination arm were peripheral edema, hypoalbuminemia, back pain, dyspnea, nausea, acneiform dermatitis, and rash. **Conclusions:** The phase III study did not confirm the efficacy results observed in the phase II study. Exploratory analyses based on molecular subgroups are pending. Clinical trial information: NCT01456325.

**8001 Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Efficacy and safety of crizotinib in patients with advanced *c-MET*-amplified non-small cell lung cancer (NSCLC).** *Presenting Author: D. Ross Camidge, University of Colorado Cancer Center, Aurora, CO*

**Background:** *c-Met*-amplified NSCLC defines a subset of NSCLC that may be sensitive to the small-molecule tyrosine kinase inhibitor crizotinib, approved multinationally for the treatment of advanced *ALK*-positive NSCLC. Efficacy and safety data are presented for crizotinib in patients with advanced *c-Met*-amplified NSCLC within 3 categories of amplification MET/CEP7 ratio ≥1.8-≤2.2 (Low), >2.2-<5 (Intermediate) and ≥5 (High). **Methods:** *c-MET*amplification status was determined by FISH, with 10-12 patients to be enrolled into each amplification category. If 2 or more objective responses occur in a category, 19 additional patients are to be enrolled. This study is part of an ongoing phase 1 crizotinib study (NCT00585195). Patients received crizotinib 250 mg BID. Responses were assessed using RECIST v1.0. **Results:** At data cut-off, 16 patients were enrolled; 3 were subsequently determined not to have an amplification meeting MET/CEP7 criteria. 13 patients with *c-MET*-amplified NSCLC [Low (n=1), Intermediate (n=6) and High (n=6)] enrolled and received crizotinib, with 12 evaluable for response. Median age was 63 years (range 42-79), 92% of patients were ECOG 0 or 1 and 77% were ex-smokers. To date 4 PRs (33%; 95% CI: 10,65) have been observed (Low (n=0), Intermediate (n=1; 20%) and High (3; 50%). Median duration of response was 35 weeks [95% CI: 16,112]. Median treatment duration was 15.7 weeks (range 4 -188), and 6 patients were on treatment at the data cut-off; 5 patients have died (all disease-related). 75% of the 16 patients enrolled had treatment-related adverse events (AEs): most commonly diarrhea (50%), nausea (31%), vomiting (31%), peripheral edema (n=25%) and visual impairment (25%). Most AEs were grade 1 in severity. There were no treatment-related serious AEs or treatment-related permanent discontinuations. Accrual of patients with *c-Met*-amplified NSCLC is ongoing. **Conclusions:** Crizotinib appears to have antitumor activity in patients with *c-Met*-amplified NSCLC and a generally tolerable and manageable AE profile. These findings warrant further study of crizotinib in advanced *c-MET*-amplified NSCLC and ongoing exploration of the MET/CEP7 ratio associated with clinical benefit. Clinical trial information: NCT00585195.

**8002 Poster Highlights Session (Board #52), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**First-line crizotinib versus pemetrexed–cisplatin or pemetrexed–carboplatin in patients (pts) with advanced *ALK*-positive non-squamous non-small cell lung cancer (NSCLC): results of a phase III study (PROFILE 1014)** *Presenting Author: Tony Mok, The Chinese University of Hong Kong, Hong Kong, China*

**Background:** The efficacy of the oral ALK inhibitor crizotinib as 1st-line treatment for advanced *ALK*-positive NSCLC compared with standard chemotherapy is unknown. A multicenter, randomized open-label phase III study was conducted to compare the efficacy and safety of crizotinib vs. pemetrexed–platinum chemotherapy (PPC) in this setting. **Methods:** Between Jan 2011 and Jul 2013, 343 pts with previously untreated advanced non-squamous *ALK*-positive NSCLC were randomized 1:1 to receive crizotinib 250 mg PO BID (n=172) or PPC (pemetrexed 500 mg/m$^2$ + either cisplatin 75 mg/m$^2$ or carboplatin AUC 5–6; all IV q3w for ≤6 cycles; n=171). Continuation of/crossover to crizotinib after PD (per independent radiologic review) was allowed for pts randomized to crizotinib or PPC, respectively. The primary endpoint was PFS. Secondary endpoints included ORR, OS, safety, and pt-reported outcomes. **Results:** Proportions of pts in the crizotinib and PPC treatment groups with each stratification factor were 45% and 47% Asians, 94% and 95% with ECOG PS 0/1, and 26% and 28% with previously treated brain metastases, respectively. The study met its primary objective, demonstrating superiority of crizotinib over PPC in prolonging PFS (median 10.9 vs. 7.0 mo; HR: 0.454; 95% CI: 0.346−0.596; P<0.0001). The ORR was significantly higher with crizotinib (74% vs. 45%; P<0.0001). With 68% of pts still in follow-up, a statistically significant improvement in OS was not demonstrated (HR: 0.821; 95% CI: 0.536−1.255; P=0.1804). At time of data cut-off 109 pts on PPC had crossed over to crizotinib. AEs with crizotinib and PPC were consistent with those previously reported in patients with advanced *ALK*-positive or unselected NSCLC, respectively. The most common all-causality AEs with crizotinib were vision disorder and GI symptoms. **Conclusions:** First-line crizotinib treatment showed significant improvements in PFS and ORR compared with standard chemotherapy and had an acceptable safety profile. These findings establish crizotinib as the standard of care for pts with previously untreated advanced *ALK*-positive non-squamous NSCLC. Clinical trial information: 2010-021336-33.

**8003^ Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Ceritinib in advanced anaplastic lymphoma kinase (ALK)-rearranged (ALK+) non-small cell lung cancer (NSCLC): Results of the ASCEND-1 trial.** *Presenting Author: Dong-Wan Kim, Seoul National University Hospital, Seoul, South Korea*

**Background:** ALK+ NSCLC is sensitive to crizotinib (CRZ) but patients (pts) invariably progress. Ceritinib (LDK378) is a novel ALK inhibitor (ALKi) more potent than CRZ in enzymatic and cell-based assays and CRZ-resistant animal models. Prior results from this Phase I study (ASCEND-1) established a MTD of 750 mg/d. **Methods:** Adult pts with advanced ALK+ cancers received oral ceritinib q.d. After MTD determination, pts were enrolled to expansion groups: ALKi pretreated (PT) NSCLC; ALKi naive NSCLC; non-NSCLC diseases. Results are reported for all NSCLC pts receiving ceritinib at the recommended dose (750 mg/d). **Results:** 255 pts from 11 countries were treated at 750 mg/d. 246 pts had ALK+ NSCLC, with 4.5 months' median follow-up; of these, 67% had received ≥2 anticancer therapies; ORR was ≥60% in each subgroup of pts with 0, 1, 2, and 3 prior anticancer regimens. 83 pts were ALKi naïve. All 163 ALKi PT pts had received CRZ – 78% as their last prior therapy – and 92% had progressive disease on prior ALKi. Investigator efficacy assessments are presented for 180 NSCLC pts who received first dose of ceritinib ≥18 wks prior to cut-off (2 Aug 2013). Of all 255 pts, the most common AEs were diarrhea (84%), nausea (77%), vomiting (57%), fatigue (36%), and ALT increased (36%). The most common Grade 3/4 AEs were ALT increased (21%), and AST increased (8%). Ceritinib treatment is ongoing for 58% of pts. During the dosing period dose reductions occurred in 133 pts (52.2%), all due to an AE. Only 24 (9.4%) pts discontinued ceritinib due to an AE. **Conclusions:** Ceritinib 750 mg/d has rapid, durable and high antitumor activity in ALK+ NSCLC pts, regardless of prior treatment with ALKi, providing effective treatment in this pt population. Clinical trial information: NCT01283516.

| Endpoint | ALKi PT N=121 | ALK naive N=59 | All N=180 |
|---|---|---|---|
| ORR, n (%) [95% CI] | 67 (55.4%) [46.1, 64.4] | 41 (69.5%) [56.1, 80.8] | 108 (60.0%) [52.4, 67.2] |
| DOR (Median [95% CI]) | 7.4 mos [5.4, 10.1] | NE[a] [5.6, NE] | 9.7 mos [6.9, 11.4] |
| Time to first response (Median [min, max]) | 6.1 wks [4.6, 24.1] | 6.1 wks [3.0, 24.1] | 6.1 wks [3.0, 24.1] |
| PFS (Median [95% CI]) | 6.9 mos [5.4, 8.7] | NE[b] [6.7, NE] | 7.0 mos [6.2, 10.1] |

Abbreviation: NE, not estimable. [a] DOR rate at 12 mos: 71.1% (95% CI: 49.8, 84.6). [b] PFS rate at 12 mos: 58.1% (95% CI: 41.6, 71.5).

**8004^** **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Overall survival (OS) in patients (pts) with advanced non-small cell lung cancer (NSCLC) harboring common (Del19/L858R) epidermal growth factor receptor mutations (EGFR mut): Pooled analysis of two large open-label phase III studies (LUX-Lung 3 [LL3] and LUX-Lung 6 [LL6]) comparing afatinib with chemotherapy (CT).** *Presenting Author: James Chih-Hsin Yang, National Taiwan University Hospital, Taipei, Taiwan*

**Background:** Afatinib (A) is an oral, irreversible ErbB family blocker of EGFR, HER2, ErbB3 and ErbB4 signalling. LL3 compared A with cisplatin/pemetrexed in 345 pts recruited globally and LL6 compared A with gemcitabine/cisplatin in 364 Asian pts. The primary analysis (2012) showed improved progression-free survival (PFS) with A versus CT in the overall EGFR mut positive population (HR=0.58 [LL3], HR=0.28 [LL6]) and pts with common (Del19/L858R) EGFR mut (HR=0.47 [LL3], HR=0.25 [LL6]). The FDA has approved A for the first-line treatment of pts with advanced NSCLC harboring common EGFR mut. Here we present a pooled analysis of mature OS data among such pts. **Methods:** Treatment-naïve pts with EGFR mut stage IIIB/IV NSCLC were randomized 2:1 to 40 mg A or up to 6 cycles of standard CT and stratified by EGFR mut and race (LL3). The primary endpoint was PFS, with OS as a key secondary endpoint. Adverse events were also recorded. **Results:** The pooled analysis included 631/709 pts randomized into LL3 and LL6 with common EGFR mut (Del19=355, L858R=276); 419 pts received A and 212 received CT. At the time of analysis (January 2014), 404 (64%) pts had died. Median follow-up for OS was 36.5 months. Following progression, 78% of pts received subsequent systemic therapies (median of 3 regimens); 68% in the CT group received EGFR TKIs and 70% in the A group received CT. OS was significantly improved with A versus CT (median 27.3 vs 24.3 months, HR=0.81 [CI 0.66, 0.99; p=0.037]). Individual HRs for OS in LL3 and LL6 were consistent with the pooled analysis. Among Del19 pts the HR=0.59 (CI 0.45, 0.77; p<0.001) and in L858R pts the HR=1.25 (CI 0.92, 1.71; p=0.160). Updated PFS and safety findings were consistent with earlier primary reports. **Conclusions:** This pooled analysis reveals that first-line A significantly improves OS in pts with advanced NSCLC harboring common EGFR mut (Del19/L858R) compared with CT. This is the first analysis to show that genotype-directed therapy for EGFR mut pts can improve survival. Clinical trial information: NCT00949650, NCT01121393.

**8005** **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Erlotinib plus bevacizumab (EB) versus erlotinib alone (E) as first-line treatment for advanced EGFR mutation–positive nonsquamous non-small cell lung cancer (NSCLC): An open-label randomized trial.** *Presenting Author: Terufumi Kato, Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan*

**Background:** Despite the development of EGFR tyrosine kinase inhibitors, median progression-free survival (PFS) is only about 13 months in patients with EGFR mutation–positive NSCLC. However, results from the BeTa Lung study for a subgroup of patients with EGFR mutation suggest that EB may prolong PFS in these patients. **Methods:** Open-label randomized trial. Patients with stage 3b/4 or recurrent non-squamous EGFR mutation–positive NSCLC, ECOG performance status 0/1, and no previous chemotherapy were randomly allocated to receive EB (E, 150 mg/day; B, 15 mg/kg every 3 weeks) or E (150 mg/day) until disease progression or unacceptable toxicity. The primary endpoint was PFS determined by blinded independent review committee. Secondary endpoints included overall survival, objective response rate (ORR), safety, and quality of life. The planned sample size was 150, with an alpha error of 0.2 and a power of 80% for a target hazard ratio (HR) of 0.7. **Results:** From February 2011 to March 2012, 154 patients were enrolled (EB group, $n = 77$; E group, $n = 77$). There were no major differences in patient characteristics, including age, gender, stage, and EGFR mutation type, between the two groups. Median PFS was 16.0 months for EB and 9.7 months for E (HR, 0.54; 95% CI, 0.36–0.79; log-rank $p = 0.0015$). In the EGFR exon 19 deletion subgroup, median PFS was 18.0 months for EB and 10.3 months for E. In the L858R subgroup, median PFS was 13.9 months for EB and 7.1 months for E. ORR was 69.3% for EB and 63.6% for E. There were 3 and 1 complete responses to EB and E, respectively. Grade 3 or 4 rash was more common in the EB group (25.3% versus 19.5%). Grade 3 or 4 bleeding was more common in the EB group (2.7% versus 0.0%). However, most adverse events were manageable, and no new safety signals arose. Five patients experienced grade 1–3 interstitial lung disease, but there was no difference between the groups. One treatment-related death occurred in the E group. **Conclusions:** EB results in significantly longer PFS than E in patients with EGFR mutation–positive NSCLC. Clinical trial information: JapicCTI-111390.

**LBA8006^** **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**REVEL: A randomized, double-blind, phase III study of docetaxel (DOC) and ramucirumab (RAM; IMC-1121B) versus DOC and placebo in the treatment of stage IV non-small cell lung cancer (NSCLC) following disease progression after one prior platinum-based therapy.** *Presenting Author: Maurice Perol, Léon-Bérard Cancer Centre, Lyon, France*

**The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, May 31, 2014, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2014, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.**

**8007** **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Safety and clinical activity of MK-3475 as initial therapy in patients with advanced non-small cell lung cancer (NSCLC).** *Presenting Author: Naiyer A. Rizvi, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Programmed death-1 (PD-1) receptor-ligand interaction inhibits T cell activation against tumor cells. MK-3475 is a potent and highly selective humanized monoclonal antibody against PD-1 designed to directly block its interaction with its ligands, PD-L1 and PD-L2, thus removing the inhibition of T cell activation against cancer. MK-3475 led to prolonged anti-tumor activity in previously treated NSCLC patients. This Phase I study evaluated the safety, tolerability, and clinical activity of MK-3475 as initial therapy in patients with locally advanced or metastatic NSCLC. **Methods:** Patients with no prior systemic therapy for metastatic disease whose tumors expressed PD-L1 by a preliminary immunohistochemical assay were randomized to MK-3475 10 mg/kg every 2 or 3 wks (Q3W). The first 11 patients were randomized to 2 mg/kg and 10 mg/kg Q3W. At least 1 measurable tumor lesion, ECOG performance status of 0 to 1, adequate organ function and adequate tumor biopsy were required for enrollment. Prior adjuvant therapy was allowed if it preceded relapse by at least a year. Tumor response was assessed every 9 weeks until confirmed disease progression per immune related response criteria (irRC; investigator review); RECIST 1.1 by independent central review will also be performed. **Results:** 84 patients submitted tissue for PD-L1 assessment and 57 patients had tumors that expressed PD-L1. Between Feb 2013 and Oct 2013, 45 patients started treatment (n=6 2Q3W, n=23 10Q3W, n=16 10Q2W). Preliminary data indicate an ORR (confirmed and unconfirmed) of 36% (67% 2 mg/kg Q3W, 27% 10 mg/kg Q3W, 35% 10 mg/kg Q2W) by irRC. 25 patients (55%), including all but 2 responders, remain on treatment (treatment duration from 12+ to 48+ wks). 52% of patients experienced a drug-related adverse event (AE), usually grade 1-2 in severity, most commonly fatigue (14%), pruritus (8%), dermatitis acneiform (6%), diarrhea (6%) and dyspnea (6%). There was a single drug-related grade 3-5 AE, a grade 3 pericardial effusion. **Conclusions:** These data suggest that MK-3475 is generally well-tolerated and provides robust antitumor activity in a first-line setting in patients with locally advanced or metastatic NSCLC that expresses PD-L1. Clinical trial information: NCT01295827.

**8008^ Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**A randomized, multicenter, open-label, phase III study of gemcitabine-cisplatin (GC) chemotherapy plus necitumumab (IMC-11F8/LY3012211) versus GC alone in the first-line treatment of patients (pts) with stage IV squamous non-small cell lung cancer (sq-NSCLC).** *Presenting Author: Nick Thatcher, The Christie Hospital NHS Foundation Trust, Manchester, United Kingdom*

**Background:** Necitumumab (N), a human IgG1 anti-EGFR monoclonal antibody, inhibits ligand-binding and receptor activation. EGFR is detectable in the vast majority of advanced sq-NSCLC tumors. **Methods:** Pts with pathologically proven stage IV sq-NSCLC were randomized 1:1 to GC (G=1250 mg/m$^2$ iv, days 1 and 8; C=75 mg/m$^2$ iv, day 1) plus N (800 mg iv, days 1 and 8) (GC+N arm), or GC alone (GC arm) every 21 days for up to 6 cycles. GC+N pts with no progression continued on N alone until progressive disease or intolerable toxicity. The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and safety. EGFR protein expression level by immunohistochemistry (H-score) in tumor tissue was an exploratory analysis. Planned sample size was 1080 pts, with 90% power and a 2-sided alpha level of 0.05. **Results:** 1,093 pts were randomized (n=545, GC+N; n=548, GC). Baseline characteristics were balanced between GC+N and GC, respectively, including males (82.6% and 83.6%), ECOG PS 0/1 (91.0% and 91.2%), and PS 2 (9.0% and 8.6%). Exposure to chemotherapy was similar in both arms; median dose intensity (DI) for G and C was 86% and 95%, respectively, and DI for N was 94%. 51% of GC+N pts continued N alone for a median of 4 additional cycles. The addition of N to GC statistically significantly improved OS (HR=0.84, $p$=0.012) and PFS (HR=0.85, $p$=0.020); mOS was 11.5 vs 9.9 mo in GC and mPFS was 5.7 vs 5.5 mo in GC. ORR was 31% vs 29% in GC ($p$=0.400), and the disease control rate (DCR) was 82% vs 77% in GC ($p$=0.043). Post-progression anticancer therapy was similar (47% vs 45%). Several prespecified subgroup analyses of OS and PFS showed a consistent treatment effect, including pts with ECOG PS 2. Grade ≥3 adverse events with GC+N (measured by preferred MedDRA terms) that showed a >2% increase over GC were hypomagnesemia (8.7% vs 1.1%) and skin rash (3.7% vs 0.2%). **Conclusions:** The addition of N to GC statistically significantly improved OS, PFS, and DCR. The safety profile of GC+N is acceptable. Clinical trial information: NCT00981058.

**8009^ Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

**Clinical activity of the mutant-selective EGFR inhibitor AZD9291 in patients (pts) with EGFR inhibitor–resistant non-small cell lung cancer (NSCLC).** *Presenting Author: Pasi A. Janne, Dana-Farber Cancer Institute, Boston, MA*

**Background:** AZD9291 is a selective, third generation EGFR-TKI, effective against both EGFR-TKI sensitizing and resistance T790M mutations in preclinical models. We are conducting a phase I study of AZD9291 in EGFR mutant (EGFRm+) NSCLC pts. **Methods:** EGFRm+ NSCLC pts, with acquired resistance to EGFR-TKIs, were enrolled in a multicenter trial (NCT01802632) into dose escalation and expansion cohorts. AZD9291 was administered orally, at doses of 20–240 mg once daily. Stable brain metastases were allowed. All pts were assessed for pharmacokinetics (PK), response to therapy, and adverse events (AEs). Prospective mandatory central T790M testing was required in the expansion cohorts and was optional for dose escalation cohorts. **Results:** As of 16 January 2014, 199 pts (62% female, median age 60, Asian/Caucasian 65%/32%, immediate prior EGFR-TKI therapy: 57%) were enrolled including 31 across 5 dose levels in the dose escalation and 168 in 8 dose expansion cohorts. Median number of prior EGFR therapies: 1 (range, 1-5). PK was dose proportional, median t1/2 ~50 h. Plasma exposures achieved at all doses are predicted to be efficacious in preclinical models. Among all evaluable pts to date, the confirmed+unconfirmed overall response rate (c+uORR) was 51% (91/177). RECIST responses were observed at all dose levels and in brain metastases. In 132 pts with centrally confirmed T790M, the c+uORR in 89 EGFR T790M+ pts was 64% (95% CI; 53%, 74%) and in 43 EGFR T790M- pts was 23% (95% CI; 12%, 39%).The overall disease control rate (CR+PR+SD) in T790M+ pts was 96% (85/89). Among the 60 pts with a confirmed response, 97% (58/60) were ongoing at data cut-off; longest duration of response to date >8 months. No dose limiting toxicities were observed. Most common AEs (≥15%), mostly CTCAE Grade 1, were: diarrhea (30%), rash (24%), and nausea (17%). Grade 3/4 AEs occurred in 16% of pts. Six pts (3%) had dose reductions. Five reports of ILD-like events are under investigation. **Conclusions:** AZD9291 has robust efficacy and is well tolerated in EGFRm+ NSCLC pts with acquired resistance to EGFR-TKIs. Pts with EGFR T790M+ tumors have higher ORR with AZD9291 compared with those with EGFR T790M- tumors. Clinical trial information: NCT01802632.

**8010^ Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

**First-in-human evaluation of CO-1686, an irreversible, highly selective tyrosine kinase inhibitor of mutations of EGFR (activating and T790M).** *Presenting Author: Lecia V. Sequist, Massachusetts General Hospital, Boston, MA*

**Background:** Efficacy of existing EGFR tyrosine kinase inhibitors (TKIs) in NSCLC is limited by emergence of the T790M mutation in approximately 60% of patients, and significant skin rash and diarrhea, caused by wild-type (WT)-EGFR inhibition. CO-1686 is an oral, covalent TKI that targets common activating EGFR mutations and T790M, while sparing WT-EGFR. **Methods:** This is a completed dose finding study in patients with EGFR mutated advanced NSCLC. Patients were previously treated with EGFR TKI and had a tumor biopsy in screening for central EGFR genotyping. CO-1686 was administered twice daily. Endpoints included safety, pharmacokinetics (PK), and efficacy. **Results:** As of 17$^{th}$January 2014, 88 patients were treated: 57 with CO-1686 free base (up to 900 mg BID); 31 with CO-1686 HBr (500 to1000 mg BID). 10 transitioned from free base to HBr. 63% were T790M+, median age 61 years, 77% female, 76% white, and 72% ECOG 1. Median number of previous therapies was 3 (1- 7); 40% had >1 prior line of EGFR TKI. PK of the CO-1686 HBr formulation was dose proportional with three times greater exposure than the equivalent free base dose. The dose limiting toxicity (DLT) rate at all doses was <33%. Related AEs (all grades) in ≥ 20% patients were: nausea (25%), fatigue (21%), impaired glucose tolerance/hyperglycemia (21%). Hyperglycemia was well managed with oral hypoglycemics and/or dose reduction. A recommended phase 2 dose of 750 mg BID has been selected. Nine T790M+ patients treated with 900 mg BID (free base) were evaluable for response; 6 (67%) achieved PRs, 2 (22%) achieved SD, one of whom subsequently achieved a PR after transition to CO-1686 HBr. Eight of nine progressed on EGFR TKI immediately before CO-1686. PRs have occurred among patients treated with CO-1686 HBr, however the majority of patients have not reached the first restaging. Efficacy data for at least 41 patients on CO-1686 HBr will be presented at the meeting. **Conclusions:** CO-1686 has demonstrated promising efficacy against T790M+ EGFR mutant NSCLC. CO-1686 HBr delivered higher exposures than free base and was equally well tolerated. Dose-related WT-driven diarrhea and rash has not been seen. The phase 2/3 program will open in 2014. Clinical trial information: NCT01526928.

**8011 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

**Clinical activity and safety of HM61713, an EGFR-mutant selective inhibitor, in advanced non-small cell lung cancer (NSCLC) patients (pts) with EGFR mutations who had received EGFR tyrosine kinase inhibitors (TKIs).** *Presenting Author: Dong-Wan Kim, Seoul National University Hospital, Seoul, South Korea*

**Background:** HM61713 is a novel, oral, selective inhibitor for EGFR mutations including both activating mutations and T790M, but not EGFR wild-type. This phase 1 trial was conducted to evaluate the safety, pharmacokinetics, and preliminary efficacy of HM61713 in the pts with advanced NSCLC harboring EGFR mutations who had failed to previous EGFR-TKIs (NCT01588145). **Methods:** EGFR TKIs pre-treated, advanced NSCLC pts with EGFR mutation positive tumors were enrolled. The 3+3 dose-escalation scheme was used in dose-escalation cohort. Expansion cohort was implemented at the dose 300mg qd; pts were assigned to either arm A or B according to elapsed time interval after prior EGFR-TKIs (Arm A: <4 weeks; Arm B: ≥4 weeks) and underwent mandatory tissue biopsy at baseline to analyze EGFR T790M mutation status. **Results:** To date, a total of 93 pts have been enrolled in both dose escalation and expansion cohorts (35:58 respectively). These pts received HM61713 up to 500 mg/day and maximum tolerated dose has not been determined yet and subsequent dose escalation is ongoing. Drug-related adverse events (AEs) reported in ≥10% of pts were skin exfoliation, nausea, diarrhea, rash, decreased appetite and pruritus. Most of AEs were typically Gr 1/2, easily manageable and reversible without interruption of dosing. Two cases of Gr3 or more drug-related AEs were reported. A total of 7 unconfirmed partial responses (uPR) were observed so far out of 42 evaluable pts (arm A: 3/16; arm B: 4/26) in expansion cohort. Disease control rate was 76.5% and 73.1% in arm A and B, respectively. Among 27 patients who had T790M mutation at baseline biopsy, 18 pts showed decreased size in the target lesions and all the uPR observed were T790M mutation positive cases. **Conclusions:** HM61713 showed good safety profile and promising anti-tumor activity in pts with EGFR mutated NSCLC who failed to EGFR-TKIs, especially in pts with T790M mutation. Clinical trial information: NCT01588145.

**8012 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

**Overall response rate (ORR) as a potential surrogate for progression-free survival (PFS): A meta-analysis of metastatic non-small cell lung cancer (mNSCLC) trials submitted to the U.S. Food and Drug Administration (FDA).** *Presenting Author: Gideon Michael Blumenthal, U.S. Food and Drug Administration, Silver Spring, MD*

**Background:** Targeted therapies (TT) administered as single agents in molecularly defined mNSCLC subsets are yielding high ORR. Improvements in PFS of large magnitude with favorable benefit-risk have served as the basis of drug approval in mNSCLC. The relationship between ORR with PFS or Overall Survival (OS) in mNSCLC is not established. Therefore, we conducted a meta-analysis of mNSCLC trials submitted to the FDA, including 3 trials of TT in molecularly enriched populations with high ORR. **Methods**: We identified 15 trials of 12,534 patients (median N = 698) of 9 experimental agents (tyrosine kinase inhibitor = 5, chemotherapy = 2, monoclonal antibody = 2) submitted for treatment of mNSCLC in initial or supplemental New Drug or Biologics License Applications since 2003. Criteria for inclusion of the trials in this analysis were: randomized, active-controlled, multicenter, N ≥ 150. Three trials tested TT in defined populations (EGFR mutant = 2, ALK+ = 1). The estimated PFS hazard ratio (HR- ratio of hazard of treatment versus hazard of control group) and OS HR versus the estimated odds ratio (OR) of ORR (ratio of odds of response in controls to odds of response in treatment) on the log-scale was calculated. Weighted least square (WLS) regression analyses (weight equal to the number of patients) were performed on log-transformed effects. **Results**: For the PFS HR vs. ORR OR analysis, the $R^2 = 0.89$, the slope of the WLS = 0.41 (95% CI: 0.32, 0.49). For the OS HR vs. ORR OR analysis, $R^2 = 0.12$, slope = 0.05 (95% CI: -0.03, 0.13). Using trials ≥ 500 patients (n=12), $R^2 = 0.50$, slope = 0.16 (95% CI: 0.04, 0.3). For the OS HR vs. PFS HR analysis, $R^2 = 0.1$, slope = 0.1 (95% CI: -0.1, 0.3). Using trials with ≥ 500 patients, $R^2 = 0.39$, slope = 0.32 (95% CI: 0.04, 0.6). **Conclusions**: On a trial level, the meta-analysis of randomized, active-controlled trials indicates a strong correlation between ORR and PFS. A correlation between ORR or PFS and OS is not established and may be confounded by cross-over in the TT trials. At the trial level, a TT in a molecularly defined subset of mNSCLC with a large magnitude of effect on ORR will likely have a large effect on PFS.

**8013 Poster Highlights Session (Board #27), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Pan-Canadian rash trial with EGFR inhibitors.** *Presenting Author: Barbara L. Melosky, British Columbia Cancer Agency, Vancouver, BC, Canada*

**Background:** Erlotinib prolongs survival in advanced non-small cell lung cancer (NSCLC), as a first-line treatment for EGFR mutation, and second-/third-line upon progression on chemotherapy. Rash is a major side effect of erlotinib; studies have retrospectively illustrated a relationship between rash and efficacy. The primary objective of this study was to determine the optimal treatment of rash secondary to erlotinib **Methods:** The Pan Canadian Rash Trial studied rash in patients who received erlotinib for advanced NSCLC in the second or third-line setting. This trial was initiated before *EGFR* mutational testing was available. Patients were randomized to one of three arm: Prophylactic (Arm 1) minocycline (150 po bid) on day 1 of erlotinib; Reactive (Arm 2) treatment with topical clindamycin + hydrocortisone +/- minocycline upon rash occurrence depending on grade; Observation (Arm 3) no treatment of rash unless severe (Gr 3). Endpoints included the overall incidence and severity of rash and relationship to survival. **Results:** 150 patients were enrolled. 75% were Caucasian and 76% were current/former smokers. Overall incidence of rash was 83%. Time to occurrence of rash was significantly longer in Arm 1. (Table) Prophylactic minocycline reduced the probability of rash by 39.8% compared to Arms 2 and 3 combined (odds ratio 0.602, p = 0.3210). The incidence of Grade 3 rash was greater in Arm 3 (34.1%) versus Arms 1 (14.3%) and 2 (9.5%). Patients in Arm 1 were on erlotinib 50% longer than in arms 2 and 3 (6.34 months vs 4.02 and 4.16 respectively). Although not statistically significant, Arm 1 had the longest overall survival. **Conclusions:** Incidence of rash secondary to erlotinib treatment is common. Prophylactic minocycline reduced occurrence and severity of rash, was well tolerated and conferred a non-significant survival advantage. This may reflect improvement in patient compliance. Observation until severe rash (Gr 3) led to the worst outcome. Prophylactic treatment did not reduce erlotinib efficacy, and should be considered in patients upon initiation of erlotinib therapy. Clinical trial information: NCT00473083.

**Time to first presentation of rash, all grades.**

| | Incidence of rash n (%) | Median (days) | Mean (days) | P value |
|---|---|---|---|---|
| **ARM 1 (N=50)** | 42 (84) | 12.0 | 17.4 | p 0.0147 |
| **ARM 2 (N=50)** | 42 (84) | 9.0 | 13.3 | |
| **Arm 3 (N=50)** | 41 (82) | 8.0 | 12.0 | |

**8014 Poster Highlights Session (Board #28), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Phase II trial of XL184 (cabozantinib) plus erlotinib in patients (pts) with advanced EGFR-mutant non-small cell lung cancer (NSCLC) with progressive disease (PD) on epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy: A California Cancer Consortium phase II trial (NCI 9303).** *Presenting Author: Karen L. Reckamp, City of Hope National Medical Center, Duarte, CA*

**Background:** MET and VEGF are important in mediating NSCLC tumorigenesis and EGFR TKI resistance. We hypothesized that treatment with the dual MET-VEGF inhibitor cabozantinib plus erlotinib in EGFR mutation-positive NSCLC following PD on EGFR TKI therapy may allow for tumors to overcome this resistance or restore sensitivity to therapy. **Methods:** Eligible pts were required to have known EGFR mutation and PD on an EGFR TKI immediately prior to enrollment without intervening therapy. Pts received erlotinib 150 mg daily + cabozantinib 40 mg daily on a 28 day cycle. This was a single-arm study to distinguish between a promising response rate of 20% and a discouraging response rate of 5% (requiring at least 4/37 responders). There was a pre-planned analysis of the percent of patients with at least a 30% increase in the tumor doubling time (DT), reflecting a reduction in the tumor growth rate with the addition of cabozantinib using each patient's tumor growth rate during prior TKI treatment as their own control. Secondary endpoints include the evaluation of specific EGFR mutations and MET amplification in pre-treatment tissue. **Results:** 37 patients were registered between 5/2013 and 1/2014 in 4 centers; 35 have been treated. Median age was 63 years, 63% female and 51% ECOG PS 0. 4 pts had a PR (2 confirmed, 2 unconfirmed), with 13 patients remaining on treatment. In addition, 20/23 demonstrated significant growth rate reduction corresponding to a greater than 30% increase in DT. Diarrhea (10/35, 29%) was the most common grade 3 AE; 2 patients (6%) had a grade 3 maculopapular rash. Grade 4 AE's include vomiting (1), elevated lipase (2), elevated amylase (1). Ongoing correlative studies are to determine correlation of response with MET amplification and T790M mutation. **Conclusions:** Combination erlotinib and cabozantinib demonstrates anti-tumor activity in pts with EGFR mutation and PD on EGFR TKI. Supported by NCI N01CM2011-00038 and U01CA062505. Clinical trial information: NCT01866410.

**8015 Poster Highlights Session (Board #29), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Phase II study of the AKT inhibitor MK-2206 plus erlotinib (E) in patients (pts) with advanced non-small cell lung cancer (NSCLC) who progressed on prior erlotinib: A California Cancer Consortium Phase II trial (NCI 8698).** *Presenting Author: Primo Lara, University of California, Davis Medical Center, Sacramento, CA*

**Background:** Preclinical modeling in NSCLC cell lines shows that in some E-sensitive cells (whether epidermal growth factor receptor [EGFR] mutated or wild type), stimulation with HGF reverses the cytostatic and cytotoxic effects of E. Inhibitors of AKT signaling mitigated this HGF-mediated resistance, partially restoring E activity. We conducted a phase II trial of E plus MK2206, a highly selective inhibitor of AKT, in NSCLC pts previously benefiting from E. **Methods:** Eligible pts must have had progression (PD) following prior benefit from E [response or stable disease > 12 weeks]. Treatment consisted of E 150 mg po QD + MK-2206 45 mg po QOD on a 28-day cycle. Pts were accrued into 2 strata: 1) presence of EGFR activating mutation; and 2) EGFR wild type. Primary endpoints: RECIST response rate (RR) > 30% (stratum 1) and disease control rate (DCR) > 20% at 12 weeks (stratum 2). Up to 41 pts per stratum were planned in a two-stage design. **Results:** Eighty pts were enrolled with median age 64 years (range 40-86); tumor EGFR status: mutant – 46, wild type-34; females - 51 (64%); performance status 90-100% - 53 (66%); and median time from diagnosis – 2.3 years (range 0.2-11.1). Most common attributable adverse events (all grade 3) were rash (12), diarrhea (11), fatigue (7), and mucositis (5). There was one treatment-related death (pneumonia). Efficacy results are shown in the Table. **Conclusions:** Combination MK2206 and E met its primary endpoint (DCR 47%) in E-pretreated pts with EGFR wild type NSCLC while its activity in EGFR mutants appears modest (RR 9%). Treatment was generally tolerable and toxicities manageable. AKT pathway inhibition merits further clinical evaluation in pts with E-refractory EGFR wild type NSCLC (N01-00038). Clinical trial information: NCT01294306.

| Stratum | RR, N (%) | DCR at 12 weeks, N (%) | Median progression-free survival, months (95% CI) |
|---|---|---|---|
| **1: EGFR mutant (N=46)** | 4 (9%) | 18 (39%) | 4.4 (2.7,6.6) |
| **2: EGFR wild-type (N=34)** | 1 (3%) | 16 (47%) | 4.6 (2.9, 8.5) |

**8016 Poster Highlights Session (Board #30), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Randomized phase II study of concurrent gefitinib and chemotherapy versus sequential alternating gefitinib and chemotherapy in previously untreated non-small cell lung cancer (NSCLC) with sensitive *EGFR* mutations: NEJ005/TCOG0902.** *Presenting Author: Satoshi Oizumi, First Department of Medicine, Hokkaido University School of Medicine, Sapporo, Japan*

**Background:** The first-line combination of an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) plus platinum-based doublet chemotherapy has yet to be sufficiently evaluated for patients with *EGFR*-mutant NSCLC. This randomized phase II trial was designed to identify an effective combined regimen of gefitinib (G) plus carboplatin/pemetrexed (CP) for subsequent use in phase III study. **Methods:** Chemotherapy-naïve patients with advanced non-squamous *EGFR*-mutated NSCLC were randomly assigned to receive either a concurrent regimen (C group) or a sequential and alternating regimen (S group). Patients in the C group received concurrent G (250 mg daily) and CP (AUC = 6 and 500 mg/m$^2$, day 1) of a 3-week cycle for 6 cycles, followed by concurrent G and P maintenance. Patients in the S group initially received G (days 1 to 28) and then CP (day 29 and 51); the cycle was repeated for 3 cycles, followed by alternating G and P maintenance. The primary endpoint was progression-free survival (PFS). **Results:** All 80 patients enrolled were eligible and evaluable for efficacy. Median PFS was 17.2 months in the C group and 15.1 months in the S group (p = 0.41). Although overall survival data are immature (with a median follow-up time of 24.6 months, 10 and 19 death events), median survival times were not reached in the C group, and were 30.0 months in the S group (p = 0.049). Response rates were similar in both groups (87.8% in the C group and 82.1% in the S group). The most common grade 3 or greater adverse events were neutropenia (48.8% and 46.2%), thrombocytopenia (41.5% and 28.2%), and anemia (34.1% and.12.8%). G-related skin rash or diarrhea was not severe, and interstitial lung disease was not frequent (two cases in each group; 5% of all patients). No treatment-related deaths occurred. **Conclusions:** To the best of our knowledge, this is the first randomized study to investigate the efficacy of a combination of EGFR-TKI and chemotherapy in the *EGFR*-mutated setting. Both regimens had promising efficacy with predictable toxicities, although concurrent regimens might provide better overall survival. Clinical trial information: UMIN000002789.

**8017 Poster Highlights Session (Board #31), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Safety and efficacy of INC280 in combination with gefitinib (gef) in patients with *EGFR*-mutated (mut), MET-positive NSCLC: A single-arm phase Ib/II study.** *Presenting Author: Yi-Long Wu, Guangdong Lung Cancer Institute, Guangdong General Hospital (GGH) and Guangdong Academy of Medical Sciences, Guangzhou, China*

**Background:** Despite high response rates to EGFR tyrosine kinase inhibitors (TKIs), most patients (pts) with *EGFR*-mut NSCLC ultimately relapse. Dysregulation of the MET pathway is implicated as a therapeutically tractable resistance mechanism, occurring in 15–20% of cases. INC280 is a highly selective, oral MET inhibitor with preclinical activity in *EGFR*-mut/MET-activated NSCLC when combined with EGFR TKIs. **Methods:** This Ph Ib/II, open-label, dose-escalation study of INC280 plus gef was performed in pts (age ≥18 yrs, ECOG PS ≤2) with *EGFR*-mut NSCLC who progressed after prior EGFR TKI, and have confirmed MET dysregulation (amplification [FISH ≥5 CN] or overexpression [IHC 2/3+]). The primary objective (Ph Ib) was to determine the MTD/recommended Ph II dose (RP2D) of INC280 plus gef; secondary objectives were safety, efficacy, pharmacodynamics and PK. An adaptive Bayesian logistic regression model with overdose control guided dose escalation to establish the MTD. **Results:** As of December 2, 2013, 41 pts were enrolled in the ongoing Ph Ib part of the study (59% female, median age 58 years). Pts were treated with INC280 at 7 dose cohorts of 100–800 mg QD and 200–600 mg BID, in combination with gef 250 mg QD. Dose-limiting toxicities (DLTs) occurred in 2 pts: dizziness (800 mg QD) and dyspnea (600 mg BID). The most frequent drug-related AEs (any grade [Gr]) were nausea (27 %), vomiting, diarrhea, and rash (all 22%). The most common drug-related Gr 3/4 AEs were increased lipase (7 %), and increased amylase (5%). For one death, causality to INC280 was not ruled out. INC280 exposure increased with dose from 100–800 mg QD and 200–400 mg BID; preliminary data show no PK interactions with gef. Partial responses were seen in 6/41 (15%) evaluable pts; 5 confirmed, 1 unconfirmed, including 3/7 pts (43%) on 400 mg BID; 5/6 responders had EGFR TKIs as a last treatment prior to study entry. All responders had high MET status. **Conclusions:** Oral INC280 in combination with gef is well tolerated; the RP2D has not yet been defined. Preliminary clinical activity supports further evaluation of INC280 combined with gef in MET-positive NSCLC resistant to EGFR TKIs. Clinical trial identifier: NCT01610336. Clinical trial information: NCT01610336.

**8018 Poster Highlights Session (Board #32), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Randomized, double-blinded study of dacomitinib, an irreversible pan-human epidermal growth factor receptor (HER) inhibitor, versus erlotinib for second-line/third-line therapy of locally advanced/metastatic non-small cell lung cancer (ARCHER 1009).** *Presenting Author: Suresh S. Ramalingam, The Winship Cancer Institute of Emory University, Atlanta, GA*

**Background:** Dacomitinib, an irreversible pan-HER kinase inhibitor, has demonstrated anti-cancer activity in phase 2 studies for patients with EGFR activating mutation and in those with EGFR and K-RAS wild-type (WT) NSCLC. **Methods:** Patients (pts) with locally advanced/metastatic NSCLC were randomized following progression with 1 or 2 prior chemotherapy regimens to treatment with Dacomitinib (D) (45 mg PO QD) or Erlotinib (E) (150 mg PO QD) with placebo control for both arms. Archived tumor tissue, ECOG performance status (PS) of 0-2, adequate organ function and informed consent were required. The primary endpoint was progression-free survival (PFS) per independent review in the co-primary populations [all patients and those with KRAS WT]. The estimated sample size was 800 pts, using 1-sided stratified log rank test for all pts to detect HR≤ 0.75, at significance = 1.5% with 90% power and to detect HR≤ 0.69 for KRAS WT at significance = 1% with 80% power. Secondary endpoints: overall survival, objective response (OR), safety, and patient reported outcomes. **Results:** 878 pts with the following baseline characteristics were enrolled; approximate median age of 63 years, 64% males, 76% Caucasians, 90% with PS 0/1, 69% adenocarcinoma and 18% never-smokers. Activating EGFR mutation was present in 41 pts in each arm. Discontinuation for treatment-related toxicity was more frequent with D (8% vs. 4.8%). Diarrhea, stomatitis, paronychia, and mucositis were more common with D. **Conclusions:** Irreversible EGFR inhibition with Dacomitinib is not superior to Erlotinib in the second-/third-line therapy of advanced NSCLC. Overall survival and outcomes for pts with EGFR mutation are not mature. Clinical trial information: NCT01360554.

| | All pts | | KRAS WT | |
|---|---|---|---|---|
| **Population** | **Dacomitinib** | **Erlotinib** | **Dacomitinib** | **Erlotinib** |
| **N** | 439 | 439 | 256 | 263 |
| **Response rate** | 11.4% | 8.2% | 13.3% | 11% |
| **Median PFS** | 2.6 m<br>HR 0.941, P=0.229 | 2.6 m | 2.6 m<br>HR 1.022 P=0.587 | 2.6 m |
| **Median OS (95% CI)** | 7.9 m<br>(6.8,9.0) | 8.4 m<br>(7.4,9.7) | 8.1 m<br>(6.8,9.5) | 8.5 m<br>(7.5,10.2) |

**8019^ Poster Highlights Session (Board #33), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Continuation of afatinib beyond progression: Results of a randomized, open-label, phase III trial of afatanib plus paclitaxel (P) versus investigator's choice chemotherapy (CT) in patients (pts) with metastatic non-small cell lung cancer (NSCLC) progressed on erlotinib/gefitinib (E/G) and afatanib—LUX-Lung 5 (LL5).** *Presenting Author: Martin H. Schuler, West German Cancer Center, University Duisburg-Essen, Essen, Germany*

**Background:** Improved disease control with continuation of EGFR inhibition beyond progression has been suggested in retrospective/non-randomized studies, however, this has yet to be prospectively evaluated in a randomized trial. LL5 is a randomized trial, which assessed the efficacy of continuation of the irreversible ErbB family blocker, afatinib (A), beyond progression with the addition of P in NSCLC pts with prior benefit from reversible EGFR tyrosine kinase inhibitors (E/G) and A. **Methods:** In this open-label, global phase III trial, pts with NSCLC who had failed ≥1 line of CT and E/G (after ≥12 wks treatment) were treated with A (50 mg/day) in Part A (n=1154). Upon progression, those with ≥12 wks on A were eligible to be randomized 2:1 to A+P (40 mg/day; 80 mg/m$^2$/week) or single agent investigator's choice CT in Part B. Primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), overall survival (OS), and safety. **Results:** 202 pts were randomized (A+P, n=134; CT, n=68) and baseline characteristics were well balanced (median age 60 yrs, females 49%, ECOG PS 0–1 91% overall). A statistically significant improvement in PFS was observed on A + P vs CT arm (median 5.6 vs 2.8 months, hazard ratio (HR) 0.60 (95% CI 0.43, 0.85; p=0.003). ORR was also significantly higher in A+P arm vs CT (32.1% vs 13.2%; p=0.005). OS was similar in both arms 12.2 vs. 12.2 months, HR 1.00 (95% CI 0.70, 1.43; p=0.994). Most common related adverse events (AEs) with A+P vs CT were diarrhea (53.8% vs 6.7%), alopecia (32.6% vs 15.0%) and asthenia (27.3% vs 28.3%). **Conclusions:** ContinuedErbB family blockade with A with the addition of P significantly improved PFS and ORR vs CT alone in heavily pretreated pts with acquired resistance to E/G and progression on A monotherapy. AEs were considered manageable. Our data support that tumors progressing on E/G and A continue to depend on signalling through the receptors of the ErbB family and can benefit from continuous ErbB family blockade with A. Clinical trial information: NCT01085136.

**8020 Poster Highlights Session (Board #34), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Safety and clinical activity of MK-3475 in previously treated patients (pts) with non-small cell lung cancer (NSCLC).** *Presenting Author: Edward B. Garon, University of California, Los Angeles, Los Angeles, CA*

**Background:** This Phase I study evaluated the safety, tolerability, and clinical activity of MK-3475, a selective anti-PD-1 antibody that blocks the interaction between programmed death-1 (PD-1) on T-cells and PD-L1 and PD-L2 on tumor cells in pts with previously-treated, progressive locally advanced or metastatic NSCLC. **Methods:** Previously-treated pts with NSCLC whose tumors expressed any detectable PD-L1 using a preliminary immunohistochemical assay were randomized to MK-3475 at 10 mg/kg every 2 weeks (Q2W) or 3 weeks (Q3W). Some pts with tumors without PD-L1 expression who had received ≥2 prior lines of therapy were treated with MK-3475 at 10 mg/kg Q2W. At least 1 measurable tumor lesion, ECOG performance status of 0-1, adequate organ function, and new tumor biopsy ≤60 days prior to study entry were required. Tumor response was assessed every 9 wks until disease progression by investigator review using immune-related response criteria (irRC) and independent central review using RECIST 1.1. **Results:** 450 pts provided tissue for PD-L1 assessment; 305 were eligible based on PD-L1 tumor staining. 221 pts (n=102, Q2W [including 43 whose tumors did not express PD-L1]; n=119, Q3W) began treatment between Feb 2013 and Oct 2013. 48% of pts experienced drug-related adverse events (AEs), usually grade 1-2 in severity, most commonly fatigue (13%), decreased appetite (6.5%), arthralgia (6.1%), pruritus (5.4%), rash (4.7%), and pyrexia (3.6%). The incidence of grade 3/4 drug-related AEs was 6%. There were 3 cases of drug-related grade 3/4 pneumonitis. The preliminary ORR (confirmed & unconfirmed by irRC/RECIST) in all pts was 15%/21% (16%/24% for pts with PD-L1 expressing tumors [19%/31% 10 mg/kg Q2W, 15%/22% 10 mg/kg Q3W], 10%/8% for pts without PD-L1 tumor expression. 40% of pts had <18 wks of follow-up and 69 pts (33%) remain on treatment. A mature dataset will be available for presentation, including correlation between level of tumor PD-L1 expression and response rates. **Conclusions:** In this cohort of over 200 pts, treatment with MK-3475 was generally well tolerated and provided robust antitumor activity in previously-treated pts with progressive locally advanced or metastatic NSCLC that expressed PD-L1. Clinical trial information: NCT01295827.

**8021^ Poster Highlights Session (Board #35), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Clinical activity and biomarkers of MEDI4736, an anti-PD-L1 antibody, in patients with NSCLC.** *Presenting Author: Julie R. Brahmer, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

**Background**: Lung cancer is the leading cause of cancer death in both men and women. PD-L1 is upregulated in NSCLC and may be associated with a poor prognosis. MEDI4736 is a human IgG1 antibody which binds specifically to PD-L1 preventing binding to PD-1 and CD80. **Methods**: An ongoing phase 1, multicenter, open-label study (NCT01693562) is evaluating the safety and efficacy of MEDI4736 administered IV every 2 wks (q2w) or every 3 wks (q3w) using a 3+3 dose escalation followed by expansion cohorts. NSCLC pts were assigned to expansion cohorts by histology and line of therapy (including treatment- naïve pts). Retreatment was permitted for progression after 12 mos of therapy. Response is assessed by immune-related response criteria (irRC) in escalation and RECIST v1.1 in expansion. **Results**: As of Jan 17, 2014, 13 NSCLC pts in dose escalation (median age 65 yrs; 40-76), all PS 0-1, with a median of 4 prior treatments, received a median of 7 doses (1-25) of MEDI4736 across 6 cohorts (0.1 – 10 mg/kg q2w; 15 mg/kg q3w). Treatment-related AEs occurred in 43% of pts, all of which were Grade 1-2; none led to discontinuation of study drug. No pneumonitis or colitis was reported in dose escalation. Of 13 pts, 3 PRs were observed, with 2 additional pts achieving tumor shrinkage not meeting PR per irRC (46% and 48% decreases). Tumor shrinkage was reported as early as first assessment (6 wks) and benefit was durable; 4/13 pts remain on study (10+, 10+, 11.1+, 14.9+ mos) as of the data cutoff. Expansion cohorts opened Sep 2013; 43 pts (including treatment-naïve pts) have been dosed, with the opportunity to enroll > 300 NSCLC pts in total. Preliminary clinical activity has been observed with acceptable safety, no ≥ grade 3 pneumonitis, and no apparent differences in toxicity between treatment-naïve vs pretreated pts. Assessment of clinical activity by PD-L1 expression, underlying mutation, smoking history, and line of therapy patient-reported outcomes is ongoing. **Conclusions:** The preliminary safety and durable clinical efficacy profile of MEDI4736 in NSCLC supports continued clinical development; AEs are manageable, even in highly pretreated pts. Recruitment continues and development of MEDI4736 in NSCLC as monotherapy and in combination is ongoing. Clinical trial information: NCT01693562.

**8022 Poster Highlights Session (Board #36), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Safety and response with nivolumab (anti-PD-1; BMS-936558, ONO-4538) plus erlotinib in patients (pts) with epidermal growth factor receptor mutant (EGFR MT) advanced NSCLC.** *Presenting Author: Naiyer A. Rizvi, Memorial Sloan-Kettering Cancer Center, New York, NY*

**Background:** Erlotinib is FDA-approved for the first-line treatment of EGFR MT NSCLC, with a median progression free survival (PFS) of 10.4 months. Nivolumab, a fully human IgG4 programmed death-1 (PD-1) immune checkpoint inhibitor antibody, demonstrated encouraging safety and survival outcomes as monotherapy in advanced NSCLC pts. Preclinical data support EGFR pathway activation of PD-L1 expression and immune escape in EGFR driven lung tumors. Interim results from a phase I study evaluating nivolumab + erlotinib in an EGFR MT advanced NSCLC cohort are reported. **Methods:** Stage IIIB/IV EGFR MT chemotherapy-naïve NSCLC pts (EGFR TKI naïve or progression post prior TKI therapy) received nivolumab 3 mg/kg IV Q2W + erlotinib 150 mg PO daily until progression/unacceptable toxicity. Objective response rate (ORR) and PFS were evaluated by RECIST 1.1. **Results:** All pts (n=21) began study treatment ≥10 months prior to data analysis; only 1 pt was EGFR TKI naïve. Any-grade treatment-related AEs were reported in all 21 pts; treatment-related grade 3–4 AEs (4 pts) were increased AST (n=2) or ALT (n=1), weight decrease and diarrhea (1 pt each); 2 pts discontinued due to treatment-related AEs (grade 3 AST increase and grade 2 nephritis). No pneumonitis (any grade) was observed. ORR was 19% (4/21 pts) and 24 wk PFS rate was 47%; median duration of response (DOR) was not reached (range 6.1+ to 27.1+ wks). Of the 20 pts with acquired erlotinib resistance, 3 (15%) achieved partial response (PR, all ongoing; DOR 6.1+, 16.3+ and 27.1+ wks); 9 pts (45%) had stable disease with 3/9 (33%) ongoing (time to progression/death 9.9+, 15.7, 21, 22.3, 24.4+, 31.1+, 35.9, 52.7 and 53 wks), and 1 pt had an unconventional "immune related" response (ongoing), with 46% reduction in target lesions after progression in non-target lesions. The EGFR TKI-naïve pt achieved PR with DOR 24.3+ wks (ongoing). **Conclusions:** These interim results suggest that nivolumab + erlotinib may provide durable clinical benefit and an acceptable safety profile in TKI refractory, EGFR MT advanced NSCLC, supporting further evaluation of nivolumab in pts with EGFR MT NSCLC. Additional follow up will be presented. Clinical trial information: NCT01454102.

**8023 Poster Highlights Session (Board #37), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Nivolumab (anti-PD-1; BMS-936558, ONO-4538) and ipilimumab in first-line NSCLC: Interim phase I results.** *Presenting Author: Scott Joseph Antonia, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

**Background:** Nivolumab, a fully human IgG4 programmed death-1 (PD-1) immune checkpoint inhibitor antibody, and ipilimumab, an IgG1 CTLA-4 checkpoint receptor blocking antibody, have shown activity in advanced NSCLC; clinical data in melanoma showed improved responses and a manageable safety profile when combined. We report interim results from a phase I study evaluating first-line nivolumab + ipilimumab (N+I) in advanced NSCLC patients (pts). **Methods:** Chemotherapy-naive pts (n=46) with squamous (sq) or non-sq NSCLC received the 3 + 1 mg/kg or 1 + 3 mg/kg combination dose IV Q3W for 4 cycles followed by nivolumab 3 mg/kg IV Q2W until progression/unacceptable toxicity. Objective response rate (ORR; RECIST 1.1) was evaluated overall and by baseline tumor PD-L1 status (Dako immunohistochemistry assay). After an amendment, a 1 + 1 mg/kg cohort was added (n=30, data immature at Dec 2013 analysis). **Results:** In the 4 cohorts with ≥4 months follow up, any-grade treatment-related adverse events (managed with protocol algorithms) were reported in 39 pts (85%; grade 3–4 in 22 pts [48%]) and led to discontinuation in 16 pts. Treatment-related deaths (n=3) were due to respiratory failure, bronchopulmonary hemorrhage and toxic epidermal necrolysis. Responses occurred in all 4 cohorts (Table); overall ORR[b] was 22% (median duration of response [mDOR] not reached [NR]) and stable disease (SD) 33% (range 13 – 34.1+ wks); 2 pts exhibited unconventional "immune related" responses. In 29 evaluable tumor samples from the study, ORR did not correlate with PD-L1 status. **Conclusions:** These interim data in pts with advanced NSCLC suggest that a nivolumab + ipilimumab immunotherapy regimen is feasible and demonstrates antitumor activity in both PD-L1+ and PD-L1– pts. Safety will be further assessed at the 1 + 1 mg/kg dose. The recommended combination dose for phase II/III evaluation has not been determined. Clinical trial information: NCT01454102.

| | N1 + I3 Sq | N1 + I3 Non-sq | N3 + I1 Sq | N3 + I1 Non-sq |
|---|---|---|---|---|
| **N** | 7 | 15 | 8 | 16 |
| **ORR,[a] n (%)** | 1 (14) | 1 (7) | 2 (25) | 2 (13) |
| **ORR,[b] n (%)** | 1 (14) | 2 (13) | 3 (38) | 4 (25) |
| | 3 (14) | | 7 (29) | |
| **SD, n (%)** | 2 (29) | 6 (40) | 4 (50) | 3 (19) |
| **mDOR (Kaplan-Meier),[a] wk (range)** | NR (9+) | NR (21+) | 17 (12, 21) | NR (24+, 25+) |
| **Ongoing responders,[a] n (%)** | 1 (100) | 1 (100) | 0 | 2 (100) |

[a] Confirmed OR only. [b] Confirmed + unconfirmed OR.

**8024 Poster Highlights Session (Board #38), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**First-line nivolumab (anti-PD-1; BMS-936558, ONO-4538) monotherapy in advanced NSCLC: Safety, efficacy, and correlation of outcomes with PD-L1 status.** *Presenting Author: Scott N. Gettinger, Yale Cancer Center, New Haven, CT*

**Background:** The fully human IgG4 programmed death-1 (PD-1) immune checkpoint inhibitor antibody nivolumab has demonstrated durable responses and tolerability in patients (pts) with previously treated advanced NSCLC. Tumor PD-1 ligand (PD-L1) expression is being studied as a potential biomarker for nivolumab. We report interim phase I results of first-line nivolumab in chemotherapy-naïve advanced NSCLC pts. **Methods:** Pts with squamous (sq) or non-sq advanced NSCLC received nivolumab 3 mg/kg IV Q2W until progression or unacceptable toxicity (post-progression treatment allowed based on protocol-defined criteria). Responses (RECIST 1.1) were evaluated overall and according to tumor PD-L1 status (PD-L1+ = ≥5% tumor cells expressing PD-L1 [Dako immunohistochemistry assay]). Results on the first 20 pts are included. **Results:** After ≥6 months follow up, 17 pts (85%) experienced any-grade treatment-related adverse events (AEs), managed with standard algorithms. Treatment-related grade 3-4 AEs (3 pts, 15%) were AST or ALT elevations, hyperglycemia, and rash (n=1 each). No pneumonitis (any grade) was observed. Objective response rate (ORR) was 30% (Table); 5/6 responders (83%) achieved response by first scan (wk 11). Two pts had >80% target lesion reduction at 18 wks. Of 15 evaluable tumor samples, 9 were PD-L1+. ORR was 67% in PD-L1+ pts; no responses were observed in the 6 PD-L1- pts. Responses were durable (median duration of response [mDOR] not reached [NR]; 5 ongoing responses). **Conclusions:** In this phase I study, nivolumab led to early, durable responses in advanced NSCLC pts, with a tolerable safety profile. PD-L1 status appeared to correlate with ORR/progression-free survival (PFS). Follow up and responses of 30 additional treated pts will be reported. These data support further studies of first-line nivolumab monotherapy in advanced NSCLC. Clinical trial information: NCT01454102.

| | ORR | mDOR | Median PFS |
|---|---|---|---|
| | n/N (%) | wk (range) | |
| **All pts** | 6/20 (30) | NR (11.1+, 37.7+) | 29.6 (5.9, 47.6+) |
| **Non-sq** | 4/11 (36) | NR (36.1, 37.7+) | 45.6 (9.6, 47.6+) |
| **Sq** | 2/9 (22) | NR (11.1+, 27.9+) | 15.1 (5.9, 37.9+) |
| **PD-L1+** | 6/9 (67) | NR (11.1+, 37.7+) | NR (8, 47.6+) |
| **PD-L1-** | 0/6 | n/a | 23.1 (9.6, 47.3+) |
| **PD-L1 unknown** | 0/5 | n/a | 15.1 (5.9, 35.7+) |

**8025 Poster Highlights Session (Board #40), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Molecular characterization of an extensive lung cancer patient-derived xenograft (PDX) resource.** *Presenting Author: Philip C. Mack, UC Davis Comprehensive Cancer Center, Sacramento, CA*

**Background:** A large series of non-small cell lung cancer (NSCLC) PDX models has been established through direct implantation of patient tumor material into immune compromised mice. Here we report the molecular characterization of this resource, reflecting the biologic diversity and heterogeneity inherent to NSCLC with implications for drug development. **Methods:** Patient tumor acquired from biopsy, resection or pleural effusion was implanted subcutaneously into the flank of NOD.Cg-Prkdc$^{scid}$ Il2rg$^{tm1Wjl}$/SzJ (NSG) mice. The contributing patient tumor (PT) and the resultant PDX were analyzed for driver mutations (Response Genetics Inc., and Illumina TSCAP); copy number variants (CNV) and global RNA expression (Affymetrix arrays). Normalized gene expression across all PDX models was analyzed using Principal Component Analysis (PCA). Clustering was performed based on shared patterns of gene expression, analyzed using Gene Set Enrichment Analysis to identify biological themes. **Results:** At time of submission, 55 NSCLC models from 53 patients were fully established & characterized. Contributing patients: Median age 62 (36-82); 62% female; 22% stage IV; 32 adenocarcinoma, 19 squamous cell carcinoma (SCC), 2 large cell. All driver mutations detected in PTs were retained in resultant PDXs: 10 EGFR, 11 KRAS, 1 ALK, 1 NRAS. PCA revealed 6 clusters with subgroups differentiated by genes associated with signal transduction, epithelial-mesenchymal transition and DNA repair. SCC models predominantly populated two clusters, with one group almost exclusively comprised of PI3KCA amplified models with upregulated/amplified FGFR1-3 signaling components. KRAS mutants showed divergent cluster patterns, with several models grouping with EGFR/ALK mutants, potentially influenced by PI3K mutation status. **Conclusions:** The UC Davis Cancer Center/The Jackson Laboratory NSCLC PDX resource is one of the largest, most characterized collections currently in use for advanced therapeutic development. PCA subgrouping, along with mutation and CNV status, suggest strategies to refine patient selection and treatment algorithms.

**8026 Poster Highlights Session (Board #41), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Clinical activity of LY2835219, a novel cell cycle inhibitor selective for CDK4 and CDK6, in patients with non-small cell lung cancer.** *Presenting Author: Jonathan Wade Goldman, UCLA Santa Monica Hematology-Oncology, Santa Monica, CA*

**Background:** LY2835219, a novel cell cycle inhibitor selective for the cyclin-dependent kinases CDK4 and CDK6 (CDK4/6), has shown antitumor activity in human NSCLC xenograft models. Importantly, KRAS mutant xenografts exhibit greater sensitivity to LY2835219 compared to KRAS wildtype xenografts. To evaluate the safety and clinical activity of LY2835219, we conducted a Phase I study with cohorts for multiple cancers. Here, we report results for a cohort of 49 NSCLC patients: 19 KRAS wildtype, 26 KRAS mutant, and 4 with unknown KRAS status. **Methods:** Patients with advanced NSCLC that progressed or relapsed after standard treatments received continuous therapy with LY2835219 orally every 12 hours (Q12H) on Days 1-28 of a 28-day cycle. RECIST v1.1 was used to assess tumor response. Progression-free survival (PFS) was described using the Kaplan-Meier method. **Results:** In the NSCLC cohort, 49 patients with a median of 4 prior systemic therapies received single-agent LY2835219 either at the maximum tolerated dose of 200 mg Q12H (n=25) or, to gain additional safety and efficacy data, at 150 mg Q12H (n=24). The most common possibly related treatment-emergent adverse events across all grades were diarrhea (including 2% G3), nausea (4% G3), fatigue (2% G3), vomiting (2% G3), and anemia (2% G3); there were no Grade 4 events. The disease control rate (DCR = complete response [CR] + partial response [PR] + stable disease [SD]) was 51% with 1 confirmed PR. The median duration of SD was 5.6 months and the median PFS (n=49) was 2.1 months. Among the 49 NSCLC patients, 20 (41%) reached at least 4 cycles and 13 reached at least 6 cycles, with 5 of these 13 patients still receiving LY2835219 therapy (range: 7-12 cycles). Consistent with NSCLC xenograft studies, the DCR in this clinical trial was 37% for KRAS wildtype (n=19) and 54% for KRAS mutant (n=26) NSCLC. **Conclusions:** In a cohort of patients with advanced NSCLC and a median of 4 prior systemic therapies, single-agent LY2835219 demonstrated acceptable safety and achieved an overall DCR of 51%, reflecting in part the higher DCR of 54% for KRAS mutant NSCLC. Thus, LY2835219 merits further clinical investigation for NSCLC, including KRAS mutant disease. Clinical trial information: NCT01394016.

**8027 Poster Highlights Session (Board #42), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Rictor amplification to define a novel and unique subset of lung cancer patients.** *Presenting Author: Haiying Cheng, Department of Medical Oncology, Montefiore Medical Center, Bronx, NY*

**Background:** Recent advances in molecularly tailored therapy have shifted the treatment paradigm in lung cancer. We recently identified amplification of *RICTOR*, a key component of the mTORC2 complex, as a new and sole genomic alteration in an 18-year-old never smoker with lung adenocarcinoma. We hypothesizethat *RICTOR* amplification, unlike previously reported molecular changes in the PI3K/AKT/mTOR pathways, may identify a new subgroup of lung cancer patients amenable to molecularly targeted therapy. **Methods:** The index patient had *RICTOR* amplification identified by next generation sequencing (NGS)- genomic profiling of 182 cancer-related genes performed with extracted DNA from FFPE specimens. We then reviewed the database of 1128 lung cancer patients who had profiling performed by Foundation Medicine. Additionally, we examined the *in vitro* cytotoxicity of 6 classes of drugs against different components of the PI3K/AKT/mTOR pathways in *RICTOR*-amplified H23 lung cancer cells. **Results:** *RICTOR* amplification in the index case was confirmed by FISH and IHC of RICTOR and its downstream targets. *RICTOR* amplification was found in 8.2% (92/1128) lung cancer patients from the NGS database. In 11% (10/92) of cases, *RICTOR* amplification was the only potentially actionable target. Additionally, 13% (12/92) and 27% (25/92) of these patients had concomitant alterations in *KRAS* and *EGFR*, exclusively in lung adenocarcinomas. One third of the patients (29/92) had alterations in other genes within the PI3K/AKT/mTOR pathway. Among all the examined agents targeting the PI3K/AKT/mTOR pathways, BEZ235 (dual PI3K/mTOR inhibitor) and AZD2014 (dual mTOR1/2 inhibitor) were the most active in *RICTOR*-amplified H23 lung cancer cells. As a proof of concept, our index patient has been treated on a phase I clinical trial with a dual mTOR1/2 inhibitor (CC223) and has had stable disease for over 8 months. **Conclusions:** *RICTO*R amplification may define a novel and unique molecular subset of lung cancer patients. Our observation provides the rationale for testing *RICTOR* amplification as a potential biomarker for targeted therapy with mTOR1/2 inhibitors in lung cancer patients.

**8028 Poster Highlights Session (Board #43), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Extended cohort study of OPB51602, a novel inhibitor of STAT3/5 activation, in non-small cell lung carcinoma.** *Presenting Author: Joline Si Jing Lim, National University Cancer Institute, Singapore, Singapore, Singapore*

**Background:** STAT3, a signal transduction protein of growth factor receptors including EGFR, is constitutively activated in many solid malignancies, leading to tumor angiogenesis, cell proliferation and immune tolerance. Inhibition of STAT3 in vitro and in vivo induces apoptosis in STAT3-activated tumor cells. OPB51602 is an oral small molecule inhibitor of STAT3 phosphorylation with favorable preclinical profile that has entered clinical development. **Methods:** We analyzed a subgroup of patients with non-small cell lung cancer (NSCLC) from a phase I study of OPB51602 including an extension cohort at the recommended dose of 4mg daily in NSCLC. Dosing included dosing daily for 2 weeks every 3 weeks, and continuous dosing of 4mg daily. Archival tissue was analyzed for oncogenic mutations and STAT3/5 phosphorylation. Patients were evaluated for treatment response, and pharmacodynamic effects of STAT3 phosphorylation assessed in peripheral blood mononuclear cells by flow cytometry (PBMCs). **Results:** 25 patients were treated at doses of 2mg, 4mg and 5mg. 23 patients (92%) had adenocarcinoma, and 11 (44%) had tumor EGFR mutations. Two patients treated at doses of 4mg and 5mg had partial response(PR), with progression free survival of 5 and 7 months respectively; both had EGFR mutations that responded and then progressed on EGFR TKIs. Overall disease control rate was 12.5% at 3 months, and duration of disease control was longer in EGFR mutant patients. Patients who achieved PR/stable disease (n=6) had a higher incidence of *EGFR* mutations compared to those with PD (n=8), (83% *vs* 50%). 12 patients had repeat FDG PET CT during cycle 1, with metabolic response by EORTC criteria observed in 5 patients(42%). Immunohistochemistry showed pSTAT3($Ser^{727}$) overexpression in 44% of patients, and PBMC analysis revealed downregulation of pSTAT3 with treatment (mean decrease 22.1±14.1%), with maximal effect at 4h post-dosing. There was no correlation between extent of downregulation of pSTAT3 and tumor response. **Conclusions:** OPB51602 demonstrates evidence of clinical activity in treatment refractory NSCLC, particularly for EGFR mutants. Further evaluation of its efficacy and biomarker exploration is warranted in NSCLC.

**8029 Poster Highlights Session (Board #44), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Next-generation sequencing (NGS) to identify actionable genomic alterations (GA) in "pan-negative" lung adenocarcinomas (ADC) from patients with no smoking or a light smoking (NS/LS) history.** *Presenting Author: Alexander E. Drilon, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Testing for an increasing number of biomarkers has become essential to the care of lung ADC patients (pts). This commonly requires multiple technologies and often is limited by inadequate tissue. Hybrid capture-based targeted NGS has the ability to identify relevant GAs in a single test. We undertook this study to estimate the frequency of GAs in "pan-negative" lung ADC pts with NS/LS history. **Methods:** Eligible pts had ≤15 pack-year smoking history (high likelihood of undetected GA) and advanced lung ADC that were "pan-negative" for mutations (*EGFR, ERBB2, KRAS, NRAS, BRAF, MAP2K1, PIK3CA,* and *AKT1* by hotspot testing and/or multiplex sizing assays) and fusions (*ALK, ROS1,* and *RET* by break apart FISH). Tumor required contained ≥20% tumor nuclei on FFPE material yielding ≥50 ng of DNA. NGS was performed by hybridization capture of coding exons in 287 cancer-related genes and 47 introns in 19 frequently rearranged genes (Foundation Medicine). **Results:** 34 pts were eligible. Previous testing required additional biopsies in 71% (n=24/34). Tissue exhaustion precluded testing in 9 of 34 pts (26%) and NGS was successfully performed in 25 pts. NGS uncovered ≥1 GA in 92% (n=23/25) of cases [median 3; 42% base substitution, 35% amplification (amp), 10% fusions, 9% in/del, 4% homozygous loss]. NGS uncovered an actionable GA with a targeted agent based on NCCN guidelines in 36% (n=9/25: *EGFR* G719A, *EGFR* L747P, *ERBB2* exon 20 ins, *BRAF* V600E, *SOCS5-ALK, CD74-ROS1*, *KIF5B-RET, CCDC6-RET, MET* amp), and a targeted agent available on a clinical trial in 32% (n=8/25: 2 *EGFR* exon 18 del, *FGFR1* T141R, *KRAS* Q61H, *BRCA1* E1011K, *MDM2* amp, *CDK4* amp, *CDKN2A* loss) of pts. A GA not previously detected in lung ADCs (*SHC2-ERBB2*) was found in 1 pt. Reasons why non-NGS testing had not detected these GAs include lower sensitivity, test failure, use of different biopsies, technical issues, and complex or intrachromosomal rearrangements undetectable by FISH. **Conclusions:** NGS identified actionable GAs in 68% of NS/LS pts with "pan-negative" lung ADCs. This suggests that initial profiling of lung ADCs using NGS may be a more efficient and sensitive strategy.

**8030^ Poster Highlights Session (Board #45), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**A phase I trial of X-396, a novel ALK inhibitor, in patients with advanced solid tumors.** *Presenting Author: Leora Horn, Vanderbilt-Ingram Cancer Center, Nashville, TN*

**Background:** X-396 is a novel, potent anaplastic lymphoma kinase (ALK) small molecule TKI with significant anti-tumor activity in both ALK TKI naive and crizotinib resistant models of *ALK* fusion-positive NSCLC. **Methods:** In this multicenter phase I study, patients with advanced solid tumors were enrolled and given X-396 on a continuous 28-day schedule. This was an accelerated titration design with the dose starting at 25 mg once daily. At the first DLT cohorts were expanded to the classic 3+3 design up to 250 mg daily. All pts were assessed for adverse events (AEs) using CTCAE version 4.0, response to therapy was assessed using RECIST 1.1, and pharmacokinetics (PK) were measured. **Results:** As of the January 23, 2014 cutoff, 30 patients enrolled (21 NSCLC patients, 13 ALK+ - 3 crizotinib naïve and 10 crizotinib resistant), 4 H&N, 2 SCLC, 2 colorectal,1 breast). Median age 58, 12 ECOG PS 0 and 18 PS 1. The most common drug related AEs include rash (36%, G1-G3), fatigue (30%, G1-G2), nausea (27%, G1), vomiting (27%, G1) and edema (20%, G1-G2). Grade3/4 treatment related AEs were rash (2patients), edema (1patient). X-396 exhibited linear PK at doses 25 – 250mg. At 200mg QD, the $t_{1/2}$ is ~23 hours, and the trough level (~300nM) is sufficient to inhibit most crizotinib resistant mutations in vitro. To date, 18 patients are evaluable for response; SD is 28% and PR 28%. Among 8 evaluable ALK+ NSCLC cases, responses occurred in crizotinib naïve and crizotinib treated patients. In the 6 ALK+ patients treated at doses ≥ 200 mg SD is 17% and PR 83%; 2 PRs were observed in patients treated with prior crizotinib. CNS responses have been observed in 2 patients, 1 crizotinib naïve and 1 crizotinib resistant. The median duration of treatment in evaluable ALK+ patients is 20+ weeks with the longest being 58+ weeks. **Conclusions:** X-396 is generally well tolerated at doses up to 250 mg daily and induces responses in both crizotinib naïve and crizotinib resistant ALK+ NSCLC patients. Enrollment is ongoing. Clinical trial information: NCT01625234.

**8031 Poster Highlights Session (Board #46), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Evolution of resistance in ALK-positive patients treated with ALK tyrosine kinase inhibitors (TKIs).** *Presenting Author: Justin F. Gainor, Massachusetts General Hospital, Boston, MA*

**Background:** Lung cancers harboring ALK rearrangements are sensitive to treatment with ALK TKIs. Ceritinib (LDK378) is a novel, highly potent ALK TKI that has shown promising anti-tumor activity in crizotinib-resistant patients (pts); however, resistance invariably develops. **Methods:** To determine molecular mechanisms of resistance to ceritinib, we identifiedpts with ALK-positive lung cancer who underwent biopsies of progressing lesions following treatment with ceritinib. Specimens underwent ALK FISH and sequencing of the ALK tyrosine kinase domain. Similar analyses were performed in a subset of pts with pre-ceritinib/post-crizotinib biopsy specimens available. Biopsies were performed under an IRB-approved protocol. **Results:** We identified 10 ALK-positive pts who underwent biopsies at the time of resistance to ceritinib. Median duration of treatment (DOT) on ceritinib was 7.5 months (range 2.5 – 15.4 months). Nine of 10 pts had previously received crizotinib with a median DOT of 8.1 months (range 2.8 – 35.1 months). Pre-ceritinib/post-crizotinib biopsies were available for comparison in 8 pts. ALK resistance mutations were identified in 5/11 (45%) post-ceritinib biopsies (1 pt had 2 separate procedures performed). Resistance mutations included: G1202R (3), F1174C (1) and F1174V (1). Notably, 2 pts had ALK resistance mutations (S1206Y and G1269A) identified in pre-ceritinib/post-crizotinib samples. These mutations were no longer present in ceritinib-resistant biopsies performed at the same anatomic sites; however, the G1202R mutation emerged in both pts. One of these pts was also found to have an F1174V mutation at a separate post-ceritinib biopsy site. ALK FISH was positive for ALK rearrangement in 8/8 ceritinib-resistant specimens, but ALK gene amplification was not identified, including in 1 pt with high-level ALK amplification in a pre-ceritinib/post-crizotinib biopsy. Additional genetic data will be presented at the meeting. **Conclusions:** Mechanisms of acquired resistance are heterogeneous and may evolve dynamically in response to different ALK TKIs. Consistent with preclinical data, ALK mutations in two residues, G1202 and F1174, can mediate resistance to ceritinib in the clinic.

**8032 Poster Highlights Session (Board #47), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Differential expression of LKB1, PD-L1, and PD-L2 in KRAS-mutant non-small cell lung cancer in never-smokers.** *Presenting Author: Antonio Calles, Dana-Farber Cancer Institute, Boston, MA*

**Background:** *KRAS* mutation is the most common oncogenic alteration in lung adenocarcinoma and is detected in smokers and up to 15% of never smokers. The tumor suppressor LKB1 is commonly mutated in NSCLC and LKB1 mutations occur concurrently in 30% of *KRAS* mutant NSCLC. In murine models, *KRAS* mutant tumors with concurrent LKB1 loss did not respond to docetaxel/selumetinib treatment. Immune checkpoint blockade by anti-PD-1/PD-L1 monoclonal antibodies (MoAb) is being clinically evaluated. Clinical responses to these agents correlate with PD-L1 expression and smoking status. We aimed to determine the expression of LKB1, PD-L1 and PD-L2 in *KRAS* mutant NSCLC from smokers (KS) and never smokers (KNS). **Methods:** We evaluated the clinical and molecular characteristics of *KRAS* mutant NSCLC patients (pts) using an institutional database. We examined LKB1, PD-L1, PD-L2 tumor expression by immunohistochemistry (IHC). IHC was performed using the murine MoAbs Ley37D/G6 (LKB1), 9A11 (PD-L1) and 9E5 (PD-L2). LKB1 staining was scored as intact or lost, with any degree of expression qualifying as intact, PD-L1 positive if >5% of cells were stained and PD-L2 positive if >10%. **Results:** Between 8/09 and 1/14 we identified 514 *KRAS* mutant NSCLC pts (stage I 22%/II 10%/III 19%/IV 49%) of which 39 were never smokers (incidence 7.6%) We analyzed 114 pts with available tissue using IHC (30 KNS and 84 KS). LKB1 loss was detected in 29% of cases (95%CI, 21-38%) and was significantly less frequent in KNS pts (KS 34% vs KNS 13%; $P$= 0.035). *KRAS* transversion mutations were more frequent in KS vs KNS pts (78% vs 37%; $P$= 0.0001). LKB1 staining was intact in 95% of KNS pts with transition mutations. Pts with LKB1 loss had more metastatic sites and brain involvement (47% vs 24%, $P$= 0.0472). PD-L1 was expressed in 19% of *KRAS* mutant cases and PD-L2 in 45% and were inversely correlated (r=-0.86, $P$ <0.0001). PD-L1/PD-L2 expression was not related to either LKB1 status or type of *KRAS* mutation. PD-L1/PD-L2 IHC 3+ vs 1+/2+ staining was more frequent in KS vs KNS pts (50% vs 20%; 40% vs 13% respectively). **Conclusions:** *KRAS* mutant NSCLC is a heterogeneous disease. Our findings may have implications for choosing *KRAS* mutant pts for ongoing trials of MEK and PD-1/PD-L1 inhibitors.

**8033 Poster Highlights Session (Board #48), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Concurrent molecular alterations in KRAS-mutant lung adenocarcinomas and effects on overall survival.** *Presenting Author: Gregory J. Riely, Memorial Sloan Kettering Cancer Center, New York City, NY*

**Background:** *KRAS* mutations define the largest subset of oncogene-driven lung adenocarcinomas (25-30%). Among patients with *KRAS* mutations, their clinical course during treatment is heterogeneous. The presence of concurrent genetic alterations in other oncogenes and tumor suppressors, such as *TP53* or *STK11* may affect outcomes for patients with *KRAS* mutant lung cancers. We sought to use a next-generation sequencing-based assay to comprehensively describe concurrent genetic alterations present in *KRAS* mutant lung cancers and explore the effect of such alterations on patient outcomes. **Methods:** We studied tumor DNAs from 102 patients with stage IV/recurrent *KRAS* mutant lung cancers enriched for cases with longer and shorter overall survivals. All patients received standard therapies for advanced lung cancer. We performed massively parallel sequencing (Ion Torrent PGM) of all exons from 65 cancer genes using a custom AmpliSeq panel. The sequence data were analyzed for point mutations and small insertions and deletions using a custom pipeline. We collected clinical characteristics, survival, and concurrent mutations. The association of concurrent mutations and overall survival was evaluated using Kaplan-Meier methodology with log rank test for comparisons. **Results:** Among these 102 samples in which the *KRAS* (G12C=47, G12D=23, G12V=12, G12A=9, Other=11) mutation was confirmed by Ion Torrent PGM sequencing, we found 0 to 11 concurrent mutations with a majority of the patients having 1 (24), 2 (30), or 3 (16) mutations in addition to *KRAS*. The most frequent concurrent mutations included *TP53* (21), *KEAP1* (13), *SMARCA4* (7), and *ARID1A* (6). There was no difference in median overall survival between patients with or without a concurrent mutation in *TP53* (21 vs 25 mos, p=0.84), *KEAP1* (19 vs 25 months, p=0.86), *SMARCA4* (12 vs 25 months, p=0.14) or *ARID1A*(22 vs 25 months, p=0.5). **Conclusions:** This study is the largest reported series of *KRAS* mutant lung cancers with a broad analysis of concurrent molecular alterations and survival. There was no significant effect on survival for concurrent mutations in the identified cancer associated genes.

**8034 Poster Highlights Session (Board #49), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Targeting *FGFR1*-amplified lung squamous cell carcinoma with the selective pan-FGFR inhibitor BGJ398.** *Presenting Author: Lucia Nogova, Lung Cancer Group Cologne, Center for Integrated Oncology, University Hospital Cologne, Cologne, Germany*

**Background:** Identifying molecular drivers in lung squamous cell carcinoma (SCC) is a major medical need since no targeted therapy is available yet for this subtype. Fibroblast growth factor receptors (FGFRs) are physiologically involved in cell proliferation and survival. Genetic alteration of *FGFR* genes leads to deregulated activation in various cancers, and *FGFR1* amplification has been detected in lung SCC. Here, we report on patients (pts) with *FGFR1*-amplified lung SCC treated in a phase 1 study of BGJ398, a potent, selective pan-FGFR inhibitor. **Methods:** While this phase 1 dose-escalation study enrolled pts ≥ 18 years of age with any *FGFR* genetically altered tumor, we report here on the subgroup of pts with *FGFR1*-amplified advanced or metastatic lung SCC treated with 100 or 125 mg BGJ398 once daily in 28-day cycles. Pts who had progressed following at least 1 line of therapy, including platinum, were eligible for enrollment. *FGFR1*-amplified tumors were identified by fluorescent/chromogenic in situ hybridization (FISH/CISH) using, in most pts, a score recently established for lung SCC (Schildhaus, Mod Path 2012). Radiologic evaluation was performed every 8 weeks. **Results:** As of November 22, 2013, 21 pts with lung SCC were treated at the maximum tolerated dose of 125 mg/day (n = 19) or 100 mg/day (n = 2). Screening for *FGFR1* amplification was most commonly performed locally (n = 17) vs centrally (n = 4) and was assayed by FISH in all but 1 case (CISH). Of 17 evaluable pts at data cutoff, 2 achieved partial responses (PR; 1 confirmed by RECIST). PRs were durable, lasting about 8 and 3 months, respectively. Of note, 2 additional pts achieved PR (1 confirmed) after the data cutoff date. Additionally, 3 pts had stable disease with tumor regressions noted (up to 11% reduction). The adverse event profile for pts in this study with lung SCC included manageable and reversible hyperphosphatemia, as well as stomatitis, alopecia, decreased appetite, and fatigue. **Conclusions:** Here we report on the first molecularly targeted therapy in lung SCC demonstrating clinical efficacy. These data encourage further development of BGJ398 in *FGFR1*-amplified lung SCC and efforts to optimize predictive biomarkers for FGFR inhibitor sensitivity. Clinical trial information: NCT01004224.

**8035 Poster Highlights Session (Board #50), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**A phase 1b open-label multicenter study of AZD4547 in patients with advanced squamous cell lung cancers: Preliminary antitumor activity and pharmacodynamic data.** *Presenting Author: Paul K. Paik, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Squamous cell lung cancers (SQCLC) account for 25% of all NSCLCs. Prognosis is poor with few treatment options. Amplified *FGFR1* is one of the most common oncogenic events in SQCLCs and occurs in ~20% of cases. AZD4547 is a potent and selective FGFR1-3 inhibitor with activity in *FGFR1* amplified SQCLC cell lines and patient-derived xenografts. Prior work identified a recommended dose of 80mg po bid. **Methods:** This was a multicentre Phase 1 expansion of AZD4547 in patients with previously treated stage IV *FGFR1* amplified SQCLCs (NCT00979134). *FGFR1* amplification (*FGFR1:CEP8*≥ 2) was confirmed through central FISH (N=13) or review of local results (N=2). Primary endpoint was safety/tolerability. Secondary endpoints were preliminary anti-tumor activity, PK, and PD. CT scans were performed at baseline and every 6 weeks. **Results:** 15 patients were treated. Median age=66 (48-72); female=46%; former/current smoker=100%; WHO restricted PS=69%. 8 patients had FISH ratios between 2-2.8 (low amplification). 7 patients had FISH ratios > 2.8 (high amplification). Mean relative dose intensity= 97%. The most common related AEs were GI and dermatologic. Grade ≥ 3 related AEs occurred in 3 patients (20%) (central serous retinopathy (CSR), hyponatremia, dehydration). Related SAEs occurred in 3 patients (CSR,dehydration, asthenia and dyspnea). There were 3 discontinuations due to AEs and no deaths due to drug. 14 patients were evaluable for tumor response assessment. There were: 1 PR, 4 SD, 9 PD (7 progressions and 2 deaths). The 1 PR was observed in a patient with high *FGFR1*amplification. Preliminary analysis found an increase in serum phosphate following treatment with AZD4547. Exon-sequencing of 283 cancer-related genes in 6 patient tumors, including 1 with a PR, showed no clear response modifiers. **Conclusions:** AZD4547 was well-tolerated in patients with *FGFR1* amplified SQCLC but did not meet its pre-specified efficacy endpoint in terms of overall response rate for continuation. The increase in serum phosphate concentration observed in this study provides evidence that AZD4547 at this dose and schedule causes pharmacologic target inhibition. Clinical trial information: NCT00979134.

**8036^ Poster Highlights Session (Board #51), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**NCIC CTG BR.26: A phase III randomized, double blind, placebo controlled trial of dacomitinib versus placebo in patients with advanced/metastatic non-small cell lung cancer (NSCLC) who received prior chemotherapy and an EGFR TKI.** *Presenting Author: Peter Michael Ellis, Juravinski Cancer Centre, Hamilton, ON, Canada*

**Background:** Dacomitinib (D) is an irreversible pan-HER inhibitor with evidence of activity in previously treated NSCLC patients (pts). **Methods:** BR26, a phase III randomized double blind placebo (P) controlled trial of D (45mg daily oral) vs P in NSCLC pts after one to three lines of chemotherapy and an EGFR TKI, randomized pts 2:1 to D or P. Response was assessed at 4, 8 then every 8 weeks during treatment. The primary endpoint was overall survival (OS). Secondary endpoints included OS in pts with *KRAS* wild type (WT) NSCLC, progression free survival (PFS), response rate (RR), toxicity, quality of life, biomarker analyses and resource utilization. **Results:** 720 pts were randomized: median age 64 yrs (range 32-90), male 51%, PS 0/1 75%, adenocarcinoma 73%, never smokers 36%. D did not improve OS compared with P (median OS 6.8m v 6.3m, HR 1.0, 95%CI 0.83-1.21, p=0.99). There was significant improvement in PFS favoring D (median PFS 2.7m v 1.4m, HR 0.66, 95%CI 0.55 – 0.79, p<0.0001). The RR was 7% v 1%, p=0.001. *EGFR* /*KRAS* status were known in 531/418 pts, respectively. The effect of D on OS was similar in pts with *EGFR* WT and *EGFR* mutation positive NSCLC (HR 0.93 vs 0.98, interaction p=0.69). The effect of D on OS appeared to differ by *KRAS* status: improving OS in pts with *KRAS* WT tumors (7.0m v 5.2m, HR 0.79, 95%CI 0.61 – 1.03), but worsening OS in pts with *KRAS* mutation positive NSCLC (5.8m v 8.3m, HR 2.1, 95%CI 1.05 – 4.22, interaction p=0.08). Pts on D had significantly longer time to deterioration of cough (p<0.0001), dyspnea (p=0.049) and pain (p=0.041). Pts treated with D vs. P [%] experienced more diarrhea (80 vs. 20), acneiform rash (60 vs. 10), oral mucositis (43 vs. 3), paronychia (30 vs. 0), dry skin (36 vs. 11), nausea/vomiting (36/28 vs. 25/16). Systemic therapy use after PD was 37% in pts. on D vs. 41% on P. **Conclusions:** D has activity in heavily pretreated pts with NSCLC. Although there was no improvement in OS, BR26 demonstrated a significant improvement in RR, PFS and time to symptom deterioration, and a trend to improved OS in pts with *KRAS* WT NSCLC. Further evaluation of D in biomarker defined subgroups appears warranted. Clinical trial information: NCT01000025.

**8037 Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Randomized phase III trial of stereotactic radiosurgery (SRS) versus observation for patients with asymptomatic cerebral oligo-metastases in non-small cell lung cancer (NSCLC).** *Presenting Author: Sung Hee Lim, Department of Medicine, Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

**Background:** In patients with non-small cell lung cancer (NSCLC) with asymptomatic cerebral oligo-metastases, it is unclear whether treating brain metastasis before starting systemic chemotherapy is beneficial effects on survival compared with upfront systemic chemotherapy. This study was aimed to determine if early treatment with stereotactic radiosurgery (SRS) improve overall survival (OS) in NSCLC patients with asymptomatic oligo-brain metastases. **Methods:** We undertook a randomized controlled trial of 105 patients with asymptomatic oligo (1 to 4) brain metastases, each less than 3 cm in diameter, enrolled at Samsung Medical Center between 2008 and 2013. Patients older than 18 years with NSCLC and synchronous asymptomatic brain metastasis were randomly assigned to receive SRS initially (53 patients) followed by systemic chemotherapy or upfront systemic chemotherapy alone group (52 patients). The primary end point was OS and secondary end points included time to CNS disease progression, salvage brain treatment. **Results:** The median age of all patients was 58 years (range, 29-85) with good ECOG performance status(0,1), and most patients had adenocarcinoma (87%). The median overall survival time was 15.8 months (95% CI, 8.1-23.5) in SRS group and 17.6 months (95% CI, 12.4-22.8) for observation group (P=0.346). There was no significant difference in time to CNS disease progression (median, 9.4 months vs. 8.7 months, P=0.579). Salvage treatment for progression of CNS disease was required more frequently in observation group (52.8%) than SRS group (47.2%) which did not show statistical significance (P=0.201). The multivariate analysis revealed that higher extra-cranial disease activity, number of brain metastases (≥2), age older than 65 years, non-adenocarcinoma histology were independent risk factors associated with poor OS. **Conclusions:** These results suggest that SRS treatment followed by systemic chemotherapy did not improve overall survival in asymptomatic oligo-brain metastases NSCLC patients compared with upfront chemotherapy alone.

**8040 General Poster Session (Board #221), Sat, 1:15 PM-5:00 PM**

**Sunitinib (S) switch maintenance in advanced non-small cell lung cancer (NSCLC): An ALLIANCE (CALGB 30607), randomized, placebo-controlled phase III trial.** *Presenting Author: Mark A. Socinski, University of Pittsburgh, Pittsburgh, PA*

**Background:** This study compared switch maintenance with S versus placebo (P) in patients (pts) with advanced NSCLC following four cycles of first-line chemotherapy. The primary endpoint was progression-free survival (PFS) after randomization. Overall survival (OS) was a secondary endpoint. **Methods:** Stage IIIB/IV pts, PS 0-1 with stable/responding disease after 4 cycles of platinum-based therapy were randomized to S (37.5 mg po qd) vs P. Pts were assessed for progression every 6 weeks. PFS and OS were measured from the time of randomization. The trial was designed to have 90% power to detect a 6 week improvement in PFS using a log rank test at a 2-sided significance level of 0.05. Planned accrual was 244 pts. All p values are 2-sided. **Results:** The trial crossed the superiority boundary on the primary endpoint at an interim analysis. 210 pts were randomized (106 S, 104 P). Median age 66 yrs (range 25-89), 55.7% male, 60.5% ECOG PS 1, 87.6% stage IV, 22.4% received bevacizumab (which had to be discontinued at randomization), 91.7% current/past smokers. 45.9% had adenocarcinoma, 33.2% squamous, 13.7% undifferentiated NSCLC and 4.4% large cell. PFS was 4.3 mos on the S arm vs 2.8 mos on the P (HR 0.59, p=0.0008). PFS was improved for both squamous (4.3 S vs 2.4 P mos, HR=0.55, p=0.02) as well as non-squamous histology (4.3 S vs 2.8 P mos, HR=0.64, p=0.02). OS was not different (11.2 mos S vs 11.2 mos P, HR 1.05, p=0.77). Protocol treatment discontinuation was most commonly due to disease progression for P (90.6% for P vs 51.1% on S) and adverse event for S (28.7% for S vs 4.2% for P). Grade 3/4 toxicities (%) occurring in >5% of patients (S vs P) were anemia (6 vs 0), neutropenia (6 vs 1), thrombocytopenia (12 vs 0), hypertension (8 vs 0), fatigue (25 vs 4), rash (11 vs 0) and mucositis/stomatitis (11 vs 0). The rate of subsequent therapy was 74% on the P arm vs 61% on the S arm (p=0.049). **Conclusions:** CALGB 30607 met its primary endpoint by demonstrating a significant improvement in PFS for S switch maintenance therapy in advanced NSCLC. No effect on the secondary endpoint of OS was seen. Clinical trial information: NCT00693992.

**8041 General Poster Session (Board #222), Sat, 1:15 PM-5:00 PM**

**Randomized phase III study comparing gefitinib (G) with erlotinib (E) in patients (pts) with previously treated advanced lung adenocarcinoma (LA): WJOG 5108L.** *Presenting Author: Nobuyuki Katakami, Division of Integrated Oncology, Institute of Biomedical Research and Innovation, Kobe, Japan*

**Background**: Second-line therapy for advanced LA pts after progression on platinum-based regimens typically employs chemotherapy (CT) or EGFR-TKIs. Both G and E improved progression free survival (PFS) in pts with activating *EGFR*-mutation. We conducted a multicenter randomized phase III study designed to demonstrate noninferiority of G to E. **Methods**: Eligible pts were those with pathologically proven LA with stage IIIB/IV (AJCC version 6) or recurrence, previously treated with at least one chemotherapy regimen, evaluable disease, age ≥20 years and ECOG PS 0-2. Pts were randomized 1:1 to E (150 mg, daily), or G (250mg, daily) according to gender, stage, *EGFR* mutation status, performance status, smoking history, CT line, and institution. Target sample size was 560 based on the assumption that G was not inferior to E in PFS (2 – 4 months, $\alpha$ =0.025 [one sided], $\beta$ =0.80).Noninferiority was to be concluded if the upper CI limit was < 1.30. The primary endpoint was PFS, and secondary endpoints included overall survival (OS), response rate (RR), disease control rate (DCR), safety, and time to treatment failure (TTF). **Results**: From 2009/7 to 2012/10, 561 pts were accrued, and 280 and 279 were randomly assigned to E and G in FAS, respectively, including 185 (66.1%, E) and 186 (66.7%, G) with *EGFR* activating mutation tumors. Other baseline factors were balanced between arms except PS: median age 67/68 years; % female 54/55; % PS=0, 50/40; PS=1, 43/54; % stage IV, 69/69; % 2nd line, 69/71, % smoker, 50/50; for E v G. Median PFS, TTF and OS for E v G were 7.5 m v 6.5 m (p=0.257, HR=1.125, 95% CI: 0.940-1.347), 5.3 m v 5.6 m (HR=1.032, 95% CI: 0.866-1.231), and 24.5 m v 22.8 m (HR=1.038, 95% CI: 0.833-1.294), respectively. RR and DCR for E v G were 43.9% v 46.1%, and 75.0% v 71.2%, respectively. Median PFS and OS in pts with activating mutation for E v G were 10.1 m v 8.9 m (p=0.532), and 32.0 m v 26.6 m (p=0.111), respectively. Main grade 3/4 toxicities were rash (18.1% [E] v 2.2% [G]) and elevation of AST/ALT (2.2%/3.3% [E] v 6.1%/13.0% [G]). **Conclusions**: Noninferiority in PFS between E and G was not demonstrated according to predefined criteria, however, there was no statistically significant difference in PFS. Clinical trial information: UMIN000002014.

**8042 General Poster Session (Board #223), Sat, 1:15 PM-5:00 PM**

**BATLLE-2: *KRAS* mutation and outcome in a biomarker-integrated study in previously treated patients (pts) with advanced non-small cell lung cancer (NSCLC).** *Presenting Author: Vassiliki Papadimitrakopoulou, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** BATTLE-2 is building on the personalized medicine approach pioneered in the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE-1) trial, and is designed to address mutant *KRAS* and identify predictive biomarkers for targeted therapies in chemo-refractory pts. **Methods:** Pts refractory to at least 1 prior therapy, were adaptively randomized (AR), in this phase II, multi-center study, after tumor biopsy and exclusion of sensitizing *EGFR* mutations (mut+) or *ALK* fusions to 4 arms: erlotinib (E) 150 mg qd, E plus the AKT inhibitor MK-2206 (M) 135 mg q week, M 100 mg q week plus the MEK inhibitor AZD6244 (A) 100 mg qd, and sorafenib (S) 400 mg bid. The primary objective is 8-week disease control rate (DCR). In Stage 1, 200 pts are randomized and in Stage 2, AR of 200 pts will incorporate the best predictive biomarkers from Stage 1, to be derived from protein expression, gene expression profiling, 16-gene Sequenom mutation analysis and next generation sequencing (NGS) of 182 genes by Foundation Medicine. **Results:** From 6/2011 to 11/2013, 198 pts randomized to E (22 pts), EM (42 pts), MA (73 pts), S (61 pts). Demographics: Median age 62 (range 22-82); male 48%; ECOG PS 0-1 83%, PS 2 17%; Caucasian 89%, Asian 3%, other 8%; never/former/current smokers 33%/60%/7%; adenocarcinoma 73%, squamous 19%, other NSCLC 8%; prior E 37%, *KRAS* mut+ 23%, median prior therapies for metastatic NSCLC: 2 (range 1-9). Treatment was well tolerated. With 167 pts evaluable, overall 8-week DCR was 47%, worse with E (20%) than with EM (51%), MA (53%) and S (43%) (Fisher's exact test p= 0.06, 0.02, and 0.14). For *KRAS* wild type pts, DCR was worse for E (25%) than all other 3 arms (53%, 50%, and 44%, for EM, MA and S). For *KRAS* mut+ pts, DCR was highest for MA (61%) (0%, 40%, and 43% for E, EM, and S).Partial responses to MA were seen in 2 pts (*KRAS* mut+/ *ARAF* mut+, and *CDKN2A/FBXW7/TP53*mut+). **Conclusions:** Improved DCR was observed with EM and MA compared with E. The MA combination is active in KRAS mut+ NSCLC and merits further study. Biomarker analysis is ongoing to define better predictive markers and Stage 2 of BATTLE-2 is being redesigned. (Supported by NCI RO1CA155196-01A1). Clinical trial information: NCT01248247.

**8044 General Poster Session (Board #225), Sat, 1:15 PM-5:00 PM**

**Tivantinib plus erlotinib versus placebo plus erlotinib in Asian patients with previously treated nonsquamous NSCLC with wild-type *EGFR*: First report of a phase III ATTENTION trial.** *Presenting Author: Koichi Azuma, Division of Respirology, Neurology and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Kurume, Japan*

**Background:** A randomized phase II study suggested that adding a c-Met inhibitor tivantinib (T) to an EGFR-TKI erlotinib (E) may prolong PFS in non-squamous NSCLC patients (pts) with 1-2 prior chemotherapy. Furthermore, the subset analysis suggested that survival benefit was more prominent in pts with wild-type *EGFR* (WT-*EGFR*) than in those with *EGFR* mutation. Therefore we conducted the phase III ATTENTION trial to compare overall survival (OS) between T+E vs. placebo (P)+E, in Asian pts with pretreated NSCLC with WT-*EGFR*. **Methods:** Four-hundred-and sixty Asian (Japan, Korea, and Taiwan) pts who had been treated with 1-2 chemotherapy for non-squamous NSCLC with WT-*EGFR* were planned to be randomized between T+E and P+E. The doses of T were 360mg BID and 240mg BID, for CYP2C19 extensive metabolizers (EM) and poor metabolizers (PM), respectively, whereas that of E was 150 mg QD for both EM and PM. The primary endpoint was OS, and secondary endpoints included PFS, ORR, and safety. Exploratory analysis tested biomarkers including c-Met expression and *KRAS* mutation. **Results:** New enrollment was stopped when 307 pts had been randomized, following the Safety Review Committee's recommendation based on an observed imbalance in interstitial lung disease (ILD) between the groups. Accordingly,153 and 154 pts were treated with T+E and P+E, respectively. Patient backgrounds including CYP2C19 genotype were well balanced. Results are summarized below. Typical ≥Gr.3 adverse events in T+E were anemia (13.2 %), neutropenia (10.5 %), and leukopenia (6.6 %). Fourteen pts (including 3 deaths) and 6 pts (0 deaths) developed ILD in T+E and P+E, respectively. **Conclusions:** Although this trial lacked a statistical power due to the prematurely termination owing to toxicity concern, our results indicated some sign for benefit for adding T to E in this population. OS was numerically prolonged but this did not reach statistical significance. Exploratory biomarker analysis may identify subsets in which benefit and risk from this treatment is well balanced. Clinical trial information: NCT01377376.

| | Median OS | Median PFS | ORR |
|---|---|---|---|
| **T+E** | 12.9 mo | 2.9 mo | 8.4% |
| **P+E** | 11.2 mo | 2.0 mo | 6.5% |
| **HR** | 0.891 | 0.719 | |
| **P value** | 0.427 | 0.019 | |

**8045 General Poster Session (Board #226), Sat, 1:15 PM-5:00 PM**

**Phase 2 HERALD study of patritumab (P) with erlotinib (E) in advanced NSCLC subjects (SBJs).** *Presenting Author: Joachim Von Pawel, Asklepios-Fachkliniken München-Gauting, Gauting, Germany*

**Background:** P is a fully human anti-HER3 antibody that inhibits HER3 binding with its ligand heregulin (HRG). Preclinically, P enhances anti-tumor activity with EGFR inhibitors, prevents HER3 reactivation after anti-EGFR treatment, and inhibits HRG-dependent activation. Phase Ib showed that P, with E (150mg/day PO), was tolerated at 18mg/kg IV q3w. **Methods:** This Ph2 randomized, placebo-controlled double-blind study assessed safety and efficacy of P+E vs. placebo (Pbo)+E in E-naïve sbjs with advanced NSCLC (2nd or later line). 215 sbjs were randomized to: 1) High Dose [HD]: P 18 mg/kg IV q3w; 2) Low Dose [LD]: P: 18 mg/kg IV X 1, 9 mg/kg IV q3w maintenance; or 3) Pbo q3wk. All subjects received E 150 mg/day PO. Endpoints included PFS (primary), and OS and safety (secondary). HRG, measured as mRNA, was prospectively hypothesized to be the primary predictive biomarker before database lock. High/Low HRG cutoff was set at the median of the blinded data. **Results:** 212 sbjs comprised the ITT. Median (m) PFS for ITT for HD, LD, and Pbo arms was 1.4 mos (HR 0.98), 2.5 mos (HR 0.77), and 1.6 mos, respectively (p=NS). 101 sbjs (51 HRG high) had adequate tissue for HRG testing. PFS was significantly improved in the HRG high subgroup (Table). HRG low subgroup showed no improvement in PFS (HR 0.92) and OS (HR 1.05) vs. Pbo. Grade >3 AE's (HD, LD, Pbo) included: diarrhea (11.4%, 8.5%, 4.2%) and rash (5.7%, 7.0%, 2.8%). **Conclusions:** P showed improved PFS in the HRG high, but not in the ITT population. P safety was similar to Pbo with the exception of manageable rash and gastrointestinal effects. HRG appears to be a predictive biomarker for P, confirming preclinical findings (Schneider et al, Yonesaka et al, ASCO 2014). HERALD is the first randomized Pbo controlled trial in NSCLC to report a predictive biomarker for HER3. Based on these results, a 2-part (A, confirmation of HRG predictive value; B, pivotal HRG high only) Phase 3 study was initiated. Clinical trial information: NCT01211483.

| | High dose P + E | Low dose P + E | Pooled doses P + E | E alone (Pbo) |
|---|---|---|---|---|
| **mPFS (mos)** | 3.4 | 3.0 | 3.0 | 1.4 |
| **PFS HR (95% CI)** | 0.37 (0.16, 0.85)* | 0.29 (0.13, 0.66)† | 0.32 (0.16, 0.67)† | |
| **mOS (mos)** | 6.1 | 10.7 | 9.7 | 5.0 |
| **OS HR (95% CI)** | 1.15 (0.50, 2.61) | 0.60 (0.25, 1.41) | 0.81 (0.39, 1.67) | |

Log-rank p value: *<0.03, †<0.003).

**8046 General Poster Session (Board #227), Sat, 1:15 PM-5:00 PM**

**Efficacy and safety results from CurrentS, a double-blind, randomized, phase III study of second-line erlotinib (150 mg versus 300 mg) in current smokers with advanced non-small cell lung cancer (NSCLC).** *Presenting Author: Egbert F. Smit, VU University Medical Center, Amsterdam, Netherlands*

**Background:** Pts with NSCLC who are active smokers may have increased erlotinib metabolism v non-smokers, which reduces exposure. **Methods:** Pts with stage IIIB/IV NSCLC (failed first-line platinum-based chemotherapy, current smokers) were randomized to receive standard dose erlotinib (150 mg/day; E150) or an experimental dose (300 mg/day; E300) until progression/death/unacceptable toxicity. Pts were assessed every 6 wks. Primary endpoint: progression-free survival (PFS). Secondary endpoints included: overall survival (OS), disease control rate (DCR), and safety. Planned sample size: 300 randomized pts; 277 PFS events needed to show a HR of 0.714 (median PFS improvement from 10 to 14 wks; E300 was expected to provide a longer median PFS v E150) with 80% power (5% 2-sided $\alpha$). **Results:** Baseline characteristics were balanced (Table). Efficacy and safety results are reported (Table). **Conclusions:** CurrentS, the first and largest trial in active smokers with NSCLC to date, did not show a statistically significant increase in PFS (primary endpoint) when erlotinib was given at 300 mg v 150 mg. OS (secondary endpoint) was not different between the arms. There was a numerical increase in AESIs with the higher dose. PK data will be presented. Clinical trial information: NCT01183858.

| | | E150 | E300 |
|---|---|---|---|
| | **ITT population** | **N=154** | **N=159** |
| **Ethnicity, n (%)** | Caucasian | 97 (63.0) | 99 (62.3) |
| | Asian | 46 (29.9) | 49 (30.8) |
| | Other/not reported | 11 (7.1) | 11 (6.9) |
| **Histology, n (%)** | Adenocarcinoma | 100 (64.9) | 96 (60.4) |
| | Squamous cell carcinoma | 42 (27.3) | 48 (30.2) |
| | Large cell carcinoma | 6 (3.9) | 7 (4.4) |
| | Other | 6 (3.9) | 8 (5.0) |
| **ECOG PS, n (%)** | 0–1 | 145 (94.2) | 148 (93.1) |
| | 2 | 9 (5.8) | 11 (6.9) |
| **Smoking status** | Median pack yrs | 31.3 | 30.0 |
| **PFS** | Events, n (%) | 143 (92.9) | 140 (88.1) |
| | Median, wks | 6.9 | 7.0 |
| | *HR (95% CI) | 1.05 (0.83–1.33) | |
| | *Log-rank p | 0.671 | |
| **OS** | Events, n (%) | 122 (79.2) | 123 (77.4) |
| | Median, mo | 6.8 | 6.8 |
| | *HR (95% CI) | 1.03 (0.80–1.32) | |
| | *Log-rank p | 0.846 | |
| **DCR, % (95% CI)** | | 40.3 (32.4–48.5) | 36.5 (29.0–44.5) |
| | **Safety population** | **n=154** | **n=158** |
| **Relative dose intensity (% of planned), mean (SD)** | | 98.6 (5.9) | 97.1 (8.4) |
| **AEs of special interest (AESI; all grades), n (%)** | Rash | 63 (40.9) | 97 (61.4) |
| | Diarrhea | 30 (19.5) | 47 (29.7) |
| | Interstitial lung disease | 0 (0.0) | 2 (1.3) |

* Unstratified.

**8047 General Poster Session (Board #228), Sat, 1:15 PM-5:00 PM**

**Updated efficacy and safety of the ALK inhibitor AP26113 in patients (pts) with advanced malignancies, including ALK+ non-small cell lung cancer (NSCLC).** *Presenting Author: Scott N. Gettinger, Yale University, New Haven, CT*

**Background:** AP26113 is a novel orally-active tyrosine kinase inhibitor with preclinical activity against ALK and all 9 clinically-identified crizotinib-resistant mutants tested. **Methods:** The Phase (Ph) 2 portion of a Ph1/2 single arm, multicenter study in pts with advanced malignancies is underway. We report updated safety for all treated pts and efficacy data for ALK+ NSCLC pts previously treated with crizotinib. NCT01449461. **Results:** As of 16 Dec 2013, 114 pts were enrolled: 65 in Ph1 (30-300 mg) and 49 in Ph2 (180 mg). Baseline characteristics: 59% female, median age 57 yr; diagnoses: NSCLC n=106, other n=8. 66 pts remain on study; median follow-up for all pts is 3.6 mo (max= 21.4 mo, ongoing). The most common treatment-emergent AEs (≥20%) were nausea (38%), diarrhea (31%), fatigue (31%), cough (23%), and headache (20%), which were generally grade 1/2 in severity. Early onset of pulmonary symptoms (dyspnea with hypoxia and/or findings on imaging) observed in 6/45 (13%) pts at 180mg QD. These symptoms, requiring immediate medical attention, were not observed at 90mg QD (n=8) or in the lead-in dose cohort (n=19; initiated at 90mg QD, escalated to 180mg QD after 1 wk). Pts continue to be enrolled with this dose escalation scheme, and an additional cohort of 90mg QD without escalation will be added. Among 38 evaluable ALK+ NSCLC pts with prior crizotinib, 24 (63%) responded (23 partial response, 1 complete response). Duration of response was 1.6 - 14.7 mo (ongoing). 15 pts had confirmed responses; 5 await confirmation, 4 are unconfirmed. Among 42 evaluable pts with ALK+ NSCLC, median progression free survival is 47 wk. Independent radiological review conducted on 10 pts enrolled with untreated or progressing brain metastases showed 6/10 pts with response in brain, including 4 with undetectable brain metastases following AP26113; 2 pts had stable disease, 2 pts progressed; 8/10 remain on study (range 5-17 mo). **Conclusions:** AP26113 has promising anti-tumor activity in pts with crizotinib-resistant ALK+ NSCLC, including pts with brain metastases. A randomized Ph2 trial evaluating 90 mg QD vs. 90mg QD escalating to 180mg QD in crizotinib-resistant ALK+ NSCLC will begin shortly. Clinical trial information: NCT01449461.

**8048 General Poster Session (Board #229), Sat, 1:15 PM-5:00 PM**

**Analysis of *NTRK1* gene fusion incidence in an unselected cohort of non-small cell lung cancer patients.** *Presenting Author: Robert Charles Doebele, University of Colorado Cancer Center, Aurora, CO*

**Background:** The identification and therapeutic targeting of oncogenic drivers in lung adenocarcinoma has led to significant clinical improvements for patients with *EGFR* mutations or *ALK* fusions. We recently discovered a new oncogenic fusion involving *NTRK1* that can be targeted by kinase inhibitors against the TRK family of receptor tyrosine kinases. We therefore investigated *NTRK1*cytogenetic patterns of tumor samples from NSCLC patients to determine the incidence and clinical characteristics of patients in this unselected cohort. **Methods:** A tumor microarray (TMA) previously analyzed by *ALK (12/445=2.7%)*, *ROS1 (5/429=1.2%)* and *RET* (6/348=1.7%) FISH containing 447 tumor samples from patients with NSCLC was analyzed. Clinical characteristics of the TMA have been reported previously. Fluorescence in situ hybridization (FISH) screening using a novel dual color *NTRK1* break-apart assay was performed. RT-PCR was performed on RNA extracted from corresponding tumor blocks to confirm the presence and identify of the *NTRK1*fusion partner. A novel proximity-ligation assay (PLA) to detect TRKA activation by detecting TRK-SHC1 protein complexes was developed as a complimentary, proteomic method for the detection of TRK activation, regardless of the mechanism of activation. **Results:** *NTRK1* FISH analysis was successfully performed on 443 of 447 tumor samples (99.1%). Five of 443 (1.1%) tumor samples exhibited patterns indicating an *NTRK1* rearrangement with split (n=1), single 3' (n=1), or single 5' (n=3) signals. Clinical characteristics of the 5 *NTRK1*+ patients are as follows: 3 female; 2 never-smokers; and 3 adenocarcinoma, 1 squamous cell carcinoma, and 1 large cell neuroendocrine carcinoma histology. An additional 5 samples had atypical cytogenetic patterns and 7 samples demonstrated focal *NTRK1*gene amplification warranting further exploration by alternate methodologies. **Conclusions:** *NTRK1* gene rearrangements were detected in 1.1% of tumor samples from an unselected cohort of NSCLC patients. Additional *NTRK1* cytogenetic patterns were observed and warrant further evaluation. Confirmatory testing by PCR to evaluate the specific *NTRK1* fusion transcripts and a novel TRK PLA method will be presented.

**8049 General Poster Session (Board #230), Sat, 1:15 PM-5:00 PM**

**Identifying *ALK* rearrangements that are not detected by FISH with targeted next-generation sequencing of lung carcinoma.** *Presenting Author: Siraj M. Ali, Foundation Medicine, Inc., Cambridge, MA*

**Background:** Genomic rearrangements of *ALK* are the defining feature of a subset of lung non-small cell carcinomas (NSCLC), and predict response to ALK-targeted therapies. We reviewed our experience with *ALK* rearranged lung carcinomas (LC) as detected by a clinical next generation sequencing (NGS)-based assay. **Methods:** Genomic profiling of 1,070 lung carcinomas was performed on >50 ng of DNA extracted from formalin fixed, paraffin embedded specimens, from either primary tumors or metastatic sites. Libraries constructed from such DNA were subjected to hybrid capture of all exons of 236 cancer related genes and 47 introns of 19 genes frequently rearranged in cancer, and followed by clinical NGS with high uniform coverage to a median exon coverage depth exceeding 700x. Data regarding prior diagnostic studies for genomic alterations and response to targeted therapies was provided by treating physicians. **Results:** Of 1.070 total lung carcinomas profiled, 47 harbored *ALK* rearrangements (4.4%); including lung adenocarcinomas (n=39/724), NSCLC (n=4/146), adenosquamous carcinomas (n=2/12), and mucoepidermoid and large cell neuroendocrine carcinomas (n=1/3 and n=1/23). The median age of the patients was 52 years, with an equal sex ratio, and 38 patients had Stage IV disease. Of the 28 *ALK* rearranged specimens also tested by *ALK* FISH, 9 (32%) were negative, and 19 were positive. Of the 47 *ALK* rearranged cases, all fusions had a breakpoint in intron 19 of *ALK*. Six cases harbored non-*EML4* 5' partners. Of the 41 *EML4-ALK* fusions, there were 17 cases with a breakpoint in intron 13 of *EML4* (variant1), 2 cases in intron 18, 2 cases in intron 2(v5), 4 cases in intron 20 (v2), and 16 cases in intron 6 (v3). Twenty-two patients were treated with crizotinib and had response data available; 19 responded by investigator assessment. Of the 9 cases negative by FISH, 5 patients responded to crizotinib, 2 patients did not, and the response data for the remaining 2 patients is unavailable. **Conclusions:** Targeted NGS may be more sensitive for the detection of *ALK* rearrangements than FISH. In light of the responsiveness of *ALK* NGS+/FISH- tumors to crizotinib, the use of FISH as the gold standard for *ALK* detection in LC warrants prospective study.

**8050 General Poster Session (Board #231), Sat, 1:15 PM-5:00 PM**

**A randomized phase 2 study of a human antiplatelet-derived growth factor $\alpha$ (PDGFR$\alpha$) monoclonal antibody (olaratumab, IMC-3G3) with paclitaxel/carboplatin or paclitaxel/carboplatin alone in previously untreated patients with advanced non-small cell lung cancer (NSCLC).** *Presenting Author: David E. Gerber, The University of Texas Southwestern Medical Center, Dallas, TX*

**Background:** In NSCLC, the PDGF-PDGFR axis mediates angiogenesis, local invasion, and tumor interstitial pressure. Olaratumab (IMC-3G3), a fully human monoclonal antibody, selectively binds human PDGFR$\alpha$ and blocks ligand binding. This open-label phase 2 study assessed the safety and efficacy of olaratumab added to paclitaxel/carboplatin (P/C) versus P/C alone in previously untreated patients (pts) with advanced NSCLC. **Methods:** Pts were randomized to receive up to 6 cycles of P 200 mg/m$^2$and C AUC 6 (day 1) with (Arm A) or without (Arm B) olaratumab 15 mg/kg on days 1 and 8. The primary endpoint was progression-free survival (PFS), estimated by the Kaplan-Meier method. Olaratumab maintenance therapy was continued in Arm A until disease progression. At the time of progression, pts in Arm B could cross over to olaratumab monotherapy. **Results:** A total of 131 pts were randomized to Arm A (n=67) or Arm B (n=64). Demographics were similar between arms (57% male, 84% white, and median age 65 years). Most pts (74%) had nonsquamous NSCLC. Median PFS (Arm A: 19.1 weeks, Arm B: 19.0 weeks; p=0.21; hazard ratio [HR]: 1.29 [0.86–1.93]), median overall survival (OS) (Arm A: 51.3 weeks, Arm B: 50.1 weeks; p=0.87; HR: 1.04 [0.68–1.57]), and objective response rate (ORR) (Arm A: 42%, Arm B: 34%; p=0.47) were similar between arms. The 2 arms had similar toxicity profiles (Table). Adverse events leading to death occurred in 4 pts in Arm A (dyspnea, sepsis, disease progression, and myocardial infarction) and 2 pts in Arm B (respiratory failure and pneumonia). **Conclusions:** Adding olaratumab to P/C did not result in significant prolongation of PFS, OS, or ORR among previously untreated pts with advanced NSCLC. Clinical studies of olaratumab in other pt populations and biomarker analyses are underway. Clinical trial information: NCT00918203.

**Most frequent grade ≥3 treatment-emergent adverse events, % of patients.**

| | Arm A | Arm B |
|---|---|---|
| **Neutropenia** | 30 | 19 |
| **Thrombocytopenia** | 13 | 5 |
| **Leukopenia** | 12 | 2 |
| **Fatigue** | 10 | 3 |
| **Dyspnea** | 8 | 6 |
| **Anemia** | 6 | 9 |
| **Hyperglycemia** | 6 | 3 |
| **Febrile neutropenia** | 6 | 2 |
| **Dehydration** | 6 | 2 |
| **Lymphopenia** | 6 | 2 |
| **Pulmonary embolism** | 3 | 8 |

**8051 General Poster Session (Board #232), Sat, 1:15 PM-5:00 PM**

**A randomized phase 2 trial of MM-121, a fully human monoclonal antibody targeting ErbB3, in combination with erlotinib in EGFR wild-type NSCLC patients.** *Presenting Author: Lecia V. Sequist, Massachusetts General Hospital, Boston, MA*

**Background:** Heregulin induced activation of ErbB3 has been implicated as a mechanism of resistance to many targeted therapies such as EGFR-TKIs in preclinical models. MM-121 is a monoclonal antibody designed to interfere with this mechanism of resistance. **Methods:** This Phase 2 trial was a global, multi-center, open-label, parallel cohort study of MM-121 and erlotinib in 3 predefined NSCLC patient groups. Here we report final results from one of the 3 groups: EGFR WT patients. This group comprised 132 patients with WT EGFR who progressed on ≥1 platinum-based SOC therapy and were EGFR TKI-naive. Patients were randomized 2:1 to receive MM-121 20 mg/kg every other week plus daily erlotinib at 100 mg (M) or daily erlotinib alone at 150 mg (E). The primary objective was to compare the progression-free survival (PFS) between M and E. Fresh tissue biopsies were mandatory for evaluation of a pre-specified set of biomarkers mechanistically-linked to ErbB3 signaling. **Results:** 121 patients (85 (M), 36 (E)) were included in the safety and efficacy analyses. PFS was analyzed after 105 events (73 (M), 32 (E)). Median PFS was 8.1 weeks for arm M and 7.7 weeks for arm E with a HR of 0.898 (95%CI [0.592, 1.363]), log-rank p=0.6129. The objective response rate was 4.7% (95%CI [1.85 - 11.48]) on arm M, and 5.6% (95%CI [1.54 - 18.14]) on arm E. The median overall survival estimate was 27.3 weeks for arm M and 37.3 weeks for arm E, with a HR of 1.499 (95% CI [0.855, 2.629]). The majority of adverse events were reported as mild to moderate in severity and included the following (M vs. E): rash (74% vs. 37%), diarrhea (59% vs. 27%), dermatitis acneiform (28% vs. 11%), dry skin (54% vs. 47%), nausea (29% vs. 14%), fatigue (31% vs. 13%), stomatitis (20% vs. 5%), decreased appetite (37% vs. 16%), weight decreased (27% vs. 11%), and dyspnea (22% vs. 9%). The adverse events were overall manageable and did not impact compliance on treatment. **Conclusions:** Addition of (M) to (E) was not effective at prolonging PFS in this study population. Overall survival favored the control arm. The observed safety profile is consistent with the expected adverse events associated with ErbB-family inhibitors. Biomarker data will be presented. Clinical trial information: NCT00994123.

**8052 General Poster Session (Board #233), Sat, 1:15 PM-5:00 PM**

**Phase II study of erlotinib plus tivantinib in patients with *EGFR*-mutation–positive NSCLC who failed in immediately previous EGFR-TKI therapy.** *Presenting Author: Tomonori Hirashima, Department of Thoracic Malignancy, Osaka Prefectural Hospital Organization Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Osaka, Japan*

**Background:** Although driver mutations in *EGFR* gene are often associated with initial dramatic response to EGFR-TKI, those patients inevitably develop acquired resistance. It is suggested that dual inhibition of EGFR and c-Met may overcome or delay emergence of this resistance. Therefore, we conducted a multicenter, open-label, single arm Phase II combining erlotinib and a c-Met inhibitor tivantinib, in *EGFR*-mutated NSCLC patients with EGFR-TKI resistance. **Methods:** NSCLC patients who developed progressive disease during their immediately previous treatment with either erlotinib or gefitinib were enrolled. Fresh tumor biopsy was mandatory prior to starting the combination. All patients received daily oral erlotinib and tivantinib, until discontinuation criteria were met. Tumor response was evaluated by the independent radiological committee. The biopsy specimens were used for a comprehensive biomarker analysis, such as IHC assay of c-Met and HGF, and for multiplex mutation analysis (LungCarta Panel) of lung cancer associate genes including *KRAS*, *c-MET*, *PTEN*, *EGFR* and *TP53*. Plasma concentration of soluble c-Met and 8 angiogenic cytokines were also determined by ELISA and Luminex assay, respectively. **Results:** Forty-five patients were treated. The Table below shows objective response rate (ORR) and progression free survival (PFS) in the overall population, and in a subpopulation defined by c-Met expression or resistance mutations in *EGFR* (i.e. T790M or Exon 20 ins). Most of AEs were similar to the previous trials. **Conclusions:** In patients with *EGFR*-mutated NSCLC with EGFR-TKI resistance, erlotinib/tivantinib combination therapy may be beneficial to those with high c-Met expression or in those without resistance mutations in *EGFR*. The more detailed multivariate analyses regarding biomarkers will also be reported. Clinical trial information: NCT01580735.

| Population | N | ORR (%) | Median PFS (days) |
|---|---|---|---|
| Overall | 45 | 4.4 (95% confidence interval [CI]; 0.5-15.1) | 83 (CI; 43-128) |
| c-Met high | 22 | 9.1 (CI; 1.1-29.2) | 125 (CI; 43-212) |
| c-Met low | 22 | 0.0 (CI; 0.0-15.4) | 43 (CI; 42-127) |
| Resistance mutations positive | 23 | 0.0 (CI; 0.0-14.8) | 44 (CI; 42-129) |
| Resistance mutations negative | 22 | 9.1 (CI; 1.1-29.2) | 86 (CI; 43-132) |

**8053 General Poster Session (Board #234), Sat, 1:15 PM-5:00 PM**

**Variation in mechanisms of acquired resistance (AR) among EGFR-mutant NSCLC patients with more than one post-resistant biopsy.** *Presenting Author: Zofia Piotrowska, MGH Cancer Center, Boston, MA*

**Background:** AR typically develops after 9-12 mos of EGFR TKI therapy among EGFR-mutant patients (pts). Here we report a unique series of 42 EGFR mutants who had >1 post-resistant biopsy (bx) that illustrates the heterogeneity of AR within individual pts. **Methods:** We analyzed prospective data from 126 EGFR mutants with advanced NSCLC who had ≥1 bx after AR developed on EGFR TKI therapy. All biopsies underwent multiplexed CLIA-certified SNaPshot genotyping. Some pts consented to provide tissue for patient-derived cell-line (PDCL) establishment. 42 pts had >1 post-AR bx. We collected data on EGFR TKI therapy, mechanisms of AR observed over multiple biopsies, bx safety and correlations between clinical and PDCL data. **Results:** Among 42 pts with multiple post-AR biopsies, median age= 57 (range 39-88), 73% were female, 62% had EGFR exon 19 deletion and 31% had L858R. The median number of post-AR biopsies was 2 (range 2-5). While the original EGFR mutation was uniformly maintained, we observed variation in AR mechanisms among 20/42 pts, with changes in T790M status over time in 10 pts. Notably, both gain and loss of T790M were observed on serial biopsies, without a clear correlation to the timing of EGFR TKI therapy or bx site. Changes in histology (8), development of EMT (1) and EGFR amp (1) were also seen. 22/42 pts had no variations in detected mechanisms of AR on serial biopsies, including T790M (n=11), MET amp (2), EGFR amp (1), both MET and EGFR amp (1), SCLC transformation (1), BRAF mutation (1), and no AR mechanism identified (5). Repeat biopsies were safe, with 2.4% bx-related complications and no serious complications. **Conclusions:** We observed frequent and unexpected changes in the mechanism of AR, particularly T790M status, in pts undergoing serial biopsies, suggesting heterogeneity of resistant clones in these pts. Among pts with T790M, 48% gained or lost the mutation over time. Relationship of AR mechanisms to therapy at the time of bx, bx location and correlations with PDCL data to understand their biologic implications will be presented. Our data suggest serial biopsies in EGFR pts are informative and safe, and may become increasingly important as T790M-specific TKIs become available.

**8054 General Poster Session (Board #235), Sat, 1:15 PM-5:00 PM**

**Randomized phase 2 trial of plinabulin (NPI-2358) plus docetaxel in patients with advanced non-small cell lung cancer (NSCLC).** *Presenting Author: Rebecca Suk Heist, Division of Hematology and Oncology, Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA*

**Background:** Plinabulin (N) inhibits tumor growth by targeting both angiogenesis and tumor vasculature as well as directly by inducing apoptosis via the Ras-JNK pathway. This trial compared the combination of N and docetaxel (DN) to docetaxel alone (D). **Methods:** Patients (pts) with advanced NSCLC previously treated with standard chemotherapy (ChRx) were randomized between D (75 mg/m$^2$ IV) on Day 1 plus N 30 mg/m$^2$ IV on Days 1 and 8 in 21-day cycles (DN) vs D (75 mg/m$^2$ ) (30 Cohort). Pts with Stage IIIB/IV NSCLC and 1 or 2 prior ChRx were eligible. Prior D or vascular disrupting agent (VDA) were not allowed. A 2nd dose cohort (DN 20 mg/m$^2$) of pts with 1 prior ChRx (20 Cohort) was enrolled. The primary end point was overall survival (OS). **Results:** 172 pts were randomized into 2 dosing cohorts with 163 treated: 30 Cohort (50 DN; 55 D) and 20 Cohort (40 DN; 18 D). For 30 Cohort, OS (months (M)), 90% confidence interval [90% CI]) was 8.7 (6.6, 12.6) for DN and 7.5 (6.3, 10.5) for D; response rate was 14.0% for DN and 14.5% for D; and duration of response (M, 90% CI) for DN was 12.7 (4.0, 13.9) and 1.5 (1.1, 3.1) for D (p=0.049). Results appeared better for the DN 30 Cohort vs 20 Cohort. Post hoc subset analysis identified pts with large, lung tumors (>3 cm) and 1 prior ChRx as having better survival with DN. OS (M, 95% CI) for this subset was 11.5 (7.1, 15.1) DN vs 7.8 (4.1, 17.4) D. The most common adverse events were nausea, fatigue, diarrhea, constipation, and anorexia. There were fewer dose reductions of D among DN pts (10%) vs D pts (18.2%). There was a lower incidence of neutropenia in patients in the DN 30 Cohort compared to D (8.0% vs 36.4%, p<0.001) and the DN 20 Cohort compared with its companion D (7.5% vs 22.2%). A post hoc analysis showed that the DN 30 Cohort (n=50) had a significantly lower incidence of ≥ Grade 3 neutropenia vs the pooled D (n=73) at 8.0% vs 27.4%, respectively (p=0.010). **Conclusions:** Pts with large, lung tumors (>3 cm) and 1 prior ChRx may be more likely to have an increased survival with DN as compared to D. This finding is consistent with the mechanism of action of a VDA with anti-angiogenesis and apoptotic properties. A Phase 3 trial in pts with large, lung tumors is planned. Clinical trial information: NCT00630110.

**8055 General Poster Session (Board #236), Sat, 1:15 PM-5:00 PM**

**The Lung Cancer Genomic Screening Project for Individualized Medicine in Japan (LC-SCRUM-Japan): Screening for *RET* and *ROS1* fusions in advanced *EGFR* mutation-negative nonsquamous lung cancer and development of molecular targeted therapy.** *Presenting Author: Kiyotaka Yoh, Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

**Background:** *EGFR* mutations and *ALK* fusions have emerged as important oncogenic drivers in non–small cell lung cancer (NSCLC). *RET* and *ROS1* fusions have identified as new drivers of lung adenocarcinomas and these fusions are reported to be promising druggable targets. However, these gene fusions are encountered rather rarely, that is observed in only 1-2% of all lung adenocarcinomas. **Methods:** This study was established in February 2013 as a new nationwide genomic screening project for developing individualized medicine of advanced NSCLC patients in Japan. Tumor samples of advanced *EGFR* mutation-negative non-squamous lung cancer patients were eligible for submission. The specimens were screened for *RET*, *ROS1* and *ALK* fusions by RT-PCR and FISH methods. **Results:** As of January 22th in 2014, The LC-SCRUM-Japan is under way with the participation of 158 institutions in Japan, under aid from the public research fund of the Ministry of Health, Labour and Welfare of Japan. 507 patients were enrolled to this study and 444 tumor samples of enrolled patients (88%) were screened. A gene fusion was detected in 52 (12%) of the 444 patients as follows; *RET* 21 (5%), *ROS1* 17 (4%), and *ALK* 14 (3%). We have synchronously initiated a phase II trial of vandetanib for advanced *RET* fusion-positive NSCLC patients (LURET study) (UMIN000010095). Eight of 21 patients with positive for *RET* fusion determined in the LC-SCRUM-Japan have been already enrolled and just treated with vandetanib in the LURET study. In addition, we enrolled 5 of 17 patients with *ROS1* fusion-positive NSCLC determined in the LC-SCRUM-Japan onto a global phase II trial of crizotinib for advanced *ROS1* fusion-positive NSCLC patients (OO12-01) (NCT01945021). **Conclusions:** The prevalence of *RET* and *ROS1* fusions in our enriched population was relatively higher compared with that reported in non-selected NSCLC population. This innovative screening project in Japan leads to the activation of screening for lung cancer with rare driver mutations and developing targeted therapy trials. Clinical trial information: UMIN000010234.

**8056 General Poster Session (Board #237), Sat, 1:15 PM-5:00 PM**

**An international, multicenter, randomized, double-blind phase III study of maintenance belagenpumatucel-l in non-small cell lung cancer (NSCLC): Updated analysis of patients enrolled within 12 weeks of completion of chemotherapy.** *Presenting Author: Lyudmila Bazhenova, UC San Diego Moores Cancer Center, La Jolla, CA*

**Background:** Belagenpumatucel-L (Lucanix) is a therapeutic vaccine comprised of 4 TGF-$\beta$2 antisense gene-modified, irradiated, allogeneic NSCLC cell lines. **Methods:** The trial enrolled patients (pts) without progression after completion of frontline chemotherapy (IIIA-42, IIIB/IV-490). Pts were randomized 1:1 between 4 and 17.4 weeks (w) from the end of frontline chemotherapy. Pts were treated until disease progression or withdrawal. The primary endpoint was overall survival (OS). Secondary endpoints were PFS, RR and safety. **Results:** 532 pts were enrolled (270 vaccine and 262 placebo), 57% adenocarcinoma (non-SCC), 27% squamous (SCC). Median OS results and safety profile of belagenpumatucel-L was previously reported. A predefined Cox regression demonstrated that the time elapsed between the end of frontline chemotherapy and randomization had a significant impact on survival outcomes (p=0.002). 318 (59.8%) of pts were randomized within 12 w of the completion of chemotherapy (IIIA=13, IIIB/IV=305, 162 vaccine, 143 placebo). Pts with pretreatment radiation (XRT) enrolled within 12 w had median OS of 40.1 m (belagenpumatucel-L) vs. 10.3 m (placebo) (HR 0.45, p=0.014). Median OS of pts treated with concurrent XRT and enrolled within 12 w was not reached (belagenpumatucel-L) and 10.3 m (placebo) (HR 0.34, p=0.04). **Conclusions:** Although,trial did not meet its predefined end point, a non-statistically significant increase in OS was observed in several subsets of pts who began belagenpumatucel-L within 12 w of the completion of frontline chemotherapy. These data support another Phase III trial with IIIB/IV patients to be randomized within 12 weeks of the completion of frontline chemotherapy. Clinical trial information: 00676507.

| Stage/time from randomization (< 12 w) | N | Median OS (m) | | P | HR |
|---|---|---|---|---|---|
| | Belagenpumatucel-L | Placebo | | | |
| All | 318 | 20.7 | 13.3 | 0.092 | 0.77 |
| IIIB/IV | 305 | 20.7 | 13.3 | 0.083 | 0.76 |
| IIIB | 83 | 24.7 | 13.4 | 0.303 | 0.71 |
| IV | 230 | 19.7 | 12.7 | 0.165 | 0.76 |
| IIIB/IV SCC | 78 | 20.7 | 12.3 | 0.092 | 0.58 |
| IIIB/IV non-SCC | 227 | 22.3 | 16.4 | 0.189 | 0.66 |

**8057 General Poster Session (Board #238), Sat, 1:15 PM-5:00 PM**

**Molecular profiling of non-small cell lung cancer by histologic subtype.** *Presenting Author: Solange Peters, University Hospital of Lausanne (CHUV), Lausanne, Switzerland*

**Background:** A substantial proportion of NSCLC has been shown to harbour specific molecular alterations affecting tumour proliferation and resulting in sensitivity to inhibition of the corresponding activated oncogenic pathway by targeted therapies. Comprehensive tumor profiling can diagnose such alterations and may identify new alterations opening additional treatment options for all distinct NSCLC subtypes. **Methods:** Over 6,700 non-small cell lung cancer cases referred to Caris Life Sciences between 2009 and 2014 were evaluated; clinical diagnoses and detailed tumor pathology were collected from referring physicians. Specific profiling was performed per physician request and included a combination of sequencing (Sanger, NGS or pyrosequencing), protein expression (IHC), gene amplification/rearrangement (CISH or FISH), and/or RNA fragment analysis within potential cancer-related genes and pathways. **Results:** Patients were grouped into cohorts according to histological subtype – adenocarcinoma (AD) (n=4,286), squamous cell carcinoma (SCC) (n=1,280), large cell carcinoma (LCC) (n=153) and bronchioalveolar carcinoma (BAC) (n=94). Protein overexpression of cMET (>2+ in >50% cells) was higher in AD (35.9%) compared to other subgroups (12-20%) while RRM1 and TOP2A levels were lower in AD. ALK or ROS1 were rearranged in 5.3% of patients with AD compared to 3.7% of patients with LCC and 1.2% of patients with SCC. EGFR mutations were found at low prevalence in both the LCC (0%) and SCC cohorts (2.8%) compared to 21% in AD. Similar lower rates of BRAF mutations were observed in the LCC and SCC cohorts compared to AD (0%, 1.1% and 5.1%). Pathway analysis showed activating mutations in the ERK pathway in 40% of patients with AD. Only 10-12% of patients with LCC or SCC had activating mutations in the ERK pathway. **Conclusions:** Despite the limitations of this retrospective series, we report comprehensive profiling of the largest cohort of NSCLC. Tumor profiling reveals that ADs may be more addicted to the ERK pathway than other histological subtypes. Drugs which target cMET may also have most utility in AD. Full analysis by histological subtype and additional correlative data on protein expression, gene copy number and mutations will be presented.

**8058 General Poster Session (Board #239), Sat, 1:15 PM-5:00 PM**

**The use of improved and complete enrichment co-amplification at lower denaturation temperature (ICE COLD-PCR) method for the detection of *EGFR* and *KRAS* mutations from cell-free plasma DNA of non-small cell lung cancer (NSCLC) patients.** *Presenting Author: Hai T. Tran, MD Anderson Cancer Center, Houston, TX*

**Background:** Identification of specific molecular alterations from cell free plasma DNA (cfpDNA) holds tremendous potential as a noninvasive method to assess tumor genotype. We evaluated whether ICE COLD-PCR(ICP) can be used to identify *EGFR* and *KRAS* mutations from cfpDNA in patients enrolled in the BATTLE research clinical trial. **Methods:** Tissue genotyping of *KRAS* (Exons 2, 3) and *EGFR* (Exons 18 - 21) on DNA extracted form paraffin-embedded tumor tissue was determined using PCR-based sequencing analysis, with lower limit of sensitivity of detection of 20%. Genotyping of cfpDNA was determined using ICP for mutation enrichment followed by Sanger sequencing for mutation detection, with limit of detection of 0.05%. **Results:** DNA was isolated and extracted from 154 available plasma samples with matched tumor genotype; with volumes ranging 0.2–0.7 mL. For the overall population with or without mutations, a concordance of 92%, 91%, and 81% was observed with tissue genotypes for *EGFR* Exon 19, *EGFR* Exon 21 and *KRAS* Exon 2, respectively. Mutation specific sensitivities were 80% for *EGFR*-19del, 42.9% for *EGFR*-21-L858R, and 34.4% for *KRAS*-2. **Conclusions:** The use of cfpDNA for the determination of important *EGFR* and *KRAS* mutations provides a non-invasive method which may assist physicians with clinical care for cancer patients. The results from this analysis are encouraging, but, regardless of the methodology used for mutation detection in cfpDNA; additional assay standardization such as initial plasma volume for extraction, amount of extracted DNA and the influence of tissue heterogeneity versus cfpDNA in mutation detection are needed prior to routine clinical use. Overall, these results demonstrate the feasibility in the use of ICP for mutation determination from cfpDNA of NSCLC patients. Clinical trial information: NCT00409968, NCT00411671, NCT00411632, NCT00410059, and NCT00410189.

**8059 General Poster Session (Board #240), Sat, 1:15 PM-5:00 PM**

**Prediction of lung cancer genotype noninvasively using droplet digital PCR (ddPCR) analysis of cell-free plasma DNA (cfDNA).** *Presenting Author: Adrian G. Sacher, Dana-Farber Cancer Institute, Boston, MA*

**Background**: Noninvasive plasma genotyping has the potential to accelerate delivery of targeted therapies to genotype-defined cancer populations and obviate repeat biopsies, particularly following drug resistance. We recently reported on a new assay for plasma genotyping using ddPCR of cfDNA (Oxnard et al., Clinical Cancer Research, 2014). Here, we aimed to predict the genotype of tumor biopsies using plasma genotyping. **Methods**: We identified patients (pts) with advanced NSCLC and acquired resistance to erlotinib that underwent rebiopsy and plasma collection on three IRB-approved protocols. Rebiopsy specimens underwent clinical *EGFR* genotyping. Plasma was collected in EDTA tubes, cfDNA extracted, and *EGFR* genotype quantified using ddPCR assays for L858R, exon 19 del and T790M. Serial plasma genotyping on treatment was performed for a subset of pts. This assay was then piloted in pts with advanced NSCLC who had not yet undergone tumor genotyping. **Results**: A total of 32 pts undergoing rebiopsy had plasma available for analysis. Sensitivity of plasma genotyping for *EGFR* exon 19 del and L858R was 57%; sensitivity increased to 91% among 11 pts with symptomatic bone or visceral metastases. One additional pt with no tumor *EGFR* sensitizing mutation but response to erlotinib had high levels of plasma exon 19 del, suggesting that plasma genotyping may identify mutations missed by tumor genotyping. T790M was detected on rebiopsy in 16 pts (50%); plasma genotyping was concordant with rebiopsy T790M status in 27 of 32 pts (84%). Post-treatment plasma specimens were available for 12 pts; the 5 pts with a partial response on imaging had a significant decrease in plasma concentration compared to the 7 pts without a response (median 895 copies/mL decrease vs 2 copies/mL increase, p=0.01). In 17 NSCLC pts without a known genotype, we identified *EGFR* mutations in 3 pts with a median 3 day turnaround time, up to 19 days before tumor genotyping confirmed the result. **Conclusions**: Plasma genotyping of cfDNA with ddPCR can predict tumor genotype rapidly and quantitatively with a high degree of accuracy, potentially obviating the need for re-biopsy in some circumstances. Clinical development of this assay is ongoing.

**8060 General Poster Session (Board #241), Sat, 1:15 PM-5:00 PM**

**HER2 mutations in lung adenocarcinoma: A report from the Lung Cancer Mutation Consortium (LCMC).** *Presenting Author: Rathi Narayana Pillai, The Winship Cancer Institute of Emory University, Atlanta, GA*

**Background:** A variety of somatic mutations and gene rearrangements have been described in patients with lung adenocarcinoma. The Lung Cancer Mutation Consortium (LCMC) tested for the presence of 10 driver mutations in over 1,000 patients with metastatic adenocarcinoma of the lung. **Methods:** Tumor specimens were assessed for diagnosis and adequacy; multiplexed genotyping utilizing SNaPshot or Sequenom was performed, and mutations were recorded in GeneInsight database. We reviewed the LCMC database for patients tested for *HER2* mutations and accessed clinical characteristics, including age and stage at diagnosis, sex, smoking status, treatment history, sites of metastatic disease, and vital status. We conducted an exploratory analysis to compare survival of *HER2* mutated patients treated with HER2 targeted therapies to those who did not receive targeted therapies. **Results:** Of the 920 patients tested for human epidermal growth factor receptor-2 (*HER2*) mutation, 24 patients (2.6%) had exon 20 insertion mutations. The mutation was located at exon 20 insertion at codon 775 in all patients; 1 patient also had concurrent *MET* amplification. The median age was 62 (37-84) and the majority were never smokers (71%). Nearly 70% had advanced stage disease at the time of diagnosis. There was a slight predominance of females (n=14) over males (n=10). The median survival for patients that received HER2 targeted therapies (n=12) or not (n=12) was 18.3 months and 16.4 months respectively. *HER2*- targeted therapies included dacomitinib (n=5), dacomitinib and crizotinib (n=1), neratinib (n=2), trastuzumab (n=1), lapatanib and trastuzumab (n=1), and STA-9090 (n=1). At last assessment of vital status, 50% (6/12) of the patients treated with targeted therapy were alive as compared to only 33% (4/12) of the remainder. The overall survival for *HER2* mutated patients was worse than that for overall LCMC cohort in which median survival with genotype directed therapies was 3.5 years versus 2.4 years without targeted therapy. **Conclusions:** *HER2* mutations were detected in 2.6% of patients with lung adenocarcinoma. There was a favorable survival trend among patients that received HER2 targeted therapies.

**8061 General Poster Session (Board #242), Sat, 1:15 PM-5:00 PM**

**Retrospective analysis of type of *KRAS* mutation (mut) and response to first-line platinum-based chemotherapy (PC) in non-small cell lung cancer (NSCLC) patients (pts).** *Presenting Author: Wouter Willem Mellema, VU University Medical Center, Amsterdam, Netherlands*

**Background:** Improving clinical outcome of pts with advanced NSCLC with a *KRAS* mut is challenging. Previous research indicated that different types of *KRAS* mut respond differently to chemotherapy regimens. This may impact treatment strategy in this group of pts. **Methods:** Consecutive pts with advanced NSCLC and known *KRAS* mut status, treated with first-line PC were retrieved from different hospital databases. Primary objective: Differences in overall response rate (ORR), progression free survival (PFS) and overall survival (OS) between different types of PC per type of *KRAS* mut. $X^2$-test and log rank test were used and pts were stratified by *KRAS* amino acid substitution (sub). **Results:** 305 pts (92% stage IV) from 10 hospitals, treated between 2008 and 2013, were included. Most common mut were G12C (47%), G12V (20%) and G12D (10%); 90% of pts had a codon 12 mut. Pts were treated with cisplatin (n=155) or carboplatin (n=150), combined with pemetrexed (PEM; n=194), gemcitabine (GEM; n=50), taxanes (TAX; n=27) or paclitaxel plus bevacizumab (CPB; n=34). Treatment with CPB resulted in significant better ORR compared to other regimen (61% vs. 33% (TAX), 29% (GEM), 22% (PEM); p<0.001). The median OS for pts with codon 13 mut (n=20) was 6.4 months and for codon 12 mut (n= 262) 9.8 months (p=0.38). Pts with codon 12 mut were clustered into groups according to sub. Results are summarized in Table. **Conclusions:** CPB had best ORR in KRAS mut pts. G>A sub pts showed a trend to poor OS. PC treatment was comparable per type of *KRAS* mut. These observations encourages study in a larger group of patients.

| *KRAS* sub codon 12 (n) | ORR | Median PFS in months (95% CI) | Median OS in months (95% CI) |
|---|---|---|---|
| **G>A (34)** | 10% | 4.1 (3.6-4.5) | 8.5 (5.7-11.2) |
| **PEM (21)** | 25% | 4.0 (0-10.7) | 5.6 (0-13.3) |
| **GEM (4)** | 50% | 3.2 (1.3-5.0) | 3.6 (0.8-6.3) |
| **TAX (4)** | 40% | 2.5 (2.4-2.7) | 4.2 (0-16.4) |
| **CPB (5)** | p=.18 | | |
| **G>T (203)** | 22% | 5.0 (3.7-6.2) | 8.3 (7.3-9.4) |
| **PEM (123)** | 29% | 3.9 (1.7-6.1) | 9.3 (1.2-17.3) |
| **GEM (41)** | 29% | 4.9 (3.5-6.3) | 10.5 (0-22.8) |
| **TAX (17)** | 64% | 5.6 (2.7-8.5) | 14.3 (9.8-18.7) |
| **CPB (22)** | p<.01 | | |
| **G>C (24)** | 33% | 7.6 (3.3-11.9) | 16.6 (10.5-22.6) |
| **PEM (18)** | 0% | 14.3 (-) | 21.7 (-) |
| **GEM(1)** | 0% | 10.9 (-) | 24.8 (-) |
| **TAX(1)** | 100% | - | - |
| **CPB(4)** | p=.04 | p=.47 | p=.63 |

**8062 General Poster Session (Board #243), Sat, 1:15 PM-5:00 PM**

**Description of ALK+ NSCLC patient characteristics and ALK testing patterns.** *Presenting Author: Heather A. Wakelee, Stanford Cancer Institute, Stanford, CA*

**Background:** Anaplastic lymphoma kinase (ALK) gene rearrangements are seen in 4-8% of non-small cell lung cancer (NSCLC) patients (pts). Historically these pts have been reported to be predominantly young never-smokers with adenocarcinoma histology. ALK translocations have also been more frequently reported in Asian pts. This study investigated ALK+ NSCLC pts' characteristics and physicians' ALK testing practices in the US. **Methods:** A panel of US community oncologists was surveyed about their ALK testing practices for NSCLC pts and key considerations and challenges encountered in ALK testing. Also, ALK+ NSCLC pts' medical charts were reviewed by the responding physicians to collect pt-level information. **Results:** A total of 27 physicians participated and pt-level data was collected for 273 ALK+ NSCLC pts. In this sample, ALK+ NSCLC pts were older, racially diverse, had mixed smoking histories, and 81% had adenocarcinoma. Not all pts received ALK testing upon NSCLC diagnosis; 47 (16%) pts received one systemic therapy while 7 (14%) received 2 systemic therapies prior to ALK testing. After detection of ALK rearrangements, 181 (66%) pts received crizotinib as next-line therapy, 80 (29%) received chemotherapy, and 12 (4%) did not receive further anticancer treatment. Participating physicians reported an average ALK testing rate of 67% of pts in the past 12 months. When asked about issues encountered when testing for ALK, physicians reported inadequate tissue sample (63%), delay in reporting results (41%), and inconclusive results (37%) as the top three challenges. **Conclusions:** In this retrospective chart review in a sample of US oncology practices, ALK+ NSCLC pts were older and racially diverse with mixed smoking histories and cancer histologies. These results challenge preconceived notions of the phenotype of ALK+ NSCLC pts.

| | N=273 |
|---|---|
| **Age, mean ± SD [median]** | 65.1 ± 12.2 [67] |
| | N (%) |
| **Age ≥65 at primary diagnosis** | 152 (56) |
| **Male** | 142 (52) |
| **Race** | |
| **White** | 162 (59) |
| **Black or African American** | 49 (18) |
| **Asian** | 36 (13) |
| **Hispanic or Latino** | 22 (8) |
| **Other** | 4 (1) |
| **Smoking status** | |
| **Never smoker** | 90 (33) |
| **Light smoker (<10 pack-year)** | 91 (33) |
| **Smoker (≥10 pack-year)** | 89 (33) |
| **Not available** | 3 (1) |
| **Histology** | |
| **Adenocarcinoma** | 222 (81) |
| **Mixed** | 30 (11) |
| **Large cell carcinoma** | 13 (5) |
| **Squamous cell carcinoma** | 8 (3) |

**8063 General Poster Session (Board #244), Sat, 1:15 PM-5:00 PM**

**Regulation of tumor cell PD-L1 expression by microRNA-200 and control of lung cancer metastasis.** *Presenting Author: Don Lynn Gibbons, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Tumor cell regulation of the activity of diverse inflammatory cells creates an immunosuppressive microenvironment that favors tumor growth and metastasis. However, the mechanistic basis of how tumor cells trigger intra-tumoral immunosuppression has not been fully defined. Here we show that metastasis-prone lung adenocarcinoma cells suppress the proliferation and activity of intra-tumoral $CD8^+$T cells through a PD-L1 dependent mechanism and that PD-L1 expression is regulated by microRNA-200 (miR-200), a known mediator of tumor cell EMT. **Methods:** Publically available TCGA datasets were analyzed, along with a large MDACC cohort of resected tumors. Experimentally we utilized genetic and syngeneic mouse models of metastatic lung adenocarcinoma. **Results:** In lung adenocarcinomas from The Cancer Genome Atlas (TCGA) (n=230) and a large MDACC cohort of resected tumors (N>150), those with a mesenchymal gene expression signature displayed repression of the miR-200 family and higher levels of PD-L1. These findings were confirmed experimentally in human and murine NSCLC cell lines. In vivo experiments with a *Kras/p53* mutant mouse model of lung adenocarcinoma showed that decreased miR-200 led to increased tumor cell expression of PD-L1, causing profound $CD8^+$ T cell suppression. Upon suppression of $CD8^+$T cell activity tumors acquired a growth advantage and became metastatic. Confirmation of these results with the Lewis lung cancer model in PD-L1 knockout mice also demonstrated that PD-L1 expression on the tumor cells, rather than other cells in the tumor microenvironment, was critical to tumor immunity and metastastic ability. Genetic and pharmacologic blockade of PD-L1 suppressed metastasis. **Conclusions:** Our findings demonstrate a novel biological role for miR-200 in cancer cells by simultaneous control of the cell-intrinsic EMT program and the cell-non-autonomous PD-L1-mediated immune evasion. These findings support the conclusion that EMT-associated immunosuppression promotes metastasis and the potential use of EMT-related biomarkers to select immunomodulatory therapies.

**8064 General Poster Session (Board #245), Sat, 1:15 PM-5:00 PM**

**Domain-specific PD-L1 protein measurement in non-small cell lung cancer (NSCLC).** *Presenting Author: Joseph Francis McLaughlin, Department of Medical Oncology, Yale University, New Haven, CT*

**Background:** PD-L1 protein expression is being explored as a companion predictive test for anti-PD-1 therapies. Studies from our group, however, reveal limitations of available antibodies and indicate that different immunohistochemical (IHC) methods yield discordant results. Differential results have been seen when comparing antibodies targeting the extracellular (EC) versus intracellular (IC) domains. Here, we studied the specificity of anti-PD-L1 antibodies using quantitative fluorescence (QIF) and the performance of two of them in NSCLC. **Methods:** We measured PD-L1 protein expression using antibody clones E1L3N (IC) and E1J2J (EC) in 509 NSCLC tumor samples represented in two tissue microarrays (YTMA79, n=204 and YTMA250, n=305). Antibody specificity was tested using QIF in formalin-fixed paraffin-embedded (FFPE) samples from human placenta and Mel624 transfectants. PD-L1 signal was determined in the tumor compartment using the AQUAmethod. In YTMA79, scores were compared with previous data using 5H1 antibody (EC). Reproducibility was assessed by staining serial cuts, and the correlation coefficient ($R^2$) was calculated. For survival analysis, PD-L1 signal was used as a continuous score, or binarized with cutoffs defined by X-tile. **Results:** Of eight antibodies tested, only three (5H1, E1L3N, and E1J2J) validated. The serial section reproducibility was high for 5H1 ($R^2$>0.9), and lower for E1L3N and E1J2J ($R^2$ range 0.54-0.93). The regression coefficient of scores and dynamic range of the antibodies were dissimilar. The EC domain antibodies E1J2J and 5H1 showed no correlation with the IC antibody E1L3N. There were trends toward association with better outcome with each antibody, but the level of significance was a function of the experimental cutpoints and is only considered exploratory. **Conclusions:** Evaluation of PD-L1expression in NSCLC samples using validated antibodies targeting different protein domains produced discordant results. This could be due to different antibody affinities, cross reactivity, or distinct target epitopes. Evaluation of the predictive value of these antibodies for anti-cancer immunotherapies is currently underway.

**8065 General Poster Session (Board #246), Sat, 1:15 PM-5:00 PM**

**Improving clinical prognostic categories beyond performance status: Enhancing accuracy in survival prediction with a three-item patient-reported outcome (PRO) index from the LCSS in lung cancer and mesothelioma.** *Presenting Author: Richard J. Gralla, Albert Einstein College of Medicine, Bronx, NY*

**Background:** Accurate prediction of survival of patient groups is required for appropriate trial design. Performance status (PS) is often used both for trial eligibility and for stratification. Three global PRO items (quality of life, activity level, symptom distress) from the LCSS (Lung Cancer Symptom Scale) apply to all patients. We tested whether an index of the 3 items would predict survival in patients with lung cancer or mesothelioma, and if major differences were found within the same PS groups (with either ECOG or KPS). **Methods:** This study analyzed data from the prospective mesothelioma EMPHACIS study comparing pemetrexed + cisplatin (DDP) with DDP in 444 patients, and from the prospective AP-QL trial of 622 patients treated with docetaxel + DDP or carboplatin. Each of the 3 global items at baseline in NSCLC predicted improved survival if the value was above the median (positive factor) compared with below (negative factor) ($p < 0.003$). An index was created using the number of negative factors, 0 to 3. The LCSS can be completed in < 3 minutes. **Results:** As seen in the table, survival varied significantly for those with 0 vs 3 negative factors and for 1 or 2 vs 3 factors, at baseline in both NSCLC and mesothelioma. When we tested only for the subgroup of patients with ECOG PS =1 in NSCLC, or for KPS 80-90 (similar to ECOG 1) in mesothelioma, major survival differences were still identified by the PRO index. **Conclusions:** This analysis demonstrates that large survival differences exist within the same PS groups for both ECOG 1 and KPS 80-90. The 3-item PRO index can be rapidly and inexpensively obtained and can assist in more accurate stratification of patients in randomized trials in thoracic malignancies.

| # of negative PRO factors | Med survival: months – all patients | Median survival: months KPS 80-90 | Survival: 1 year | Survival: 1 year |
|---|---|---|---|---|
| **Mesothelioma** | (N = 444) | (n = 368) | All patients | KPS 80- 90 |
| **0** | 14.6 ** | 12.9 ** | 61% | 59% |
| **1,2** | 10.8 * | 10.1 * | 45% | 42% |
| **3** | 7.4 | 7.6 | 26% | 30% |
| **NSCLC** | (N = 622) | ECOG 1 (n = 413) | All patients | ECOG 1 |
| **0** | 16 ** | 15.4 ** | 64% | 62% |
| **1,2** | 13 * | 11.5 | 54% | 48% |
| **3** | 9 | 9.4 | 38% | 36% |

Reference group is 3 negative PRO factors. ** $p < 0.001$ by log-rank; * $p < 0.05$ by log rank.

**8066 General Poster Session (Board #247), Sat, 1:15 PM-5:00 PM**

**PD-L1 expression and survival in patients with non-small cell lung cancer (NSCLC) in Korea.** *Presenting Author: Jong-Mu Sun, Department of Medicine, Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

**Background:** Data are limited on whether programmed cell death ligand-1 (PD-L1) expression is a prognostic factor among patients (pts) with NSCLC. **Methods:** We evaluated the relationship between PD-L1 expression and overall survival (OS) in 779 NSCLC pts treated at Samsung Medical Center, Seoul, Korea, between 2001 and 2010. Tumor expression of PD-L1 was measured by immunohistochemistry, and PD-L1-positivity was defined as staining in ≥1% of cells. Kaplan-Meier methods, log-rank test, and Cox proportional hazards models were used for survival analysis, adjusting for age, gender, smoking, and stage. **Results:** Median pt age was 64 years (range, 21-86 years), and 74% of pts were male. 49% of pts had adenocarcinoma, 39% squamous cell carcinoma (SCC), and 12% large cell carcinoma or other. Disease stage was I/II in 71% and III/IV in 29%. All pts underwent surgery, and 411 pts received chemotherapy. Median follow-up time was 4.2 years. Overall, 50% of pts were PD-L1-positive. A statistically significant higher prevalence of PD-L1-positivity was observed in males and in pts with SCC or advanced-stage disease ($P < 0.001$). Overall, PD-L1-positivity was associated with worse OS, with a 5-year OS rate of 55% (95% CI, 50%-60%) for the PD-L1-positive group and 67% (62%-72%) for the PD-L1-negative group (log rank $P = 0.02$). Further analysis suggested that this association was driven mainly by the pts with adenocarcinoma. The 5-y OS rates for the PD-L1-positive and PD-L1-negative groups were 57% (50%-65%) and 59% (49%-68%), respectively, in SCC pts (log rank $P = 0.60$), and 52% (42%-61%) and 73% (66%-78%), respectively, in adenocarcinoma pts (log rank $P < 0.001$; adjusted hazard ratio [AHR] of PD-L1-positive vs PD-L1-negative, 1.47; 95% CI, 1.03-2.11). Similar trends of association between PD-L1-positivity and OS were observed among adenocarcinoma pts who received chemotherapy (log rank $P = 0.03$; AHR, 1.32; 95% CI, 0.84-2.09) and those who did not (log rank $P< 0.01$; AHR, 1.88; 95% CI, 1.03-3.43). **Conclusions:** Based on a preliminary assay and cutoff, our results suggest that PD-L1 expression may be a negative prognostic factor among non-SCC pts with NSCLC, particularly those with adenocarcinoma.

**8067 General Poster Session (Board #248), Sat, 1:15 PM-5:00 PM**

**Spatiotemporal T790M heterogeneity in individual patients with non-small cell lung cancer (NSCLC) after acquired resistance to EGFR-tyrosine kinase inhibitor (TKI).** *Presenting Author: Akito Hata, Division of Integrated Oncology, Institute of Biomedical Research and Innovation, Kobe, Japan*

**Background:** The secondary *EGFR* mutation T790M accounts for approximately half of acquired resistances to EGFR-TKI. A favorable prognosis was demonstrated in patients (pts) with NSCLC harboring T790M compared to those without T790M. Since T790M is mediated by TKI exposure, poor TKI penetration to central nervous system (CNS) and TKI withdrawal may affect T790M status and prognosis. **Methods:** We retrospectively reviewed T790M status and clinical course of pts who had undergone multiple rebiopsy in our institutes. Postprogression survival (PPS) after initial TKI failure was analyzed according to T790M status. **Results:** Between May 2008 and January 2014, 132 pts with *EGFR*-mutant NSCLC received rebiopsy after acquired resistance to EGFR-TKI. Of 132 pts, 22 underwent rebiopsy at multiple sites, and 14 received repeated rebiopsies of the same lesion. Of 19 pts who underwent rebiopsy from both CNS (18 cerebrospinal fluids [CSF] and 1 brain tumoral tissue) and thoracic lesions (5 lung tissues and 14 pleural effusions), 10 were thoracic-T790M-positive. Of these 10 pts, 9 were CNS-T790M-negative. Conversely, all 10 thoracic-T790M-negatives were CNS-T790M-negative. Median PPS of thoracic/CNS-T790M-negative was 20.1 months, and thoracic-T790M-positive/CNS-T790M-negative were 11.2 months (p=0.3798). PPS was 40 months in the only thoracic/CNS-T790M-positive. In 14 pts who received repeated rebiopsies at the same lesion (7 lung tissues, 4 CSFs, and 3 pleural effusions), T790M status of lung lesions varied in 3 pts after TKI-free interval. In all 3 pts whose T790M status changed from positive to negative, EGFR-TKI rechallenge was effective. The 2 of these pts, after progression of TKI rechallenge therapy, T790M status changed from negative to positive again. There was also a pt whose CSF T790M status changed from negative to positive after high-dose erlotinib therapy. **Conclusions:** T790M status in an individual pt can be spatiotemporally heterogeneous due to selective pressure from TKI. Our data support personalized therapeutic strategies after acquired resistance, such as local ablation for oligoprogressive CNS metastases and EGFR-TKI rechallenge.

**8068 General Poster Session (Board #249), Sat, 1:15 PM-5:00 PM**

**A phase 1 study evaluating the safety and efficacy of DKN-01, an investigational monoclonal antibody (Mab) in patients (pts) with advanced non-small cell lung cancer.** *Presenting Author: Jeff Edenfield, GHS Institute of Transitional Oncology Research, Greenville, SC*

**Background:** DKN-01 is a high affinity neutralizing humanized Mab targeting extracellular dickkopf-1 (Dkk-1). Dkk-1 inhibits the canonical Wnt/β-catenin signaling pathway and modulates other biological pathways required for cell growth/ differentiation. Prior studies have demonstrated elevated Dkk-1 expression in lung, esophageal and gastric cancer tissue. Preclinical studies have demonstrated that a reduction of free Dkk-1 led to clinical benefit in xenograft models. **Methods:** A two-part (A and B) phase I, dose-finding study determined safety, maximum tolerated dose and antitumour activity infusing DKN-01 to pts with advanced malignancies with emphasis on pts with non-small cell lung cancer (NSCLC). Other endpoints were progression free survival [PFS], overall response rate [ORR], and overall survival [OS]. Part A of the study tested intravenous (IV) DKN-01 at dose levels between 75 and 600 mg administered weekly or biweekly in a 28 day cycles. For Part B, DKN-01 was administered to refractory NSCLC pts at 300 mg IV on days 1 and 15 of every 28 day cycle. **Results:** 32 pts enrolled in Parts A and B; 24 with NSCLC. NSCLC pts: median age 64.5 yrs, 54% male, 75% ECOG PS1, 4 median prior therapies (1-7), and 63% adenocarcinoma. DKN-01 was well tolerated with no dose limiting toxicities (DLT) or related serious adverse events (SAE). All of the treatment related AEs were ≤ Grade 2. Treatment emergent adverse events (TEAE) ≥ 15% in decreasing frequency: nausea, fatigue, decreased appetite, dyspnea, vomiting and constipation. No TEAE led to study discontinuation. Responses in 22 evaluable NSCLC pts included partial response 4.2% and stable disease 42%. One NSCLC patient had confirmed complete resolution of target disease. Median PFS in 23 evaluable NSCLC pts was 2.2 months [95% CI 1.8-2.9]. NSCLC median OS was 6.6 months (95% CI 4.1-10.1). **Conclusions:** DKN-01 may be a promising innovative targeted treatment for NSCLC. DKN-01 monotherapy was extremely well tolerated and demonstrated clinical activity in pts with refractory NSCLC. The median PFS and safety profile suggest that further NSCLC development in combination with other agents is warranted. Clinical trial information: NCT01457417.

**8069 General Poster Session (Board #250), Sat, 1:15 PM-5:00 PM**

**Effect of angiotensin system inhibitors on survival in patients receiving chemotherapy for advanced non-small cell lung cancer.** *Presenting Author: Alex R. Menter, Kaiser Permanente, Lone Tree, CO*

**Background:** Several retrospective studies have identified an association between angiotensin system inhibitors (ASI) and improved survival for patients with advanced stage malignancies including non-small cell lung cancer (NSCLC). We examined this association in Kaiser Permanente's (KP's) integrated practice settings. **Methods:** Data from four KP regions (Colorado, Northern California, Southern California, Northwest) contributed to the analysis. The cohort (n=2,723) included patients with stage IIIb-IV non-squamous NSCLC diagnosed between 2005 and 2011 who were treated with carboplatin and paclitaxel (CP) or CP with bevacizumab (CPB). Patients were followed from chemotherapy initiation until death, disenrollment from the health plans, or December 31, 2012. Demographic, tumor, chemotherapy, comorbidity, pharmacy, and mortality data were extracted from each region's clinical databases. Exposure to ASI was defined as any angiotensin converting enzyme inhibitor or angiotensin receptor blocker dispensing between 30 days before to 90 days after the start of chemotherapy. Cox proportional hazard models adjusted for age, gender, weight, stage, smoking status, tumor grade, and comorbidity were used to estimate hazard ratios (HR) for overall survival (OS) comparing those who used an ASI to those who did not. **Results:** Of 2,277 patients treated with CP, 524 (23%) received an ASI; of 446 patients treated with CPB, 116 (26%) received an ASI. ASI patients were older and had more comorbidity. Median OS for patients receiving CP and CPB were 8.7 and 12.9 months, respectively. For CP patients with and without concomitant ASI exposure, median OS were 10.5 and 8.3 months, respectively (crude HR 0.81, 95% confidence interval (CI) 0.73-0.90). For CPB patients with and without concomitant ASI exposure, median OS was 14.9 and 12.3 months, respectively (crude HR 0.81, 95% CI 0.64-1.03). For CP and CPB patients with concomitant ASI exposure, the multivariate-adjusted HRs were 0.79 (95% CI 0.70-0.89) and 0.84 (95% CI 0.62-1.13), respectively. **Conclusions:** Concomitant ASI use during CP or CPB chemotherapy for NSCLC was associated with improved survival.

**8070 General Poster Session (Board #251), Sat, 1:15 PM-5:00 PM**

**Canadian ALK (CALK): A multicenter, prospective study of concurrent ALK immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) in NSCLC.** *Presenting Author: Jean Deschenes, Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada*

**Background:** : FISH has been considered the "gold standard" for identification of ALK rearranged (ALK+) NSCLC, but its cost-effectiveness as a screening method for ALK+ lung cancer is debated. Recent reports suggest that ALK IHC may be an alternative screening/diagnostic method. However, most studies evaluating IHC performance were retrospective or from a single-institution. ALK IHC screening and FISH confirmation have been validated across Canadian centers in a prior CALK study. This follow-up study was initiated to prospectively assess the accuracy of IHC compared to FISH in cases requiring ALK status determination. **Methods:** 3 centres conducted parallel IHC (5A4 antibody) and FISH (Abbott kit) testing of 411 consecutive clinical cases using previously validated and optimized protocols. 4 um unstained sections were used as well as published criteria for FISH scoring. The centres scored cases showing diffuse cytoplasmic staining of tumor cells clearly greater than background as ALK IHC + (2+, 3+,as well as diffuse 1+ in previously published ALK scoring systems), cases showing only focal faint staining above background (focal 1+) were scored as IHC equivocal, and cases with no tumor staining above background as IHC(-) . In almost all cases, background staining was completely absent. **Results:** Among the 411 cases, 373 (90.8%) were informative by both methods and 38 (9.2%) failed FISH testing. Of the dual informative cases, 18 (4.8%) were both IHC + and FISH +, 326 (87.4%) tested IHC (-) and FISH (-), 29 (7.8%) tested as IHC equivocal and FISH (-). 2/411 cases were initially discordant (i.e. IHC (-) and FISH borderline+). After rescoring by 2 blinded experienced readers, FISH was negative. When considering equivocal cases as positive, IHC sensitivity and specificity were 100% and 91.8 %, respectively. From the informative cases, FISH (-) / IHC (-) had 3.2% ± 3.2% abnormal FISH signal counts vs. 48.6% ± 18.7% for FISH+/IHC+ and 4.1% ± 3.7% in IHC equivocal cases. **Conclusions:** Results of this prospective study support IHC as a reliable method to screen for ALK-rearranged lung cancers. They also suggest that a clearly positive IHC result may be used to determine ALK status.

**8071 General Poster Session (Board #252), Sat, 1:15 PM-5:00 PM**

**Observational study of treatment with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) in activating EGFR-mutation–positive (EGFRm+) advanced or recurrent non-small cell lung cancer (NSCLC) after radiologic progression to first-line therapy with EGFR-TKI.** *Presenting Author: Yukio Hosomi, Department of Thoracic Oncology and Respiratory Medecine, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan*

**Background:** NSCLC with activating EGFR mutation is generally sensitive to EGFR-TKIs, but resistance is inevitable. The clinical course after radiological (RECIST-based) "progressive disease" (PD) judgment is variable and yet to be fully elucidated. **Methods:** Thirty-one institutions in Japan participated in the survey of patients with EGFRm+ advanced or recurrent NSCLC who received first-line EGFR-TKIs between 2009 and 2011. The primary endpoint was the time from RECIST-based radiological PD (R-PD) to clinical PD (C-PD) in patients who continuously received TKI beyond R-PD. C-PD was defined as one or more of the following: 1) symptomatic PD; 2) worsening performance status due to PD; 3) threat to major vital organ(s); or 4) multi-organ unequivocal PD. Durations of TKI administration, reasons for discontinuation, therapies concomitantly given with TKI, "flare" phenomenon after TKI stoppage, and overall survival were also recorded. **Results:** At the time of submission, 578 cases were registered; 412 were analyzed, of whom 38 were still on TKI without R-PD (Group E). The remaining 374 were sub-classified into the following groups: Group A, TKI stopped at R-PD concurrently occurring with C-PD (n=140); Group B, TKI stopped at R-PD without C-PD (n=104); Group C, TKI continued beyond R-PD (n=63); and Group D, TKI stopped due to other reasons (n=67). Therefore, 63/167 patients (38%) continued to receive TKI beyond clinically stable R-PD. Median time from R-PD to C-PD or TKI discontinuation in Group C was 4.2 months. Median survival time for Groups A, B, C and D were 20.6, 23.3, 27.4 and 13.6 months, respectively, whereas median periods on TKIs were 8.8, 9.9, 18.3 and 2.7 months, respectively. Disease flare was observed in 6 cases. **Conclusions:** Clinical courses and pattern of care after resistance to EGFR-TKI varied. Some 38% of the patients without clinical deterioration at R-PD were continued on TKI, for a median period to C-PD of 4.2 months. Supported by the Public Health Research Center Foundation, with fund from AstraZeneca.

**8072 General Poster Session (Board #253), Sat, 1:15 PM-5:00 PM**

**Effect of BIM and mTOR expression on clinical outcome to erlotinib in EGFR-mutant non-small cell lung cancer (NSCLC) patients (p).** *Presenting Author: Niki Karachaliou, Quirón Dexeus University Institute, Barcelona, Spain*

**Background:** Sixty percent of EGFR-mutant NSCLC p respond to erlotinib, but overall survival (OS) is the same for upfront chemotherapy. Priming BIM, a pro-apoptotic signaling BH3-only protein, induced sensitivity to erlotinib in EGFR-mutant cell lines (Costa el at. PLoS Med 2007). BIM was related to response and progression-free survival (PFS) in clinical tumor samples, but OS was not reported (Faber et al. Cancer Disc 2011). Mammalian target of rapamycin (mTOR) negatively regulates apoptosis and could influence response to erlotinib. **Methods:** We assessed static levels of total BIM, BIM-extra long (BIM-EL – a main isoform of BIM), and mTOR mRNA expression and correlated findings with response and OS in 57 erlotinib- or chemotherapy-treated EGFR-mutant NSCLC p in the EURTAC trial. **Results:** Median age 65; 70.2% female; 59.6% never-smokers; 91.2% adenocarcinoma. Response rate 88.9% for erlotinib-treated p with high total BIM levels, compared to 22.2% with low/intermediate total BIM levels (P=0.0027). Sensitivity/specificity of total BIM as a predictor of response to erlotinib was highly significant (AUC=0.80; P=0.0056). OS was 35.8 months (m) for p with high and 17.7 m with low/intermediate total BIM (P=0.023). Notably, among p with high total BIM, OS was 35.8 m for p with low/intermediate mTOR levels, compared to 20.3 m with high mTOR levels (P=0.4848). In contrast, mTOR did not affect OS in p with low/intermediate BIM (17.5 m vs 25.1 m; P=0.9498). BIM-EL assessment was only possible in 31 p, due to insufficient tumor sample in the remaining p. However, in this subset, BIM-EL seemed to have greater predictive power than total BIM. **Conclusions:** Our findings highlight the potential usefulness of BIM mRNA as a predictive biomarker of response in EGFR-mutant NSCLC p. Those with low BIM expression could derive only meager benefit from treatment with EGFR TKIs alone but could benefit from synthetic lethality combinations, including BcL-2 inhibitors. Those with high BIM expression could benefit from erlotinib or similar EGFR TKIs, but analysis of mTOR could further improve outcome by selecting p with high mTOR for combination therapy with EGFR TKIs and mTOR inhibitors.

**8073 General Poster Session (Board #254), Sat, 1:15 PM-5:00 PM**

**Exploring therapeutic targets in pulmonary sarcomatoid carcinoma by comprehensive genomic profiling.** *Presenting Author: Xuewen Liu, State Key Laboratory of Oncology in Southern China and Department of Radiology, Sun Yat-sen University Cancer Center, Guangzhou, China; Division of Hematology/Oncology, Columbia University Medical Center, New York, NY*

**Background:** Pulmonary sarcomatoid carcinoma (SC) is a rare and highly aggressive lung tumor, and it is associated with poor prognosis and high rate of resistance to conventional chemotherapy. The molecular basis of the unique dual differentiation pattern is poorly defined. New therapeutic strategies based on better knowledge of the molecular pathogenesis for pulmonary SC are needed. We used SNP array and high-throughput sequencing technology to identify novel therapeutic molecular targets. **Methods:** Ten pairs of genomic DNA samples were extracted from fresh frozen tumor tissues and paired normal tissues of patients with pulmonary SC. Whole-exome sequencing at a median of 120× coverage for tumor samples and 60× coverage for normal samples was performed at the Columbia Genome Center. Validation by Illumina TruSeq panel was performed on DNA from formalin-fixed paraffin-embedded (FFPE) tissue from these tumors. In addition, ten of the top ranked genes were chosen for validation by Sanger sequencing on DNA from these 10 cases and an additional cohort of 18 FFPE extracted DNA samples of pulmonary SC. Isolated DNA was hybridized to Affymetrix 6.0 SNP arrays and compared to a control group of 689 lung adenocarcinomas from two cohorts. **Results:** Mutations in TP53 (7/10, 70%), KRAS (2/10, 20%) and PIK3CA (2/10, 20%) were detected by whole exome sequencing and separately validated by TruSeq Illumina panel. Eight of the 10 genes at the top of the rank list, including RASA1(2/10, 20%), RYR2 (2/10, 20%), CDH4 (2/10, 20%), CDH7 (2/10, 20%), LAMB4 (3/10, 30%), MET (2/10, 20%), SCAF1 (2/10, 20%), and LMTK2 (2/10, 20%), were validated using Sanger sequencing. The validation of these genes in the cohort of 18 DNA samples extracted from FFPE tumor tissues is ongoing and functional validation of novel actionable targets will be pursued. SNP array results clearly distinguished SC from adenocarcinoma samples with significant copy number increases in chromosome 3q,7, 8q, 11p, 11q and 17q. **Conclusions:** Our study has identified novel molecular events in pulmonary SC tumors via high-throughput sequencing and SNP array analysis. The findings will be helpful for the development of new therapeutic strategies for pulmonary SC.

**8074 General Poster Session (Board #255), Sat, 1:15 PM-5:00 PM**

**Alterations in two oncogenic drivers: Impact of concurrent *PIK3CA* or *AKT1* mutations in patients with oncogene-driven lung adenocarcinomas.** *Presenting Author: Juliana Eng, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Little is known of prognosis and the efficacy of targeted therapies in patients whose lung adenocarcinomas harbor two oncogenic drivers. **Methods:** We identified patients treated at MSKCC from 2009-2013 whose lung adenocarcinomas harbored two oncogenic drivers. Molecular diagnostic testing was performed via an institutional algorithm involving ≥1 of the following: mutational hotspot testing (91 mutations in *EGFR, HER2, KRAS, NRAS, BRAF, MAP2K1, PIK3CA* and *AKT1)*, multiplex sizing assays (insertions/deletions in *EGFR* and *HER2*), and break apart FISH tests (fusions involving *ALK, ROS1* and *RET*). Overall survival (OS) and duration of response to EGFR tyrosine kinase inhibitor (TKI) therapy (*EGFR*-mutant subgroup) were assessed using Kaplan-Meier estimates. Outcomes were compared between double-driver and single-driver stage-matched control groups from the Lung Cancer Mutation Consortium study (log-rank test). **Results:** 49 patients (55% *KRAS*-mutant, 39% *EGFR*-mutant, 2% *BRAF*-mutant, 2% *MAP2K1*-mutant, 2% *ALK* fusion-positive) were found to have a driver in a second gene (*PIK3CA* 94% or *AKT1* 6%). In patients with advanced disease (stage IIIB/IV), the median OS was worse if their tumors harbored a concurrent *PIK3CA* or *AKT1* mutation (n=31, 11 mo, 95%CI 8.9-23.1) vs a single-driver (n=87, 24 mo, 95%CI 16.2-31.1, p=0.017). Median OS in subgroups (concurrent *PIK3CA* or *AKT1* vs not) were as follows: *KRAS*-mutant (8 vs 12 mo, p=0.032), *EGFR*-mutant (18 vs 34 mo, p=0.066), and *PIK3CA*-mutant (concurrent driver vs not; 14 vs 21 mo, p=0.840). In patients with *EGFR*-mutant lung cancers who received single-agent EGFR TKIs, while the median duration of therapy was similar between groups (15 vs 15 mo, single vs double, p=0.157), 33% (95% CI 19-59%) of patients with *EGFR*-mutant-only tumors versus 0% with concurrent *PIK3CA* or *AKT1*-mutated tumors remained on therapy at 2 and 3 years. **Conclusions:** In patients with metastatic oncogene-driven lung adenocarcinomas, the presence of a concurrent *PI3KCA* or *AKT1* mutation is a negative prognostic factor for OS. In *EGFR*-mutant lung cancers, continued EGFR TKI benefit at ≥2 yrs was observed only in patients without concurrent *PIK3CA* or *AKT1* mutations.

**8075 General Poster Session (Board #256), Sat, 1:15 PM-5:00 PM**

**Clinicopathologic features of lung cancer patients harboring de novo *EGFR* T790M mutation.** *Presenting Author: Young Joo Lee, National Cancer Center, Goyang, South Korea*

**Background:** *EGFR* T790M mutation drives acquired drug resistance to EGFR tyrosine kinase inhibitors (EGFR-TKI) in lung cancer harboring sensitive *EGFR* mutations. However, several studies reported the preexistence of this resistant mutation before EGFR-TKI exposure is not rare event when identified by more sensitive sequencing methods. This study aimed to evaluate clinicopathological features of lung cancer with de novo *EGFR*T790M mutations. **Methods:** We collected pretreatment tissues from 124 advanced non-small cell lung cancer patients with sensitizing *EGFR* mutations (exon 19 deletion and exon 21 L858R) that had been detected by direct sequencing at our institute between January 2009 and August 2011. Genotyping for *EGFR*T790M mutation was further performed using matrix-assisted laser desorption/ionization-time of flight/mass spectrometry. **Results:** The T790M mutation was found in 31 (25.0%) patients. The patients with T790M-positive tumor had shorter time to progression (TTP) after EGFR-TKI than those with T790M-negative tumor (median 6.3 months vs. 11.5 months; $P < 0.001$). The T790M mutation frequency at which the risk of progression to EGFR-TKI begins to increase was estimated to be 3.2%. The T790M-positive group harboring ≥3.2% of T790M (n= 24) had higher proportion of never smoker (83% vs 62%; $P = 0.047$), *EGFR* exon 21 L858R mutation (75% vs 25%; $P = 0.051$), and ≥3 of metastatic organ (71% vs 50%; $P = 0.066$) compared to the opposite group (n= 100). However, there was no significant difference in age, gender, histology, stage, and anatomical location. Peak SUV value of tissue sample sites on PET scan was not different between two groups (6.0 vs 7.9; $P = 0.317$). In terms of chemotherapy response, there was no difference in response to platinum (20% vs 33%; $P = 0.529$) and pemetrexed (10% vs 21%; $P = 0.470$) but taxane (33% vs 7%; $P = 0.057$). In the T790M-positive group, first-line EGFR-TKI users did not show longer TTP than second-line or more EGFR-TKI users (median 6.0 months vs. 3.9 months; $P = 0.197$). **Conclusions:** Lung cancer patients with 3.2% or more of de novo T790M mutation frequency showed decreased efficacy to EGFR-TKI. De novo T790M mutation are significantly associated with never smoking history and *EGFR* exon 21 L858R mutations.

**8076 General Poster Session (Board #257), Sat, 1:15 PM-5:00 PM**

**Clinicopathologic features of advanced *RET* fusion-positive lung cancers and outcomes in comparison to other fusion-positive lung cancers.** *Presenting Author: Alexander E. Drilon, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Recurrent gene rearrangements are important drivers of lung cancer growth. While *RET* fusions are recognized as actionable targets, the clinicopathologic features of these drivers in advanced (stage IIIB/IV) disease and survival in comparison to *ALK* and *ROS1* fusion-positive lung cancers are less well-characterized. **Methods:** A FISH study using dual-color break-apart probes was performed to screen for *RET* fusions in patients (pts) with advanced lung ADCs that tested negative for mutations in *EGFR, KRAS, NRAS, BRAF, MAP2K1, ERBB2, PIK3CA,* or *AKT,* and fusions of *ALK* or *ROS1*. In pts with sufficient tissue, fusion partners were identified (RT-PCR/next-generation sequencing). Pathologic review of available tumor specimens and assessment of radiographic response via RECIST v1.1 were conducted. Overall survival (OS) and progression-free survival (PFS) were determined using Kaplan-Meier estimates. Comparisons to control groups of *ALK* and *ROS1* fusion-positive lung cancers were performed (Mantel-Haenszel/log rank tests). **Results:** 17% (n=18/104, 95%CI 9-22%) of tumors from screened pts harbored a *RET* fusion (56% male, median age 61). Majority of pts had no history of chest RT [89%, n=16] and were never smokers [72% (n=13) <1, 22% (n=4) 1-15, and 6% (n=1) >15 pack-years]. In 8 pts with sufficient tissue, known upstream partners were identified in 7 pts (*NCOA4*, *TRIM33,* 6 *KIF5B*). An upstream partner not previously described in lung cancers (*CLIP1*) was found. Morphology in surgical specimens (n=8) was as follows: 63% (n=5) predominantly solid, 25% (n=2) predominantly cribriform, 13% (n=1) predominantly papillary. OS of *RET* (n=18) vs *ALK* (n=45; HR 0.84, 95%CI 0.34-2.08, p=0.71) and *ROS1* (n=10; HR 1.59, 95%CI 0.34-7.31, p=0.55) fusion-positive lung cancers was similar. In patients who received first-line chemotherapy, PFS of *RET* (n=12) vs *ALK* (n=22; HR 0.53, 95%CI 0.25-1.13, p=0.10) and *ROS1* (n=8; HR 1.19, 95%CI 0.34-4.17, p-0.78) fusion-positive lung cancers was similar. **Conclusions:** Advanced *RET* fusion-positive lung cancers represent a distinct group of tumors with clinical outcomes comparable to *ALK* and *ROS1* fusion-positive lung cancers.

**8077 General Poster Session (Board #258), Sat, 1:15 PM-5:00 PM**

**A phase II clinical trial of the CDK 4/6 inhibitor palbociclib (PD 0332991) in previously treated, advanced non-small cell lung cancer (NSCLC) patients with inactivated *CDKN2A*.** *Presenting Author: Priya Kadambi Gopalan, University of Florida, Gainesville, FL*

**Background:** The Retinoblastoma pathway is targeted for mutational or epigenetic inactivation in more than 70% of NSCLC. The most common event is loss of *CDKN2A* expression (p16 protein), usually by hypermethylation, resulting in deregulated CDK4/6 activity and cell cycle progression. Palbociclib is a highly specific CDK4/6 inhibitor and has been shown to inhibit cell cycle progression and promote cellular senescence. **Methods:** We conducted a phase II, single arm trial of palbociclib in 19 previously-treated patients with recurrent or metastatic NSCLC. Only patients whose tumors were negative for p16 expression by immunohistochemistry were eligible. The primary endpoint was response rate. A Simon's 2-stage design was employed, with 2 or more responses required to proceed to the second stage. Palbociclib at 125 mg daily was given orally on days 1-21 of a 28-day cycle. Tumors were assessed by RECIST every 2 cycles. Secondary endpoints included overall survival, progression-free survival, toxicity and biomarker analysis. **Results:** Of the 16 evaluable patients who received at least one month of therapy, there were no responses, and the trial was closed to accrual. However, 8 patients with previously progressive NSCLC had stable disease (SD) lasting 16, 17, 20, 24, 35, 38, 41 and 42 weeks. The remaining 8 patients had progressive disease within 8 weeks. The median PFS was 12.5 weeks. There was no correlation between SD and histology or EGFR mutation status. One patient experienced grade 3 and 4 toxicities as a result of transaminitis and rhabdomyolysis (generalized muscle weakness and increased CPK) thought to be due to concomitant use of high-dose (80 mg) simvastatin. Three patients developed grade 3 or 4 neutropenia, and one patient developed grade 3 thrombocytopenia. All other toxicities were grade 1 or 2. **Conclusions:** Palbociclib therapy alone was well-tolerated, and stable disease (SD) was achieved in 50% of evaluable patients, suggesting the induction of cellular senescence. PFS was comparable to other second-line chemotherapeutic agents. Molecular predictors of clinical benefit (SD) are currently under investigation. Clinical trial information: NCT01291017.

**8078^ General Poster Session (Board #259), Sat, 1:15 PM-5:00 PM**

**Ceritinib in Asian versus Caucasian patients (Pts) with advanced anaplastic lymphoma kinase (ALK)-rearranged (ALK+) NSCLC: Subgroup analysis of the ASCEND-1 trial.** *Presenting Author: Daniel Shao-Weng Tan, National Cancer Centre, Singapore, Singapore*

**Background:** Prior results from the first-in-human phase I study (ASCEND-1) of the novel ALK inhibitor (ALKi) ceritinib (LDK378), demonstrated high response rates in crizotinib (CRZ)-naïve and CRZ-resistant patients, and established 750 mg/day as maximum tolerated dose. As inter-ethnic variations can lead to differences in treatment response in Asian vs Caucasian pts, we report here a subgroup analysis of the data for pts with ALK+ NSCLC receiving ceritinib at 750 mg/day. **Methods:** In ASCEND-1, adult pts with advanced ALK+ cancers received oral ceritinib once daily. Investigator assessment of efficacy is presented for pts who received a first dose of ceritinib ≥18 wks prior to the cut-off date (2 Aug 2013). **Results:** 246 pts with ALK+ NSCLC (82 Asian, 156 Caucasian, 8 other) received ceritinib 750 mg/day with median follow-up of 4.5 months (mos). 67% of patients had received ≥2 prior anticancer therapies. Between Asian and Caucasian pts baseline demographics were similar but ALKi pretreatment had been received by 47 (29%) and 108 (66%) pts, respectively. Among Asian vs Caucasian pts, 42.7% vs 51.9% had no dose reductions while 29.3% vs 38.5% and 24.4% vs 7.1% had 1 and 2 dose reductions, respectively. Duration of ceritinib exposure was similar between groups. A modest increase (<30%) in the pharmacokinetic parameters AUCtau and Cmax at steady-state was observed in Asian vs Caucasian pts. Grade 3/4 AEs were reported in 55% Asian pts and 72% Caucasian pts; 4 (5%) and 18 (12%) pts, respectively, discontinued due to AEs. Of 173 pts analyzed for efficacy the ORR was 69% (95% CI: 55.2, 80.9) in Asian pts (38/55) and 57% (95% CI: 47.3, 65.9) in Caucasian pts (67/118). The median duration of response (DOR) among responders was 10.1 mos (95% CI: 7.3, not reached) and 6.9 mos (95% CI: 4.5, 11.4) in the Asian and Caucasian pts, respectively. The observed differences between Asians and Caucasians for ORR and DOR were not explained by differences in ALKi pretreatment. **Conclusions:** Ceritinib 750 mg/day resulted in high and durable antitumor activity and manageable tolerability with low discontinuation rates in both Asian and Caucasian pts with ALK+ NSCLC. Clinical trial information: NCT01283516.

**8079 General Poster Session (Board #260), Sat, 1:15 PM-5:00 PM**

**Phase IB study to evaluate efficacy and tolerability of olaparib (AZD2281) plus gefitinib in patients (P) with epidermal growth factor receptor (EGFR) mutation positive advanced non-small cell lung cancer (NSCLC) (NCT=1513174/GECP-GOAL).** *Presenting Author: Rosario Garcia Campelo, CHUAC, A Coruña, Spain*

**Background:** Progression-free survival (PFS) and response rate (RR) to EGFR tyrosine kinase inhibitors (TKIs) vary in P with NSCLC driven by EGFR mutations, suggesting that other genetic alterations may influence oncogene addiction. High BRCA1 mRNA expression negatively influenced PFS among EGFR mutant P treated with erlotinib. We hypothesized that since olaparib can attenuate and/or prevent BRCA1 expression, the addition of olaparib to gefitinib could improve PFS in these P. **Methods:** This is a Phase IB dose escalation study (standard 3+3 design) to identify the maximum tolerated dose (MTD), dose limiting toxicity (DLT), pharmacokinetics (PK), and clinical activity of orally administered olaparib in combination with gefitinib in EGFR mutant advanced NSCLC. P were treated with gefitinib 250mg once daily plus olaparib at escalating doses ranging from 100mg BID to 250mg TDS during a 28-day cycle. **Results:** Twenty-two P were included across four dose levels of olaparib: 100mg BID (3), 200mg BID (6), 200mg TDS (6) and 250mg TDS (7). Most common toxicities were G1-2, including anemia, leucopenia, nausea, diarrhea, asthenia, rash and anorexia; G3 drug-related events included lymphopenia (1) and anemia (3). No DLT at dose levels 1 and 2; 1 DLT at dose level 3, and 2 at dose level 4 (G3 anemia and repeated blood transfusion within 4-6 weeks). Thirteen P harbored concomitant sensitizing mutation (exon 19 del or L858R mut) plus T790M (5 previously treated, and 7 untreated P). Twenty-one P were evaluated for response: for those not previously treated, complete responses (CR) were observed in 1 r75966P (7.1%) partial responses (PR) in 9 P (69.2%), stable disease (SD) in 3 P (23%) and no progressive disease (PD) (0%). In P previously with TKI, 3 (37.5%) had PR, 3 (37.5%) SD, and 2 (25.5%) PD. Durable PR and SD were observed in both EGFR TKI-naïve and previously treated P. **Conclusions:** This phase IB trial of gefitinib plus olaparib confirms tolerability of the combination and the activity seen warrants further exploration in treatment-naïve patients. MTD of olaparib was 200mg TDS. Clinical trial information: NCT01513174.

**8080 General Poster Session (Board #261), Sat, 1:15 PM-5:00 PM**

**A prospective, multicenter phase II trial of low-dose erlotinib monotherapy for patients with previously treated non-small cell lung cancer (NSCLC) with activating mutation of epidermal growth factor receptor (EGFR): Thoracic Oncology Research Group (TORG) 0911.** *Presenting Author: Yoshiro Nakahara, Department of Thoracic Oncology and Respiratory Medecine, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan*

**Background:** Erlotinib and gefitinib have been shown to have similar activity for EGFR mutation-positive (EGFRm+) NSCLC. Since the steady-state plasma trough concentration of erlotinib is approximately 3.5 times higher than that of gefitinib when administered at the respective approved dose, treatment with low-dose erlotinib may be as effective as full-dose therapy, with less toxicity and cost. **Methods:** Eligible patients had advanced EGFRm+ NSCLC with 1 to 3 prior chemotherapy treatments. Erlotinib with the initial daily dosage of 50 mg was administered. Dose was escalated to 150 mg in case of not achieving CR or PR by RECIST criteria at the evaluation after the first 4 weeks of treatment. Erlotinib was continued until disease progression or unacceptable toxicities. The primary endpoint was independent committee-determined objective response rate (ORR) to the low-dose erlotinib, with target ORR of 70% and threshold of 50%. The sample size was calculated to be 40, and the primary endpoint was met if 26 or more patients responded. **Results:** Thirty-four patients were enrolled between Apr. 2010 and Nov. 2012. Males/females 20/14; median age 67 (range 38-81); PS 0/1 16/18; Ad/Sq 33/1. One patient was excluded from evaluation due to absence of active tumor. The study was closed early according to the protocol definition when 15 of 33 evaluable patients failed to achieve CR/PR, making it impossible to meet the primary endpoint. ORR was 54.5% (95% C.I.: 36.4% to 71.9%), with disease control rate of 84.8%. Median progression free survival and overall survival were 9.5 months and 28.5 months, respectively. Grade 3 toxicities were 2 cases with transient neutropenia, and 1 with reversible AST/ALT elevation. No grade 4 toxicity or treatment-related death was observed. **Conclusions:** This trial is the first prospective study evaluating low-dose erlotinib. Although it appeared to have a certain efficacy, the primary endpoint was not met. Because of its low toxicity, it may be worth further evaluation in elderly and/or frail patients. Trial registry UMIN #000003313.

**8081 General Poster Session (Board #262), Sat, 1:15 PM-5:00 PM**

**EGFR mutation status in cerebrospinal fluid of NSCLC patients who developed leptomeningeal metastasis after EGFR-TKI treatment.** *Presenting Author: Jing Zhao, Department of Respiratory Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Science, Beijing, China*

Background: Prognosis for these patients with leptomeningeal metastasis (LM) is very poor due to the lack of therapeutic options. It was suggested that the leptomeningeal space is protected from the systemic chemotherapy as well as EGFR-TKIs. Therefore, it would be interesting to explore the EGFR mutation status in CSF of the NSCLC patients who developed LM after the initial response to EGFR-TKI. In this study, we attempted to address two questions: 1. what is the EGFR mutation status in CSF of this group of patients? 2. what is the difference of EGFR mutation status in CSF as compared to that in the concurrent plasma samples? **Methods:** A highly sensitive droplet digital PCR (ddPCR) method was used to detect EGFR mutation in 7 CSF samples which were collected from seven patients with NSCLC who initially responded to EGFR-TKI and developed LM afterwards. Concurrent plasma samples were collected and analyzed as well for comparison. **Results:** EGFR-sensitive mutations were detected in CSF of all 7 patients (4 of 19-del and 3 of L858R), one of which (1/7, 14.3%) carried T790M mutation as well (19-del&T790M). EGFR mutations were not detected in plasma from 5 of these 7 patients (5/7, 71.4%). In additional plasma samples from remaining 2 patients, who were positive for EGFR E19-del in CSF, E19-del and T790M double mutations were detected. **Conclusions:** With development of LM after EGFR-TKI treatment, CSF remained positive for EGFR mutations dominant by sensitive mutations only, even though the plasma were either negative for EGFR mutations or carried TKI-resistant T790M mutation. This is supportive of the protection of EGFR mutation positive tumor cells within leptomeningeal space from the exposure to current EGFR-TKIs.

**EGFR mutation status of matched CSF and plasma samples from NSCLC patients who developed LM after initial response to EGFR-TKI treatment.**

| | EGFR mutation status | |
|---|---|---|
| **Patient ID** | **CSF** | **Plasma** |
| **1** | 19-del | N |
| **2** | L858R | N |
| **3** | L858R | N |
| **4** | 19-del&T790M | N |
| **5** | L858R | N |
| **6** | 19-del | 19-del&T790M |
| **7** | 19-del | 19-del&T790M |

**8082 General Poster Session (Board #263), Sat, 1:15 PM-5:00 PM**

**Clinical significance of TILs subtypes in non-small cell lung cancer.** *Presenting Author: Kurt A. Schalper, Department of Pathology, Yale School of Medicine, New Haven, CT*

**Background:** Tumor infiltrating lymphocytes (TILs) are associated with better outcome in diverse neoplasms including non–small cell lung cancer (NSCLC). TILs are usually determined using subjective semi-quantitative methods. Studies suggest that TILs subtypes have independent roles and their contribution to prognosis remains unknown. Here, we measured TILs subtypes in NSCLC using objective methods and determined their relationship with clinico-pathologic characteristics and survival. **Methods:** Using the AQUA method of quantitative fluorescence**,** we measured the levels of CD3, CD8 and CD20 in 554 stages I-IV NSCLC represented in two tissue microarrays (YTMA79 n=204 and YTMA140 n=350). TILs subtypes were simultaneously measured in different tumor compartments using multiplexed immunofluorescence for epithelial tumor cells (cytokeratin), T lymphocytes (CD3), cytotoxic T cells (CD8), B lymphocytes (CD20) and nuclei (DAPI). Associations were determined using uni/multivariate analyses with per-unit adjustments. **Results:** In both NSCLC collections CD3, CD8 and CD20 signals showed a positive non-linear relationship (R=0.3-0.7, P<0.001). CD3 levels were not correlated with age, gender, smoking, tumor size, stage and histology. High levels of CD8 and CD20 (> median) were significantly associated with adenocarcinoma histology. Using proportional hazard models and continuous scores, CD3 and CD8 were significantly associated with longer survival in YTMA79 (HR=0.59 [CI:0.41-0.81] P=0.0003 for CD3 and HR=0.34 [CI:0.12-0.74] P=0.003 for CD8) and YTMA140 (HR=0.44 [CI:0.20-0.88] P=0.01 for CD3 and HR=0.437 [CI:0.20-0.81] P=0.007 for CD8). The contribution of CD20 was less pronounced (HR=0.86 P=0.05 and HR=0.93 P=0.29, respectively). In multivariate analysis, the prognostic effect of CD3 and CD8 were independent from age, tumor size, histology and stage. **Conclusions:** Increased CD3 and CD8 positive TILs are independent prognostic factors in NSCLC.Despite the positive relationship between TILs subtypes, only CD8 and CD20 show association with adenocarcinoma histology. Objective measurement of TILs subpopulations could be useful to predict response or monitor the off-target effect of anti-cancer immunostimulatory therapies.

**8083 General Poster Session (Board #264), Sat, 1:15 PM-5:00 PM**

**Integrated genomic analysis for revealing broad remodeling of EGFR-targeted therapy resistant lung cancers.** *Presenting Author: Petros Giannikopoulos, Cancer Therapeutics Innovation Group, San Francisco, CA*

**Background**: Patients with EGFR-mutant NSCLC often respond initially to EGFR kinase inhibitor therapy but ultimately relapse. The spectrum of clinical resistance mechanisms and mechanistically appropriate therapeutic strategies to enhance EGFR inhibitor treatment responses remains incompletely defined. **Methods**: We used whole exome and transcriptome deep sequencing analysis of tumors obtained from 16 EGFR-mutant NSCLC patients both prior to EGFR inhibitor therapy and at clinical resistance to identify the spectrum and biological basis of molecular alterations that could drive therapy resistance and be targeted to enhance clinical responses. **Results**: Tumors with acquired EGFR TKI resistance harbored individual and concurrent established resistance-conferring alterations, including $EGFR^{T790M}$ and upregulation of several receptor kinases, and other molecular alterations not previously associated with this resistance, including activating KRAS mutations. Pathway analysis of the transcriptome data revealed upregulation of ERBB2 and FGFR signaling broadly in the therapy-resistant tumors and that the $EGFR^{T790M}$ positive resistant tumors exhibited therapy-induced upregulation of biological pathways underlying cell cycle progression and genome maintenance. The evolution of $EGFR^{T790M}$-positive resistance was also associated with increased genetic divergence and genomic instability. Genomic amplification and increased levels of the NF-kB inhibitor NFKBIA correlated with improved EGFR TKI response. **Conclusions**: This genome-scale characterization of the molecular landscape of EGFR inhibitor resistance uncovered biological programs and molecular events underlying the evolution of resistance, establishes the utility of whole exome and transcriptome deep sequencing in repeat biopsy specimens from NSCLC patients, and provides rationale for serial, comprehensive tumor molecular profiling in individual cancer patients to enhance therapeutic precision and response. Our findings also uncovered new molecular biomarkers of therapy response and provide new insight into the biological basis and complexity underlying the evolution of resistance.

**8085 General Poster Session (Board #266), Sat, 1:15 PM-5:00 PM**

**A phase II trial of first-line *nab*-paclitaxel/carboplatin versus gemcitabine/carboplatin in advanced squamous cell carcinoma of the lung (CTONG1002).** *Presenting Author: Jinji Yang, Guangdong Lung Cancer Institute, Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China*

**Background:** The administration of *nab*-paxlitaxel/carboplatin (*nab*-PC) as first-line therapy in patients with advanced non-small-cell lung cancer was efficacious and resulted in a significantly improved objective overall response rate (ORR) versus solvent-based PC in a phase III trial. Subgroup analysis showed the squamous histology appeared to be a predictive factor to *nab*-paclitaxel treatment. This phase II trial (NCT01236716; CTONG1002) compared the efficacy and safety of first-line *nab*-PC with gemcitabine/carboplatin (GC) in advanced squamous cell carcinoma of the lung. **Methods:** From November 2010 to June 2013, 127 untreated patients with locally advanced and metastatic squamous cell carcinoma of the lung were randomly assigned 1:1 to receive first-line *nab*-PC (*nab*-P, 135 mg/m$^2$, d1, d8, q3w; C, AUC = 5, d1, q3w ) or GC (G, 1,250 mg/m$^2$, d1, d8, q3w; C, AUC = 5, d1, q3w). The primary end point was ORR. **Results:** There were 110 cases evaluable for ORR (*nab*-PC, 54; GC, 56), 119 evaluable for survival (*nab*-PC, 57; GC, 62) and 124 evaluable for safety (*nab*-PC, 59; GC, 65), respectively. ORR was 46.3% (25/54) for the *nab*-PC arm and 30.4% (17/56) for the GC arm respectively, $P = 0.085$. There was an approximately 18.8% improvement in progression-free survival (median, 5.7 *v* 4.8 months; hazard ratio [HR], 0.907; 95% CI, 0.588 to 1.399; $P = 0.657$) in the *nab*-PC arm versus the GC arm. Overall survival was not mature. Significantly more grade $\geq$ 3 leucopenia and neutropenia occurred in the *nab*-PC arm. **Conclusions:** First-line *nab*-PC in advanced squamous cell carcinoma of the lung was efficacious and resulted in a marginally improved ORR versus GC, but not achieving the primary end point. *nab*-PC produced more leucopenia and neutropenia than GC. Clinical trial information: NCT01236716.

**8086 General Poster Session (Board #267), Sat, 1:15 PM-5:00 PM**

**Genomic characterization of non-small cell lung cancer by targeted massively parallel sequencing in African Americans.** *Presenting Author: Luiz H. Araujo, The Ohio State University Comprehensive Cancer Center, Columbus, OH*

**Background:** Technological advances have enabled the comprehensive analysis of genetic perturbations in non-small cell lung cancer (NSCLC), but African-Americans (AA) have often been underrepresented. This ethnic group presents higher lung cancer incidence and mortality, and some studies have suggested a lower incidence of EGFR mutations. Herein we used a targeted massively parallel sequencing approach to assess NSCLC samples resected from AAs. **Methods:** We designed and validated a NSCLC-specific panel comprising 80 genes of potential interest for therapy. Libraries were constructed using a custom Agilent Haloplex kit, and sequenced on an Illumina HiSeq 2500. Cell lines and clinical formalin-fixed paraffin-embedded samples with known mutation status were used for validation. NSCLC archival tissues derived from AAs were retrospective collected, and medical charts were reviewed to assess clinical data. ALK translocations were evaluated by fluorescence in situ hybridization (FISH). **Results:** Targeted capture probes covered 15,473 amplicons comprising 310,720 base pairs, with 99.29% coverage. Our platform successfully identified all known mutations in the validation samples. Ninety-nine AAs were included, with a median age of 61 years (41-76). Sixty-one percent were males, and 94% were current/former smokers. Sixty percent of samples had an adenocarcinoma component, and 31% were squamous cell carcinomas. We detected 1,465 non-silent variants in the coding sequence, after excluding known germline polymorphisms. Classic recurrent mutations were found in KRAS (16%), EGFR (5%), PIK3CA (1%), and NRAS (1%). We also identified known somatic mutations in TP53 (48%), BRAF (4%), KEAP1 (3%), PDGFRA, FBXW7, CDKN2A, and CTNNB1 (1% each). In addition, several variants of unknown significance were found and may deserve further investigation. One case was positive for ALK-FISH. EGFR and ALK-positive cases were adenocarcinomas, and no overlap was identified between major drivers. **Conclusions:** We demonstrated a relatively low frequency of classic driver mutations in NSCLC among AAs. This group may benefit from the identification of novel drivers through comprehensive genomic approaches.

**8087 General Poster Session (Board #268), Sat, 1:15 PM-5:00 PM**

**Further molecular profiling of tumors harboring therapeutic targets within non-small cell lung cancer.** *Presenting Author: Solange Peters, University Hospital of Lausanne (CHUV), Lausanne, Switzerland*

**Background:** Treatment of NSCLC has been revolutionized in recent years with the introduction of several targeted therapies for selected genetically altered subtypes of NSCLC. A better understanding of molecular characteristics of NSCLC, which features common drug targets, may identify new therapeutic options. **Methods:** Over 6,700 non-small cell lung cancer cases referred to Caris Life Sciences between 2009 and 2014. Diagnoses and history were collected from referring physicians. Specific testing was performed per physician request and included a combination of sequencing (Sanger, NGS or pyrosequencing), protein expression (IHC), gene amplification/rearrangement (CISH or FISH), and/or RNA fragment analysis. **Results:** Tumors profiles from patients with hormone receptor positive disease (HER2, ER, PR, or AR positive by IHC) (n=629), HER2 mutations (n=8) ALK rearrangements (n=55), ROS1 rearrangement (n=17), cMET amplification or mutation (n=126), and cKIT mutation (n=11) were included in this analysis and compared to the whole cohort. Tumors with ALK rearrangement overexpressed AR in 18% of cases, and 7% presented with concomitant KRAS mutation. Lower rates of PTEN loss, as assessed by IHC, were observed in ALK positive (20%), ROS1 positive (9%) and cKIT mutated tumors (25%) compared to the overall NSCLC population (58%). cMET was overexpressed in 66% of ROS1 translocated and 57% of HER2 mutated tumors. cKIT mutations were found co-existing with APC (20%) and EGFR (20%) mutations. Pathway analysis revealed that hormone receptor positive disease carried more mutations in the ERK pathway (32%) compared to 9% in the mTOR pathway. 25% of patients with HER2 mutations harbored a co-existing mutation in the mTOR pathway. **Conclusions:** Pathway profiling reveals that NSCLC tumors present more often than reported with several concomitant alterations affecting the ERK or AKT pathway. Additionally, they are also characterized by the expression of potential biological modifiers of the cell cycle like hormonal receptors, representing a rationale for dual inhibition strategies in selected patients. Further refining of the understanding of NSCLC biomarker profile will optimize research for new treatment strategies.

**8088 General Poster Session (Board #269), Sat, 1:15 PM-5:00 PM**

**A multicenter randomized phase II trial of erlotinib with and without hydroxychloroquine (HCQ) in TKI-naive patients (pts) with epidermal growth factor receptor (EGFR) mutant advanced non-small cell lung cancer (NSCLC).** *Presenting Author: Joel W. Neal, Stanford Cancer Institute, Stanford, CA*

**Background:** Erlotinib (E) is widely used in the treatment of advanced EGFR mutant NSCLC, with a historical progression free survival of about 9 months. Preclinical data showed HCQ prevented the development of resistance to E putatively via chromatin state modulation, and a prior phase I trial established safety of E+HCQ (EQ). This randomized phase II trial tested the efficacy of EQ in delaying acquired resistance to E. **Methods:** EGFR-TKI naïve pts with metastatic or recurrent EGFR mutant NSCLC were randomized to E (150 mg daily) with or without HCQ (1,000 mg daily). Tumor assessments were performed every 8 weeks until disease progression. With a sample size of 76 pts, the study was powered for a primary endpoint of improvement in 9-month progression free survival (PFS) from 50% in the E arm compared with 77% in the EQ arm. **Results:** 76 pts were enrolled at 4 sites between 12/09 and 1/13, 38 on each arm. Age, sex, race, histology, and prior chemotherapy were well balanced between the arms, but an excess of patients with a smoking history (26% E vs 47% EQ) and brain metastases (29% E vs 42% EQ) was observed on the EQ arm. E-related toxicities were mostly balanced among treatment arms, but EQ patients had an excess of grade (G) 3 fatigue (3% E vs 18% EQ) and nausea (28% G1/2 + no G3 for E, and 53% G1/2 + 3% G3 for EQ). No drug-attributed G4/5 toxicities were observed. Among 37 evaluable pts on arm E and EQ, respectively, confirmed response rates were 65% and 57% and disease control rates were 92% and 84%. 9-month PFS was 71% for E and 52% for EQ (p=NS), but median PFS was identical in each arm (10.8 months). Preliminary median overall survival (OS) was 33.5 months on E and 27.8 months on EQ (p=0.06) though OS data are not yet mature. **Conclusions:** EQ did not improve 9 month PFS compared with arm E. OS numerically favored the E arm, which may reflect imbalances between the arms. Despite strong preclinical evidence, hydroxychloroquine does not appear to delay the development of resistance to erlotinib in pts with EGFR mutant NSCLC. Clinical trial information: NCT00977470.

**8089 General Poster Session (Board #270), Sat, 1:15 PM-5:00 PM**

**A randomized phase II study of paclitaxel-carboplatin-bevacizumab (PCB) with or without nitroglycerin patches (NTG) in patients (pts) with stage IV nonsquamous non-small cell lung cancer (NSCLC): Nvalt 12 (NCT01171170).** *Presenting Author: Anne-Marie C. Dingemans, University Hospital Maastricht, Maastricht, Netherlands*

**Background:** NTG increases tumor blood flow and thereby may augment drug delivery to the tumor and inhibits HIF-1a, a major regulator of hypoxia. In mouse models addition of HIF-1$\alpha$ inhibitors to B significantly impairs tumor growth. A randomized phase II study has shown improved clinical outcome when NTG patches were added to vinorelbine/cisplatin in pts with advanced NSCLC (Yasuda, 2006). We hypothesized that adding NTG to PCB improves progression free survival (PFS), response rate (RR) and overall survival (OS) in pts with stage IV non-squamous NSCLC. **Methods:** This open-label multicenter phase II trial randomized chemo-naive pts with stage IV non-squamous NSCLC 1:1 to PCB with or without NTG. Main other inclusion criteria: performance score 0-2; measurable disease (RECIST 1.1); adequate bone marrow, liver and renal function; written informed consent; no clinical significant cardiovascular disorders; no significant bleeding. Pts were treated with P 200 mg/m2 day (d) 1-C AUC 6 d1-B 15 mg/kg d1 every 3 weeks (wks) without (Arm A) or with (Arm B) NTG 15 mg/24 h for 5 d (d -2 to +3) every cycle for 4 cycles and B and NTG until progression. Tumor measurements were assessed every 2 cycles. The study was powered (80%) to detect a decrease in the hazard of progression of 33% in arm B at $\alpha = 0.05$ with a two-sided log rank test when 222 pts were enrolled and followed until 195 events were observed. **Results:** Between 01-2011 and 01-2013 223 pts were randomized; 112 arm A and 111 arm B; 50% males; median (range) age 62 years (39-81); 85% adenocarcinoma. Pts characteristics were balanced between both arms. RR was 45% in arm A and 30% in arm B. Median (95% CI) PFS in arm A was 6.8 months (m) (5.6-7.3) and 5.0 m (4.2-5.8) in arm B, HR 1.22 (95% CI 0.91-1.63). OS was 11.6 m (8.7-14) in arm A and 9.5 m (7.8-11.9) in arm B, HR 1.12 (95% CI 0.76-1.67). In arm B no additional toxicity was observed except headache (14% arm A and 57% arm B). **Conclusions:** Adding NTG to first line PCB does not improve PFS and OS in pts with stage IV non-squamous NSCLC. No further study with this regimen is warranted. Clinical trial information: NCT01171170.

**8090 General Poster Session (Board #271), Sat, 1:15 PM-5:00 PM**

**Implementation of clinical next-generation sequencing (NGS) of non-small cell lung cancer (NSCLC) to identify EGFR amplification as a potentially targetable oncogenic alteration.** *Presenting Author: Geoffrey R. Oxnard, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Tumor genotyping has become fundamental in the care of NSCLC. Targeted NGS can simultaneously test for oncogenic mutations, rearrangements, and amplifications using one platform and specimen. Using an institute-wide prospective trial, we aimed to evaluate feasibility of NGS and clinical impact for patients (pts). **Methods:** Testing commenced in our CLIA-certified lab in 7/13. NSCLC pts were identified for whom NGS was ordered as a supplement to routine genotyping. All pts provided informed consent. A minimum of 50ng DNA was analyzed by massively parallel sequencing on an Illumina HiSeq 2500, using hybrid capture to target exonic and/or intronic sequences in 305 cancer genes. Coverage was normalized to a panel of normals and expressed as a log2ratio, with high amplification defined as log2ratio >2. **Results:** As of 12/2013, NGS was ordered on 191 NSCLC pts: 45 (24%) were screened out due to insufficient tissue, and results from another 33 are pending at time of submission. Testing was completed on 113 with a turnaround time (TAT) as short as 12 days: 86% non-squamous NSCLC, 14% squamous NSCLC, 19% never-smokers, 54% female. Using this single assay, key targetable alterations were identified in 77% of non-squamous and 50% of squamous cases (Table). Three cases showed high *EGFR* amplification; one of these, a 61 yo never-smoker, initiated second-line erlotinib 150mg daily and had a response sustained for 23 weeks, interrupted by CNS progression. One *ALK* FISH positive case showed no rearrangement by NGS and a *KRAS*Q61L mutation, potentially indicating false positive FISH. **Conclusions:** Clinical NGS of NSCLC can efficiently identify targetable mutations, rearrangements, and amplifications, with acceptable specimen requirements and TAT. This assay has now been adopted for routine clinical genotyping. *EGFR* amplification may represent a rare targetable oncogenic alteration with sensitivity to erlotinib.

| | Nonsquamous | | Squamous | |
|---|---|---|---|---|
| | N = 97 | % | N = 16 | % |
| **Point mutations** | | | | |
| EGFR | 10 | 10 | | |
| BRAF | 6 | 6 | 1 | 6 |
| PIK3CA | 6 | 6 | 4 | 25 |
| KRAS | 30 | 31 | 1 | 6 |
| **Insertions/deletions** | | | | |
| EGFR | 8 | 8 | | |
| HER2 | 1 | 1 | | |
| **Rearrangements** | | | | |
| ALK | 4 | 4 | | |
| ROS1 | | | | |
| RET | 1 | 1 | | |
| **High amplification** | | | | |
| EGFR | 3 | 3 | | |
| HER2 | | | | |
| MET | 4 | 4 | | |
| PIK3CA | 1 | 1 | 2 | 13 |
| FGFR1 | 1 | 1 | | |

**8091 General Poster Session (Board #272), Sat, 1:15 PM-5:00 PM**

**Randomized, controlled, multicenter, multinational phase 2 study of docetaxel (DCT) or AXL1717 treatment in patients with squamous cell carcinoma (SCC) or adenocarcinoma (AC) of non-small cell lung cancer (NSCLC).** *Presenting Author: Michael Bergqvist, Department of Oncology, Uppsala University Hospital, Uppsala, Sweden*

**Background:** AXL1717 (picropodophyllin) is small molecule that inhibits the IGF-1R signaling pathway as well as suppresses tumor cell division by arresting cells in mitosis through a non-IGF-1R dependent mechanism. Preclinical data have shown extensive anti-tumor effects includingcomplete regressionsin xenograft studies against a range of tumors. **Methods:** A total of 101 patients (99 treated, ITT population) with locally advanced or metastatic NSCLC (Stage IIIB or IV, SCC or AD) with 1-2 lines of previous treatmentwere randomized. Patients had ECOG PS 0–2 and a life expectancy ≥ 3 months. The patients were randomized to either AXL1717 or DCT as monotherapy, in a 3:2 ratio for each NSCLC subtype. AXL1717 was administrated as an oral suspension given twice daily ata dose of 400 mg (later changed to 300 mg) and DCT was administered at 75 mg/m2 on Day 1 of every 21-day cycle. The treatmentduration was 12 weeks. **Results:** The primary objective was to compare the rate of progression-free survival (PFS) at 12 weeks between the treatment groups. The 12-week PFS rate for the ITT population was 25.9% in the AXL1717 and 39.0% in the DCT group (p=0.19). The median follow-up time was 27 weeks. Updated data will be presented at ASCO. The median OS was 38.7 weeks (w) for AXL1717 treated patients compared with 39.6 w for DCT patients (HR 1.063, p=0.813 [log rank test]). The median OS for the 49 patients with AC was 57.3 w for AXL1717 treated and 24.8 w for DCT patients(HR 0.932, p=0.846). The main side effects were hematological, mainly reduced neutrophil counts: 22.4% of the AXL1717 treated patients reported at least one event of CTCAE grade 3/4 neutropenia compared with 53.7% of the DCT treated patients. Some of the early neutropenic episodes in the AXL1717 group developed into serious events and some of these were fatal. The side effects were managed with a dose reduction of AXL1717 coupled with increased supervision of the patients. **Conclusions:** The phase 2 data in 99 patients did not show statistically confirmed difference between the two treatment groups for all patients or any of the histological subgroups for OS or PFS. Clinical trial information: NCT01561456.

**8092 General Poster Session (Board #273), Sat, 1:15 PM-5:00 PM**

**EGFR mutation detection in ctDNA from NSCLC patient plasma: A cross-platform comparison of technologies to support the clinical development of AZD9291.** *Presenting Author: Kenneth Thress, AstraZeneca, Waltham, MA*

**Background:** EGFR tyrosine kinase inhibitors are highly effective in treating EGFR mutant+ NSCLC. Patients invariably relapse and resistance is most often associated with an EGFR T790M mutation. AZD9291 is currently in clinical development to address this primary T790M-mediated resistance. Several highly sensitive technologies have been described for detection of EGFR mutations from tumor DNA (ctDNA) shed into the circulating plasma. ctDNA may provide an option for patients unable to provide tissue biopsies for AZD9291 patient selection and disease monitoring purposes. **Methods:** Using plasma from patients enrolled on the AZD9291 clinical study (NCT01802632), we undertook a cross-platform comparison of 4 methods for the detection of EGFR mutations in ctDNA: ARMS-based detection using 1) Roche Cobas and 2) Qiagen Therascreen EGFR mutation detection kits, and digital PCR-based (dPCR) approaches using 3) BioRad ddPCR (MolecularMD) and 4) BEAMing (Inostics). **Results:** To date, 38 pre-dose plasma samples have been evaluated. ctDNA was tested for 3 EGFR mutations (T790M, L858R, Exon 19 del). Matched tumor biopsies were available for most plasma samples to enable ctDNA-tumor concordance testing. Overall, concordance of mutation status was high for all ctDNA detection methods. The false positive rate was low across platforms with specificities >90%. In contrast, dPCR methods showed increased sensitivities for T790M compared with the ARMS-based methods (67-71% vs. 29-41%) whereas sensitivity for activating mutations was equivalent between dPCR and ARMS (80-90%). The sensitivity of dPCR for T790M allowed for preliminary correlations of baseline plasma T790M levels with clinical characteristics and AZD9291 response (unvalidated). T790M was more frequently detected in the plasma from patients with metastatic vs. local disease (77% vs. 25%). Moreover, patients with quantifiable T790M at baseline showed a 71% response rate (RR) compared to a 31% RR for patients with undetectable levels of T790M. **Conclusions:** The detection of EGFR mutations from ctDNA using sensitive dPCR methods will help to inform alternative patient selection strategies for AZD9291.

**8093 General Poster Session (Board #274), Sat, 1:15 PM-5:00 PM**

**Detection of sensitizing and resistance *EGFR* mutations from circulating tumor DNA (ctDNA) in blood using multiplexed next-generation sequencing in patients with advanced *EGFR*-mutant lung adenocarcinoma.** *Presenting Author: Sarah B. Goldberg, Department of Medical Oncology, Yale University School of Medicine, New Haven, CT*

**Background:** Analysis of tumor biopsies obtained after the development of acquired resistance (AR) to EGFR tyrosine kinase inhibitors can contribute to the understanding of resistance mechanisms, but requires an invasive procedure and only provides data on a single site of disease at one timepoint. We developed a next-generation sequencing method that employs novel error-suppression techniques to measure tumor-specific mutations in plasma at levels as low as 1 variant in 5,000. Here we report on the detection of sensitizing *EGFR* mutations and the emergence of the T790M resistance mutation in ctDNA and in tumor specimens. **Methods:** We collected plasma samples from patients (pts) with advanced *EGFR*-mutant lung adenocarcinoma. When feasible, serial plasma samples were collected during treatment and repeat tumor biopsies were performed at AR. Plasma was analyzed using error-suppressed deep sequencing to quantify point-mutations and insertions/deletions in multiple genes that are commonly mutated in lung cancer, including *EGFR*. **Results:** Plasma samples were obtained from 52 pts with known activating *EGFR* mutations. Thirty-two pts had serial samples, allowing monitoring of mutant DNA levels and detection of the emergence of new mutations in the plasma. Of the 31 pts who had a repeat biopsy, the T790M mutation was found in 15 (48%) in the tumor at AR. Data for the ctDNA and repeat tumor biopsy results for the first 5 pts tested in this cohort are presented in the Table. **Conclusions:** Detection of *EGFR* sensitizing and resistance mutations in ctDNA from the plasma using multiplexed next generation sequencing is feasible and shows a high concordance with results from tumor biopsy. This novel method using plasma may allow for earlier identification of resistance in pts treated with targeted therapy without the need for invasive biopsies.

| | | Sensitizing *EGFR* mutation | | *EGFR* T790M |
|---|---|---|---|---|
| Pt # | Source of DNA | Exon 19 del | L858R | resistance mutation |
| 1 | Lymph node | - | + | - |
| | Plasma | - | + | - |
| 2 | Lymph node | + | - | + |
| | Plasma | + | - | + |
| 3 | Pleural fluid | + | - | + |
| | Plasma | + | - | + |
| 4 | Neck mass | - | + | - |
| | Plasma | - | + | - |
| 5 | Liver mass | + | - | + |
| | Plasma | + | - | - |

**8094 General Poster Session (Board #275), Sat, 1:15 PM-5:00 PM**

**Randomized, open-label trial evaluating the preventive effect of tetracycline on afatinib induced-skin toxicity in non-small cell lung cancer patients.** *Presenting Author: Oscar Arrieta, Instituto Nacional de Cancerologia - INCAN, Mexico City, Mexico*

**Background:** Afatinib has shown high objective response rates and prolonged progression-free survival in patients with metastatic non-small cell lung cancer (NSCLC). The most common toxicity of this agent is acneiform rash, which may have a negative impact on quality of life. Tetracyclines are used as treatment for this adverse event (AE). No randomized trial have evaluated the prophylactic efficacy treatment of tetracycline in afatinib induced-skin toxicity. **Methods:** We performed an open-label, randomized, controlled trial to assess the preventive effect of tetracycline for reducing afatinib skin toxicity. Patients receiving afatinib treatment (40mg/day) were randomly assigned to pre-emptive or reactive treatment (after skin toxicity developed). Pre-emptive comprised tetracycline 250 mg/d for 4 weeks and reactive treatment included the use of skin moistures, sunscreen, topical steroids and tetracycline according to the severity of toxicity. All patients were blindly monitored for rash and other adverse events at baseline, 2 weeks and 4 weeks. Cutaneous toxicity was reported according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE). The protocol is registered on ClinicalTriasl.gov with the number NCT01880515 **Results:** We included 90 patients. No differences were found in clinical and dermatological baseline characteristics. The incidence of adverse events of any grade and grade ≥2 were lesser in the pre-emptive arm versus the control arm (55.6 *vs.* 75.6%, RR 0.4 [95% CI 0.17-0.99, $p$=0.046 and 15.6 *vs.* 35.6%, RR 0.35 [0.12-0.91], $p$=0.030; respectively). No difference was found in other dermatologic adverse events like paronychia, xerosis, mucositis, folliculitis and skin fissure. Nor the presence of rash or pre-emptive treatment with tetracycline impact on response rate, progression-free survival and overall survival. No adverse events were associated with tetracycline. **Conclusions:** The incidence and severity of rash associated with afatinib was reduced by 60% in the tetracycline group compared with the control group. Its use can positively impact quality of life in patients who are candidates for afatinib treatment. Clinical trial information: NCT01880515.

**8095 General Poster Session (Board #276), Sat, 1:15 PM-5:00 PM**

**Multiplex genomic profiling of non-small cell lung cancer patients enrolled in the LETS phase III trial of first-line S-1/carboplatin versus paclitaxel/carboplatin (WJOG6611LTR).** *Presenting Author: Hiroshige Yoshioka, Department of Respiratory Medicine, Kurashiki Central Hospital, Kurashiki, Japan*

**Background:** High-throughput genotyping tests to evaluate large numbers of genetic abnormalities in non–small cell lung cancer (NSCLC) are needed. **Methods:** Archival formalin-fixed, paraffin-embedded (FFPE) tumor specimens were collected from patients with advanced NSCLC enrolled in the LETS phase III trial. With the use of the multiplex platform of Sequenom's MassARRAY assays, we performed high-throughput genotyping for 214 somatic hotspot mutations in 26 genes (LungCarta Panel) and 20 major variants of *ALK*, *RET*, and *ROS1* fusion genes (LungFusion Panel). We also evaluated *MET* amplification by fluorescence in situ hybridization. **Results:** The numbers of evaluable patients were 275 for somatic gene mutations, 240 for fusion genes, and 229 for *MET* amplification. A somatic mutation in at least one gene was identified in 105 (48%) of the 217 patients with nonsquamous cell carcinoma (non-SCC) and in 26 (45%) of the 58 patients with SCC. Overall, we identified *EGFR* mutations in 46 patients (17%), *TP53* mutations in 30 (11%), *STK11* mutations in 27 (9.8%), *MET* mutations in 21 (7.6%), *KRAS* mutations in 17 (6.2%), *PIK3CA* mutations in 6 (2.2%), and *BRAF* and *NRAS* mutations in 3 each (1.1%). Median overall survival of *EGFR* mutation–positive patients was significantly longer than that of those without *EGFR* mutations (23.7 vs. 12.6 months, $P$ = 0.004). Conversely, patients with *KRAS* mutations had a significantly shorter survival time than did those with wild-type *KRAS* (9.9 vs. 15.3 months, $P$ = 0.04). *ALK* fusions were detected in six cases (2.5%), *ROS1* fusions in five (2.1%), and *RET* fusions in one (0.4%), with these three types of rearrangement being mutually exclusive. Median overall survival was 19.5 versus 13.8 months for fusion gene–positive and –negative patients, respectively ($P$ = 0.89). De novo *MET* amplification was identified in 9 patients (3.9%). **Conclusions:** This first multiplex genotyping of NSCLC accompanying a phase III study demonstrates that MassARRAY-based testing performs well with nucleic acid derived from FFPE tissue obtained from patients with advanced NSCLC.

**8096 General Poster Session (Board #277), Sat, 1:15 PM-5:00 PM**

**Immunohistochemically determined EGFR mutations in NSCLC.** *Presenting Author: Nina Turnsek, University Clinic Golnik, Golnik, Slovenia*

**Background:** ActivatingEGFR mutations (EGFRmu), especially exon 19 deletions (del 19) and L858R point mutation in exon 21 are best predictors of response to TKI therapy in advanced non-small cell lung cancer (NSCLC) and are routinely detected by PCR. Data on immunohistochemically (IHC) determined EGFRmu are scarce. We evaluated the concordance between PCR and IHC determined del 19 and L858R EGFRmu and their predictive value in a Slovenian cohort of NSCLC patients. **Methods:** IHC using mutation specific antibodies for E746-A750 deletion in exon 19 and for L858R in exon 21 (Ventana Medical Systems) was performed on 137 formalin-fixed tissue specimens. These specimens had PCR predetermined EGFRmu status: 37/137 (27.0%) specimens with del 19, 40/137 (29.1%) with L858R, 31/137 (22.6%) with other mutations, and 29/137 (21.2%) EGFRwt specimens (Therascreen EGFR 28 Mutation Kit Qiagen). IHC staining reaction was assessed by two independent evaluators as positive or negative. 81 EGFRmu patients that received EGFR TKI for advanced disease were included in the survival analysis. **Results:** With PCR results set as gold standard, the sensitivity, specificity, positive and negative predictive value for the del 19-specific antibody were 67.6%, 99.0%, 96.2%, and 89.2%, respectively, while for the L858R-specific antibody were all 100% (Table). The median overall survival (mOS) of patients treated by TKI differs significantly for PCR+ and IHC+ patients (n=50) compared to PCR+ alone patients (n=31) (33.8 months vs. 17.1 months, respectively; p= 0.024). **Conclusions:** Both mutation-specific antibodies are highly specific, and could be used as a first-step method for EGFRmu screening. Results, including survival (mOS), are indicating that IHC positive patients could directly receive TKI therapy, while IHC negative cases should be submitted for further molecular testing.

**Results for del 19-specific antibody.**

| | | PCR | | |
|---|---|---|---|---|
| | | **Del 19+** | **Del 19-** | **Total** |
| **IHC** | Del 19+ | 25 | 1 | 26 |
| | Del 19- | 12 | 99 | 111 |
| | Total | 37 | 100 | 137 |

**Results for L858R-specific antibody.**

| | | PCR | | |
|---|---|---|---|---|
| | | **L858R+** | **L858R-** | **Total** |
| **IHC** | L858R+ | 40 | 0 | 40 |
| | L858R- | 0 | 97 | 97 |
| | Total | 40 | 97 | 137 |

**8097 General Poster Session (Board #278), Sat, 1:15 PM-5:00 PM**

**Molecular testing prior to first-line therapy in patients with stage IV nonsquamous non-small cell lung cancer (NSCLC): A survey of U.S. medical oncologists.** *Presenting Author: Mark R. Green, Xcenda, Palm Harbor, FL*

**Background:** Current ASCO, CAP/IASLC/AMP, and NCCN guidelines recommend testing tumor specimens from all patients with advanced non-squamous NSCLC for EGFR mutation status and ALK fusion gene rearrangement. Clearly defining actual rates of oncogene mutation testing among US medical oncologists (MO's) has been challenging. During 2013, we used a live, case-based, market-research vehicle to document estimated rates of oncogene testing for patients with advanced non-squamous NSCLC. **Methods:** Using unaided recall estimates, we quantitated testing rates of 385 US MO's. Response options included specified intervals between 0 and 100%. Assessments were done at 4 research events throughout 2013. Each MO participated in only one research assessment. Three questions were posed: 1) Think about the last 20 patients with stage IV non-squamous NSCLC seen by you for consideration of 1st line therapy. In what percentage of those 20 patients did you prescribe a 1stline anti-tumor therapy? 2) In thinking about those same patients, in what percentage did you (or someone prior to you) order testing for EGFR mutation status? 3) In those same patients, in what percentage did you or someone prior to you, order testing for ALK fusion gene rearrangement? **Results:** Shown in the Table are the results averaged across all events for treatment and testing for EGFR mutation status and ALK. No trends for increased rates of testing were seen over the assessment interval. **Conclusions:** Approximately 20% of US MO's estimated their EGFR and ALK testing rates as being < 40% in patients with advanced non-squamous NSCLC. Our findings demonstrate an urgent need to educate physicians on the role of molecular testing in NSCLC.

| **% of last 20 pts** | **Q1: first-line therapy rate N=366** | **Q2: EGFR testing rate N=368** | **Q3: ALK testing rate N=379** |
|---|---|---|---|
| **100%** | 10% | 25% | 17% |
| **80 - 99%** | 59% | 35% | 32% |
| **60 - 79%** | 21% | 14% | 18% |
| **40 - 59%** | 4% | 8% | 10% |
| **30 - 39%** | 3% | 3% | 6% |
| **< 30%** | 2% | 14% | 17% |
| **Can't estimate** | 1% | 1% | 1% |

**8098 General Poster Session (Board #279), Sat, 1:15 PM-5:00 PM**

**Effect of reflex testing by pathologists on molecular testing rates in lung cancer patients: Experience from a community-based academic center.** *Presenting Author: Cengiz Inal, Montefiore Medical Center Department of Medical Oncology, Bronx, NY*

**Background:** IASLC/CAP and NCCN guidelines recommend molecular testing for non-squamous non-small cell lung carcinoma (NSCLC) patients. Testing is usually performed upon request by medical oncologist. Reflex testing by pathologists for ER/PR/HER-2 is routinely done in breast cancer patients. We instituted reflex molecular testing at Montefiore Medical Center (MMC) on all non-squamous NSCLC patients in Jan 2012. **Methods:** We retrospectively reviewed our cancer registry database from Jan 2009 to July 2013 and analyzed all non-squamous NSCLC patients with pathology in our system. We examined annual molecular testing rates as well as testing rates before and after institution of reflex testing. Integrated Oncology (Labcorp) performed EGFR and KRAS testing by PCR-based technology. For patients with wild type EGFR and KRAS, the MMC cytogenetics laboratory performed ALK testing by FISH (Vysis assay). **Results:** From 2009 to July of 2013, 1,910 patients with lung cancer were identified in our cancer registry and 874 of these had non-squamous NSCLC with pathology diagnosed at MMC. At least 1 set of molecular tests was performed in 14, 25, 46, 64, and 69 % of patients in 2009, 2010, 2011, 2012 and 2013 respectively. The molecular testing rates pre (prior to 2012) and post (after 2012) reflex testing were 28% (166/598) vs 64% (177/276). The testing rates pre and post-reflex testing for EGFR, KRAS and ALK are 26 vs 62%, 6 vs 43% and 7 vs 23% respectively. Among the tested patients, the incidence of EGFR, KRAS and ALK positivity were 14% (46/326), 40% (61/152), and 1.9% (2/106) respectively. Of 276 patients post reflex testing, 52 (19%) had cytology-only NSCLC diagnoses; 75% (39/52) of these patients did not have any molecular testing. **Conclusions:** Reflex testing by pathologists increased the rate of molecular testing in a community based academic center. Despite the institution of reflex testing, ~30% of patients still do not have guideline recommended molecular testing. The reason for this is unclear; it may be in part due to lack of tissue available for molecular testing, particularly for cytology-only cases. We will further examine factors that influence the lack molecular testing in these patients.

**8099 General Poster Session (Board #280), Sat, 1:15 PM-5:00 PM**

**Lung cancer in never-smokers from the Princess Margaret Cancer Centre.** *Presenting Author: Grzegorz Korpanty, Princess Margaret Cancer Centre, Toronto, ON, Canada*

**Background:** Lung cancer in never smokers accounts for ~15-20% of cases, and globally is a growing clinical problem. **Methods:** We identified 570 never-smokers with lung cancer diagnosed from 1988-2013 at the Princess Margaret Cancer Centre. Clinical and demographic data were retrieved from the electronic patient record with the aim of characterizing the epidemiology, demographics, pathology, molecular profile, treatment, and survival in these patients. **Results:** There were 409 females (72%) and 161 males (28%), median age 62.1 years (18– 94), 46% Caucasian, 34% Asian, 6% Black, 4% South Asian, 4 % Filipino, 6% Other/Unknown. Environmental tobacco exposure was identified in only 17%. A history of prior malignancy was present in 89 (14.2%) patients (1 cancer 81; multiple cancers 8 patients). Most patients (87.3%) had adenocarcinoma and most presented in stage IV - 54.9%, followed by I - 26%, III - 12.8% and II - 6.3%. In stage IV patients, 88% were ECOG PS 0-1. Among 310 patients with molecular results to date, the mutation rate was 71% (*EGFR* mutation [mut] 76%, *ALK* 10%, *KRAS* 4%, *HER2* 1.4% *BRAF* 0.5%, other 1.8%, multiple mut 6.3%. Brain metastases at presentation occurred in 18.4% stage IV patients (77/419): 67% (52/77) with *EGFR* mut *vs* 22% (17/77) with *EGFR* WT vs 10% (8/77) with other mut (P=0.0023). Median overall survival (OS) of *EGFR* mut patients *vs EGFR* WT with brain metastases at presentation was 57 vs 16 mo (P=0.031). Stage IV patients with *EGFR* and *ALK* mut received targeted treatment in 88% (121/138) and 89% (16/18) cases, respectively, with 65% (92/138, 66% for EGFR and 14/18, 82% for ALK) staying on TKI >6 months. Overall, 68% (285/419) of patients received 1-3 lines of systemic therapy (range 0-8 lines). Median OS was 47 mos. Median OS for patients with known vs unknown mutation status was 59 mo vs 34 (P<0.001). Early stage (P<0.0001), PS 0-1 (P<0.0001), presence of *EGFR* (P=0.003) or *ALK* mut (P=0.035) were associated with longer survival, but *not* Asian ethnicity (P=0.6) or female sex (P=0.1). **Conclusions:** Lung cancer in never-smokers represents a distinct clinical and molecular entity characterized by a high incidence of targetable mutations and long survival. Updated molecular profiling results will be presented for the entire cohort.

**8100 General Poster Session (Board #281), Sat, 1:15 PM-5:00 PM**

**Antiangiogenic-specific adverse events (AEs) in patients with non-small cell lung cancer (NSCLC) treated with nintedanib (N) and docetaxel (D).** *Presenting Author: Martin Reck, Department of Thoracic Oncology, Lung Clinic Grosshansdorf, Member of the German Center for Lung Research (DZL), Grosshansdorf, Germany*

**Background:** Antiangiogenic treatments, including monoclonal antibodies and TKIs, have shown activity in tumors; however, their use is limited in part by their characteristic side effects (eg, bleeding, thrombosis, perforation, serious skin reactions, hypertension). N is an oral, twice-daily, triple angiokinase inhibitor. Here we extend our investigation of the LUME-Lung 1 study (ClinicalTrials.gov NCT00805194) and evaluate whether adding N to standard second-line D increases the frequency of characteristic adverse events (AEs) associated with antiangiogenic agents and whether these AEs restrict the use of N. **Methods:** LUME-Lung 1, a randomized, placebo-controlled Phase III trial investigating N + D in patients with advanced NSCLC after failure of first-line chemotherapy, demonstrated significant PFS improvement regardless of histology and showed significant survival improvement for patients with adenocarcinoma histology. The incidence and intensity of antiangiogenic-associated AEs according to the common terminology criteria for AEs (CTCAE version 3.0) were evaluated in all patients who received at least one dose of N, D, or Placebo (Pl). **Results:** AEs linked to VEGF inhibition that were more common (≥2% difference) in the N vs Pl arm were bleeding (all grades: 14.1% vs 11.6%; grade ≥3: 2.3% vs 1.8%) and hypertension (all grades: 3.5% vs 0.9%; grade ≥3: 0.6% vs 0.2%). When we compared histologic differences in antiangiogenic-associated AEs, we found nominal differences. More bleeding events were reported for N- treated squamous cell carcinoma (SCC) patients (all grades: 17.1% vs 10.9%; grade ≥3: 2.9% vs 1.3%) than for those with adenocarcinoma (all grades: 10.9% vs 11.1%; grade ≥3: 1.5% vs 1.3%). Fatal bleeding events, serious skin reactions, thrombosis, and perforations occurred at a low frequency and were balanced between both arms, regardless of histology. **Conclusions:** We demonstrated that adding N to standard second-line D for NSCLC therapy did not increase the frequency of AEs associated with antiangiogenic treatment to a relevant extent, except for grade 1-2 bleeding events in SCC patients. These AEs were balanced regardless of histology in LUME-Lung 1. Clinical trial information: NCT00805194.

**8101 General Poster Session (Board #282), Sat, 1:15 PM-5:00 PM**

**A meta-analysis of smoking status on clinical outcomes of non-small cell lung cancer patients harboring activating epidermal growth factor receptor (EGFR) mutations receiving first-line EGFR tyrosine kinase inhibitor.** *Presenting Author: Yoshikazu Hasegawa, Department of Medical Oncology, Izumi Municipal Hospital, Izumi, Osaka, Japan*

**Background:** In several univariate analyses from randomized phase 3 trials, ever-smokers with advanced EGFR mutated (m) NSCLC did not seem to benefit from improved progression-free survival (PFS) even when EGFR TKIs were is used compared to doublet chemotherapy as first-line treatment. **Methods:** We performedpooled analysis of PFS outcome of six published randomized phase 3 trials comparing EGFR TKI to doublet chemotherapy in EGFRm NSCLC patients (WJTOG3405, NEJ002, EURTAC, OPTIMAL, LUX Lung-3, LUX Lung-6). Hazard ratio (HR) and corresponding 95% confidence interval (CI) were collected from each study published in the literature and pooled. We computed a pooled HR and its 95% CI using random-effect model. **Results:** 1,432 EGFRm NSCLC patient data were analyzed, 1,163 (81.2%) were Asians and 430 (30.0%) were ever-smokers. A total of 592 patients, including 178 ever-smokers (30.1%), received doublet chemotherapy and 840, including 252 (30.0%) ever-smokers, received EGFR TKI. The pooled HR for never-smokers was 0.29 (95%CI: 0.21-0.39) while the pooled HR for ever-smokers was 0.54 (95%CI: 0.38-0.76). The p-value comparing HR for never-smokers and ever-smokers by meta-regression analysis was 0.007. The pooled HR for exon 19 was 0.26 (95%CI: 0.19-0.36) while it is 0.45 for exon 21 substitution (95%CI: 0.32-0.64) with a significant difference ($p = 0.019$) between the two pooled HRs. The pooled HR was 0.33 (95%CI: 0.24-0.46) for Asians and 0.48 (95%CI: 0.27-0.85) for non-Asians. Asians did not derive significantly more PFS benefit than non-Asians ($p = 0.256$). The pooled HR for erlotinib was 0.25 (95%CI: 0.16-0.41), 0.38 (95%CI: 0.24-0.59) for gefitinib, and 0.41 (95%CI: 0.24-0.68) for afatinib. No significant differential PFS benefit was noted in any one specific EGFR TKI. **Conclusions:** In this meta-analysis analysis EGFRm NSCLC patients derived significant PFS benefit from TKI over chemotherapy regardless of smoking status but the PFS benefit from EGFR TKIs over chemotherapy is significantly higher in never-smokers than ever-smokers by meta-regression analysis.

**8102 General Poster Session (Board #283), Sat, 1:15 PM-5:00 PM**

**A phase II trial of cabazitaxel in patients with metastatic NSCLC progressing after docetaxel-based treatment.** *Presenting Author: Athanasios Kotsakis, Hellenic Oncology Research Group (HORG), Athens, Greece*

**Background:** Cabazitaxel, a semi-synthetic microtubule inhibitor has shown antitumor activity in models resistant to paclitaxel and docetaxel. It has been approved for the treatment of docetaxel-resistant prostate cancer. We investigated its activity in patients with metastatic NSCLC progressing under or after docetaxel-based regimens. **Methods:** Pre-treated patients with documented, measurable, stage IV NSCLC, with an ECOG performance status 0-2 were enrolled; patients had to have up to 2 prior chemotherapy regimens for the treatment of metastatic disease from which one containing docetaxel. Treatment consisted of cabazitaxel (25 mg/m$^2$ iv, every 21 days) until disease progression. G-CSF was administered to the physician's discretion. Primary endpoint was the objective response rate. A 2-stage design was followed. **Results:** Among the 46 evaluable patients, 28% had squamous cell carcinoma, 54% adenocarcinoma and 18% low differentiated carcinoma. Eight (17.4%) patients had received one and 38 (82.6%) two prior chemotherapy regimens. Treatment compliance was 95%; 26 (16%) cycles were delayed because of toxicity (n=13) or other reasons (n=13); dose reduction was required in 6 (13%) patients because of hematologic toxicity. Six (13%) patients achieved partial response and 17 (39.5%) stable disease [Disease Control Rate of 52.5%; 95% CI: 3.6-24.3%]. The median response duration was 2.9 months. The median PFS and OS were 2.1 (95% CI: 1.0- 3.2) and 7.8 (95% CI: 5.3- 10.3) months, respectively. Grade 4 adverse events (AEs) included: neutropenia (n=8pts; 17%), febrile neutropenia (n=6; 13%); thrombocytopenia (n=3; 6.5%); anemia (n=4; 9%); infection (n=3; 6.5%) and fatigue (n=2; 4%). One patient experienced bowel obstruction and another hemorrhagic cystitis; both resolved with conservative treatment. There was no treatment-related death. **Conclusions:** Cabazitaxel monotherapy is an active agent in NSCLC patients pre-treated with docetaxel-based chemotherapy. The toxicity profile of the drug was acceptable and manageable. Further development of cabazitaxel in this indication is needed. Clinical trial information: NCT01852578.

**8103 General Poster Session (Board #284), Sat, 1:15 PM-5:00 PM**

**Antitumor activity of alectinib (CH5424802/RO5424802) for ALK-rearranged NSCLC with or without prior crizotinib treatment in bioequivalence study.** *Presenting Author: Kazuhiko Nakagawa, Department of Medical Oncology, Kinki University Faculty of Medicine, Osaka-Sayama, Japan*

**Background:** Alectinib, a potent highly selective ALK inhibitor, shows good efficacy and safety for crizotinib-naïve and -resistant patients (pts) with ALK-rearranged non-small cell lung cancer (NSCLC). However, each dose required 8 capsules (caps). Thus, a higher strength formulation was developed. **Methods:** This 2-arm crossover study (JP28927) evaluated the bioequivalence of alectinib 300 mg b.i.d. with 20 and 40 mg caps vs. 150 mg caps at steady state in ALK-rearranged NSCLC pts. Primary objectives were to evaluate bioequivalence between drug formulations and food effect with 150 mg caps; secondary objectives were to evaluate efficacy and safety. Arm 1 of Cycle 1 (30 d) consisted of 300 mg b.i.d. with 20/40 mg caps for 10 d, 150 mg caps for the next 10 d, and 150 mg caps after meals for the last 10 d. The order was different in arm 2: 150 mg caps for 10 d, 20/40 mg caps for the next 10 d, and 150 mg caps after meals for the last 10 d. After Cycle 1, to evaluate bioequivalence, pts continued alectinib 300 mg b.i.d. with 150 mg caps until the investigator determined lack of clinical benefit. Tumors were assessed on Day 31 and 59, and then every 56 d. **Results:** As of Dec 16, 2013, 35 ALK-rearranged NSCLC pts were enrolled. The exposure between formulations was similar, and no food effect was seen with 150 mg caps. Safety (median follow-up period, 4 months) was acceptable: no pt discontinued treatment due to AEs; AEs were mostly Grade 1 or 2. Preliminary efficacy was observed with 63.3% partial response (PR) (including 9 unconfirmed PR) by investigator's assessment in the 30 pts with target lesions. Among 20 crizotinib-resistant pts with target lesions (median duration from last dose of crizotinib, 18.5 d [15–361]), response rate was 60.0% (including 5 unconfirmed PR) and median time to response was 36 d (29–119). In 2 pts, non-irradiated brain metastases over 10 mm had complete response at first assessment (Day 34 and 36). **Conclusions:** The exposure of 20/40 mg and 150 mg caps was similar, and no food effect was seen with 150 mg caps. Alectinib in 150 mg caps was efficacious for ALK-rearranged NSCLC pts regardless of crizotinib treatment history, with quick and high efficacy and good safety. Clinical trial information: JapicCTI-132186.

**8104 General Poster Session (Board #285), Sat, 1:15 PM-5:00 PM**

**An updated systematic review and meta-analysis of randomized controlled trials on duration of chemotherapy for advanced non-small cell lung cancer.** *Presenting Author: Yu Yang Soon, National University Cancer Institute, Singapore, Singapore*

**Background:** We previously published a meta-analysis which identified a survival benefit with extended duration of chemotherapy in patients with advanced non-small cell lung cancer. We have updated our meta-analysis with results from new or updated randomized trials presented in June 2008 to Oct 2013. **Methods:** Biomedical literature databases and conference proceedings were searched for randomized controlled trials (RCTs) comparing: (i) a defined number of cycles versus continuation of the same chemotherapy until disease progression; (ii) a defined number of cycles versus a larger defined number of cycles of identical chemotherapy, and (iii) a defined number of cycles of identical initial chemotherapy versus the addition of cycles of alternative chemotherapy. Meta-analysis was performed using the fixed effect model. The primary outcome was overall survival (OS) and secondary outcomes included progression-free survival (PFS), adverse events (AE), and health-related quality of life (HRQL). **Results:** We identified updated results of two trials from the previous meta-analysis and found four new trials, resulting in a total of 17 trials including 5069 patients. Extending chemotherapy improved PFS substantially (hazard ratio [HR], 0.70; 95% CI 0.66 to 0.75; $P < 0.00001$, $I^2 = 72\%$, $Chi^2$ $P < 0.0001$) and OS modestly (HR, 0.91, 95% CI 0.85 to 0.96, $P = 0.001$, $I^2 = 14\%$, $Chi^2$ $P = 0.29$). Subgroup analysis revealed that the effects on PFS were greater for trials extending chemotherapy with third generation chemotherapy regimens, non-platinum regimens and maintenance therapy trial design. There was no evidence of difference in the effects on overall survival between subgroups defined by use of third generation chemotherapy regimens or platinum regimens and trial design. Extending chemotherapy was associated with more frequent AE in all trials where it was reported and impaired HRQL in two of 12 trials. **Conclusions:** This updated meta-analysis continues to demonstrate improvement in both progression- free and overall survival benefit with extended duration of chemotherapy in patients with advanced non-small cell lung carcinoma.

**8105 General Poster Session (Board #286), Sat, 1:15 PM-5:00 PM**

**PIK3CA as a prognostic marker in non-small cell lung cancer of squamous cell carcinoma type.** *Presenting Author: Odd Terje Brustugun, Oslo University Hospital - The Norwegian Radiumhospital and University of Oslo, Oslo, Norway*

**Background:** Genetic aberrations are regarded both prognostic and predicitive in NSCLC, and are found with various frequency and different significance in the subtypes. Mutation in the *PIK3CA* gene is reported frequent in squamous cell carcinomas, but little if anything is known of its potential prognostic role which is important for treatment strategy using PI3K inhibitors. We have studied the frequency and prognostic importance of *PIK3CA*mutations in a large number of early stage lung cancers of squamous carcinoma subtype. **Methods:** Tumor tissue was obtained from 156 consecutively operated lung cancer patients with squamous cell carcinoma in the period 2006-2012. Tissue was taken from the excised tumours, snap frozen in liquid nitrogen in the operation room, and stored at -80ºC until DNA isolation. The tumour cell content in the specimens was found to be more than 70% in most samples. DNA was isolated according to standard procedures, and mutation analysis was done with either the SnapShot method (Life Technologies), or using the Cobas® PIK3CA Mutation Test (Roche). Several samples were analysed on both platforms with identical results. After thorough follow-up (median 20.7 months, range 6.3-91.9), relapse-free survival was calculated with the Kaplan-Meier method using Chi-Square for significance assessment. **Results:** Tissues from 55 females and 101 males were analyzed. 92 (59%) were in stage I, 44 (28%) II and 20 (13%) stage III. 1 (0.6%) was never-smoker, and median number of pack-years was 36 (range 0-145). Overall, 15 patients (9.6%) harbored a *PIK3CA*mutation. There was a significant relapse-free survival difference (p=0.0299) in favor of the mutated group. In fact none of the mutated patients have relapsed after a median follow up of 27.5 months, whereas 39 (28%) of non-mutated patients have relapsed. **Conclusions:** *PIK3CA* mutations confer a survival advantage in non-small cell lung cancers of the squamous cell carcinoma type. This effect might have implications in therapy strategies.

**8106 General Poster Session (Board #287), Sat, 1:15 PM-5:00 PM**

**Characterization of heart rate (HR) changes during crizotinib treatment: A retrospective analysis of 1,053 ALK+ NSCLC patients.** *Presenting Author: Sai-Hong Ignatius Ou, Chao Family Comprehensive Cancer Center, Orange, CA*

**Background:** Decreases in HR have been described in patients receiving crizotinib. We performed a large retrospective analysis of HR changes during crizotinib therapy. **Methods:** Subjects with *ALK*+ NSCLC enrolled in PROFILE 1005 and in the crizotinib arm of PROFILE 1007 were included in this analysis. Sinus bradycardia (SB) was defined as HR <60 beats per min (bpm). Magnitude and timing of HR changes and changes in systolic (SBP) and diastolic blood pressure (DBP) were assessed. Subjects with no baseline or no on-treatment HR were excluded. Potential risk factors including age, gender, and race were investigated by chi-square tests of association. **Results:** 1,053 subjects were analyzed. For all subjects, median duration of therapy was 24.4 wk (range 0.6–108.3), meanHRdecrease on treatment was 25 bpm (standard deviation [SD] 15.8), and median time to within 5 bpm of the lowest HR recorded was 6.1 wk (range 0.7–60.3).441 (41.9%) subjects had ≥1 lowest HR that qualified as SB, of which 5.9% had a lowest HR of <45 bpm, 18.8% had a lowest HR of 45–49 bpm, and 75.3% had a lowest HR of 50–59 bpm. Mean decrease in HR was 30 bpm (SD 13.8) for the 441 SB subjects with a median time to within 5 bpm of the lowest HR of 9.3 wk (range 1.7–60.3). Of 4900 paired BP and HR recordings from 542 subjects without relevant concomitant medication, a ≥40-mmHg decrease in SBP was observed in 0.3% (0.6%) of recordings in the presence (absence) of SB, and a ≥30-mmHg decrease in DBP was observed in 0.6% (0.7%). Of 963 paired BP and HR recordings from 117 subjects who had concomitant beta blockers (BBs), a ≥40-mmHg decrease in SBP was observed in 0.9% (1.7%) of recordings in the presence (absence) of SB, while a ≥30-mmHg decrease in DBP was observed in 1.8% (2.0%). Only 66 instances of SB were recorded as AEs: n=55 for grade 1, n=9 for grade 2, and n=2 for grade 3. Significant associations between age (P=0.003) as well as ethnicity (P=0.039) with SB were noted in this study, with higher proportions of subjects ≥65 y as well as non-Asians developing SB. **Conclusions:** HR decreaseis common with crizotinib. Age ≥65 y and non-Asian ethnicity may predispose to the development of SB with crizotinib. Concomitant use of BBs may accentuate BP decrease with crizotinib.

**8107 General Poster Session (Board #288), Sat, 1:15 PM-5:00 PM**

**Exon 19 deletion association with progression-free survival compared to L858R mutation at exon 21 in treatment with first-line EGFR-TKIs: A meta-analysis of subgroup data from eight phase III randomized controlled trials.** *Presenting Author: Wenhua Liang, Cancer Center, Sun Yat-Sen University, Guangzhou, China*

**Background:** The superior efficacy of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) compared with cytotoxic chemotherapy in patients harboring sensitive EGFR mutations has been extensively proved by a well-known series of eight phase III randomized controlled trials (RCT). However, the question of whether the efficacy of EGFR-TKIs differs between EGFR exon 19 deletions and exon 21 L858R mutations has not been statistically answered. **Methods:** Subgroup data on hazard ratio (HR) for progression free survival (PFS) in these RCTs were extracted and were synthesized based on random-effect model. Comparison of outcomes between specific mutations was estimated through indirect methods. All calculations were performed using STATA version 11.0. **Results:** A total of 7 randomized RCTs (IPASS, WJTOG3405, EUTRAC, OPTIMAL, LUXLUNG3, and LUXLUNG6, as well as NEJ002 being included in sensitivity analysis) involving 1489 patients with either 19 or 21 exon alteration receiving first-line EGFR-TKIs were included. First-SIGNAL study was not eligible without reporting PFS on specific mutations. The pooled $HR_{TKI/chemotherapy}$ for PFS were 0.276 (95% CI 0.200 to 0.382, P<0.001) in patients with 19 exon deletion and 0.470 (95% CI 0.346 to 0.637, P<0.001) in those with exon 21 L858R mutations. Indirect comparison revealed that patients with exon 19 deletions had more favorable outcome for PFS than those with exon 21 L858R mutations ($HR_{19\ exon\ deletion/exon\ 21\ L858R\ mutations}$=0.587, 95% CI 0.376 to 0.917; P=0.02). Sensitivity analysis by incorporating direct comparison result from NEJ002 study did not affect the overall outcome. **Conclusions:** Exon 19 deletions might be associated with longer PFS compared with L858 mutation at exon 21.

**8108 General Poster Session (Board #289), Sat, 1:15 PM-5:00 PM**

**Clinical impact of gastric acid suppressing medication use on the efficacy of elrotinib and gefitinib in patients with advanced non-small cell lung cancer harboring EGFR mutations.** *Presenting Author: Yoshitaka Zenke, National Cancer Center Hospital East, Kashiwa, Japan*

**Background:** Gastric acid suppressing medications (AS), namely, proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RA), increase the gastric pH, which may reduce the absorption of the EGFR tyrosine kinase inhibitors (EGFR-TKIs) erlotinib and gefitinib. The aim of this study was to evaluate the clinical impact of the use of AS on the efficacy of erlotinib and gefitinib in NSCLC patients harboring EGFR mutations. **Methods:** From 2008 to 2011, 130 consecutive patients with advanced NSCLC harboring EGFR mutations were treated with the EGFR-TKIs erlotinib or gefitinib at our institution. The clinical characteristics of the patients were reviewed, and the efficacy and toxicity of erlotinib and gefitinib were compared between patients receiving and not receiving AS. **Results:** Among the 130 patients treated with erlotinib or gefitinib, 47 were receiving AS (AS group), while the remaining 83 patients were not receiving AS (non-AS group). The overall response rate (ORR) and median progression-free survival (PFS) in the subject population were 60.9% and 10.0 months, respectively. In the sub-analysis carried out in the AS and non-AS groups, the ORR was 61.7% in the AS group and 60.5% in the non-AS group ($p = 0.89$), and the median PFS was 8.7 in the AS group and 10.7 months in the non-AS group ($p = 0.13$). Thus, no significant difference in the ORR or PFS was observed between the AS and non-AS groups. The median overall survival in the subject population was 31.2 months. In regard to the toxicity, the frequencies of rash (83% vs. 86%, $p = 0.60$) and diarrhea (34% vs. 29%, $p = 0.55$) were similar in the AS and non-AS groups. There were no deaths that were deemed to be treatment-related in either group. **Conclusions:** Concurrent use of AS did not affect the efficacy or toxicity of the EGFR-TKIs erlotinib and gefitinib in patients with NSCLC harboring EGFR mutations.

**8109 General Poster Session (Board #290), Sat, 1:15 PM-5:00 PM**

**TRY: A phase II study to evaluate safety and efficacy of combined trastuzumab and AUY922 in advanced non-small cell lung cancer (NSCLC) with HER2 overexpression or amplification or mutation.** *Presenting Author: Lucia Nogova, Lung Cancer Group Cologne, Center for Integrated Oncology, University Hospital Cologne, Cologne, Germany*

**Background:** HER2 amplifications and/or mutations are rare genetic alterations in NSCLC accounting for approximately 4%. Preliminary clinical data suggested efficacy of trastuzumab (Herceptin) in patients with HER2 immunochemistry 3+ (IHC3+) status or positive fluorescence in situ hybridization (FISH). The heat shock protein HSP90 is a molecular chaperone modulating stability and/or transport of intracellular client proteins including HER2. In breast cancer HSP90 inhibition showed anticancer activity in HER2-positive patients after trastuzumab failure. Here we are investigating the efficacy of the combination of trastuzumab and the HSP90 inhibitor AUY922 in lung cancer patients with aberrant HER2. **Methods:** This phase II study recruits metastatic NSCLC patients with HER2 overexpression (IHC DAKO-score 3+) or amplification (FISH positive) or activating mutation after failure of at least one previous standard treatment. In the first part of the study, patients are treated with trastuzumab only (initially 4mg/kg, followed by 2 mg/kg weekly). CT scan is scheduled every 6 weeks during treatment. In case of disease progression, AUY922 (70 mg/m2) is given additionally. Patients are recruited in two German centers: in Cologne and Essen. **Results:** Within the Network of Genomic Medicine in Cologne, 3,863 NSCLC patients of all stages were screened. Patients with overexpression were tested for amplification and mutation. HER2 amplification was seen in 4% and HER2 mutations in 1.6% of all adenocarcinomas. Patients in Essen are screened separately. The study is ongoing. Five patients with HER2 amplifications were treated in the study. Two patients progressed after 6 and 12 weeks on the combination. One patient showed clinical progression within first 6 weeks on trastuzumab. Two patients are still ongoing on trastuzumab monotherapy. The best CT response was -29.3% in patient on trastuzumab and AUY922 at week 6. **Conclusions:** HER2 overexpression, amplification or mutation is a rare genetic alteration in NSCLC patients. Data on treatment with HER2 antibody trastuzumab and HSP90 inhibitor AUY922 will be presented Clinical trial information: DRKS00003301.

**8110 General Poster Session (Board #291), Sat, 1:15 PM-5:00 PM**

**Phase I trial of icotinib combined with whole brain radiotherapy for EGFR-mutated non-small cell lung cancer patients with brain metastases.** *Presenting Author: Lin Zhou, Department of Thoracic Cancer, Cancer Center, West China Hospital, Sichuan Univeristy, Chengdu, China*

**Background:** Icotinib has been demonstrated to provide similar efficacy to gefitinib in non-small cell lung cancer (NSCLC) patients. This phase I trial (NCT01516983) evaluated the dose-escalation toxicity of icotinib combined with whole brain radiotherapy (WBRT) in EGFR-mutated NSCLC patients with brain metastases, and cerebrospinal fluid (CSF) penetration rates of icotinib were assessed in the dose-escalation. **Methods:** The cohorts were constructed with a 3 + 3 design, and the dose-escalation schedule of icotinib was set as 125mg tid, 250mg tid, 375mg tid, 500mg tid, and 625mg tid. Icotinib was started 7 days before and continued during WBRT (37.5Gy/15f/21d), and maintained until disease progression or intolerable toxicities occurred. The blood and CSF samples were obtained at 7:30-8:00 a.m. just before the administration of icotinib on day 7 (before WBRT), day 29 (after WBRT) and day 57 of therapy. **Results:** Fifteen patients were enrolled in this trial. The treatment-related toxicities were generally mild (CTC AE grade 1-2), and the most frequent treatment-related toxicities were alopecia (15/15), acne-like rash (14/15) and nausea (11/15). At dose level of 500mg tid, 3 out of 6 patients experienced dose-limiting toxicity including 1 grade 3 alanine aminotransferase elevation and 2 grade 3 nausea, after reducing the dose of icotinib to 250mg tid, these toxicities disappeared. The mean icotinib CSF penetration rate was 4.04% (range: 1.23%-9.71%), and there was a good correlation between plasma and CSF concentrations ($R^2$=0.577, P<0.001). There were no statistical differences in plasma concentrations, CSF concentrations, and penetration rates of icotinib between day 7, day 29, and day 57. However, CSF concentration and penetration rate of icotinib were much higher at dose of 375mg tid (mean CSF concentration: 154.09ng/ml, $P<0.001$; mean penetration rate: 7.06%, $P<0.001$). **Conclusions:** WBRT with concurrent and maintenance icotinib (125mg tid-375mg tid) were well tolerated in EGFR-mutated NSCLC patients with brain metastases. WBRT might not increase penetration rate of icotinib, however, there were the highest CSF concentration and penetration rate at dose of 375mg tid. Clinical trial information: NCT01516983.

**8111 General Poster Session (Board #292), Sat, 1:15 PM-5:00 PM**

**Stage at diagnosis as a prognostic marker for patients with KRAS-mutant metastatic lung adenocarcinomas.** *Presenting Author: Helena Alexandra Yu, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Stage at diagnosis, age, gender, mutation status, and performance status are recognized prognostic factors in lung cancers. These variables are independently associated with survival, and are fundamental to clinical trial design and data interpretation. Stage at the time of initial diagnosis has not previously been evaluated as a prognostic factor in patients (pts) with metastatic lung cancers, and is not controlled for in prospective trials. In order to adjust for the potential impact of tumor histology and presence of a driver oncogene, we evaluated the impact of stage at initial diagnosis on survival using a cohort of patients with KRAS-mutant, metastatic lung adenocarcinomas. **Methods:** We identified all pts with KRAS-mutant metastatic lung adenocarcinomas from Feb 2005 to Aug 2011. Stage at diagnosis, age, gender, smoking history, and Karnofsky performance status (KPS) were obtained from the medical record. Overall survival (OS) from date of diagnosis of recurrent/metastatic disease was estimated using Kaplan-Meier method and compared across groups in a multivariable Cox proportional hazards model. **Results:** 635 pts with KRAS-mutant lung adenocarcinomas and known stage at diagnosis were identified. Median age: 66 (range 31-89), women: 61%, never smokers: 7%. KPS was available in 471 pts, median KPS: 80%. When compared to pts with stage IV lung cancers at initial diagnosis, patients with early stage lung cancers that later recurred/metastasized had a longer OS from date of advanced disease (18 vs 13 mo, p=0.003). Advanced stage at diagnosis (4 vs 1-3, HR 1.5 [1.2-1.8], P<0.001) and lower KPS ($\leq$70% vs $\geq$80%, HR 2.5 [2.0-3.2], P<0.001) were independently associated with shorter overall survival after adjusting for gender and smoking history in a multivariable analysis. **Conclusions:** In KRAS-mutant lung adenocarcinomas, stage at initial diagnosis was strongly associated with OS from diagnosis of recurrent/metastatic disease, with a 5 month difference in overall survival in patients with recurrent versus de novo stage IV lung cancers. Stage at diagnosis is a prognostic variable that should be accounted for in prospective randomized studies of new therapies in pts with metastatic lung cancers.

**8112^ General Poster Session (Board #293), Sat, 1:15 PM-5:00 PM**

**Nivolumab (anti-PD-1, BMS-936558, ONO-4538) in patients (pts) with advanced non-small-cell lung cancer (NSCLC): Survival and clinical activity by subgroup analysis.** *Presenting Author: Julie R. Brahmer, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

**Background:** Nivolumab, a fully human IgG4, PD-1 immune-checkpoint inhibitor antibody, has shown durable clinical activity in a large phase I trial of pts with advanced solid tumors. For NSCLC pts in this trial, we report overall survival (OS) by dose and histology and clinical activity of pt subgroups including PD-L1 tumor status. **Methods:** Previously treated pts with advanced NSCLC received IV nivolumab (1, 3, or 10 mg/kg) Q2Wk for ≤96 wk with tumor evaluation by RECIST v1.0. Clinical activity by key prognostic factors was assessed. PD-L1 tumor cell membrane expression was measured in archival specimens (n=68) by a Dako immunohistochemistry assay (positive ≥5% tumor cells). **Results:** Across doses and histologies, NSCLC pts (N=129, 54% with ≥3 prior therapies) hadmedian overall survival (mOS) of 9.2-14.9 mo and 1- and 2-y OS rates of 32-56% and 12-45%, respectively (Table). At the 3 mg/kg dose, mOS was 14.9 mo; 1- and 2-y OS rates were 56% and 45%. Objective response rate was 17% (22/129); median response duration was 17 mo. Clinical activity was observed across all pt subgroups, including <3 and ≥3 prior therapies and with/without *EGFR* or *KRAS* mutations. For pts with PD-L1(+) and (–) tumors, mOS was 7.8 mo (95% CI: 5.6, 21.7) and 10.5 mo (5.2, 21.2), respectively; mPFS was 3.6 mo (1.8, 7.5) and 1.8 mo (1.7, 2.3). Grade 3-4 treatment-related adverse events occurred in 14% of pts; most common was fatigue (3%). **Conclusions:** Nivolumab continues to demonstrate an encouraging survival profile and clinical activity across NSCLC pt subgroups with a manageable safety profile. Ongoing phase III trials are evaluating 3 mg/kg nivolumab in NSCLC pts and PD-L1 as a potential predictor of clinical outcomes. Clinical trial information: NCT00730639.

| | mOS,* mo (95% CI) | OS rate,* % (95% CI) [pts at risk] | |
|---|---|---|---|
| **Pts** | **1-Y** | **2-Y** | |
| **All† n=129** | 9.9 (7.8, 12.4) | 42 (34, 51) [48] | 24 (16, 32) [20] |
| **1 mg/kg n=33** | 9.2 (5.3, 11.1) | 32 (16, 49) [8] | 12 (3, 27) [2] |
| **3 mg/kg n=37** | 14.9 (7.3, NR) | 56 (38, 71) [17] | 45 (27, 61) [9] |
| **10 mg/kg n=59** | 9.2 (5.2, 12.4) | 40 (27, 52) [23]) | 19 (10, 31) [9] |
| **Squamous n=54** | 9.2 (7.3, 12.5) | 40 (27, 54) [19] | 24 (13, 37) [9] |
| **Nonsquamous n=74** | 10.1 (5.7, 13.7) | 43 (32, 54) [28] | 23 (13, 34) [10] |

Abbreviation: NR, not reached. *Sept 2013 analysis. †One pt had unknown histology.

**8113 General Poster Session (Board #294), Sat, 1:15 PM-5:00 PM**

**Nivolumab (anti-PD-1; BMS-936558, ONO-4538) in combination with platinum-based doublet chemotherapy (PT-DC) in advanced non-small cell lung cancer (NSCLC).** *Presenting Author: Scott Joseph Antonia, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

**Background:** First-line PT-DC has demonstrated 1-yr overall survival (OS) rates of up to 54% in NSCLC; however, there remains a need for therapies with improved long-term survival. We report an updated analysis of a phase I multi-cohort study evaluating nivolumab, a fully human IgG4 programmed death-1 (PD-1) immune checkpoint inhibitor antibody, plus PT-DC in chemotherapy-naive patients (pts) with advanced NSCLC, with longer follow up and additional pts. **Methods:** Pts (N=56) with advanced NSCLC were assigned based on histology to 4 cohorts to receive nivolumab 10 mg/kg IV Q3W plus concurrent IV gemcitabine 1250 mg/m$^2$ + cisplatin 75 mg/m$^2$ (squamous [sq]) or pemetrexed 500 mg/m$^2$ + cisplatin 75 mg/m$^2$ (non-sq), or nivolumab 5 or 10 mg/kg IV Q3W plus IV paclitaxel 200 mg/m$^2$+ carboplatin AUC6 (sq + non-sq), in a phase I dose de-escalation trial to assess dose-limiting toxicity (DLT). PT-DC was given for 4 cycles, followed by nivolumab until progression or unacceptable toxicity. Objective response rate (ORR) was assessed by RECIST 1.1. **Results:** No DLTs were seen during the first 6 wks of treatment. Grade 3-4 treatment-related adverse events were reported in 45% of pts (25-73% across arms), including pneumonitis (4 pts, 7%; managed by protocol algorithm), and fatigue and acute renal failure (3 pts [5%] each). Across arms, ORR (≥10 months follow up) was 33–50% and progressive disease (PD) as best overall response (BOR) was infrequent (Table). One-year OS rates were 59–87% (Table). **Conclusions:** Nivolumab combined with standard PT-DC regimens used for first-line treatment of NSCLC demonstrated antitumor activity, with encouraging 1-yr OS and an acceptable tolerability profile. Clinical trial information: NCT01454102.

| | Nivo 10 + gem/cis Sq | Nivo 10 + pem/cis Non-sq | Nivo 10 + pac/carb Sq + Non-sq | Nivo 5 + pac/carb Sq + Non-sq |
|---|---|---|---|---|
| **N** | 12 | 15 | 15 | 14 |
| **ORR, [a] n (%)** | 4 (33) | 7 (47) | 7 (47) | 7 (50) |
| **Median duration of response (Kaplan-Meier),[a] wk (range)** | 20.9 (12.1–41.7+) | 32.0 (13.1–42.1+) | 25.6 (11.4+–39.0+) | Not reached (11.4–37.3+) |
| **PD as BOR, n (%)** | 0 | 0 | 3 (20) | 1 (7) |
| **PFS rate wk 24, %** | 36 | 71 | 38 | 57 |
| **1-yr OS, %** | 59 | 87 | 59 | Insufficient follow-up |

[a] Confirmed responses only. + Ongoing.

**8114 General Poster Session (Board #295), Sat, 1:15 PM-5:00 PM**

**Tumor regression as a continuous variable and survival in advanced non-small cell lung cancer (NSCLC).** *Presenting Author: David J. Stewart, University of Ottawa and The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada*

**Background:** Tumor response is generally reported categorically by RECIST criteria as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). SD includes patients with minor tumor growth (1-19% increase in tumor diameter) and minor tumor regression (1-29% decrease in tumor diameter). Recent publications indicate that change in tumor size correlates linearly with survival in phase I studies (R Jain et al. J Clin Oncol 30:2684, 2012) and that change in tumor size as a continuous variable might be a useful endpoint in phase II trials (T Karrison et al. JNCI 99:1455, 2007). **Methods:** We used serial tumor measurements from 130 patients receiving platinum-based therapy for advanced NSCLC to further assess the correlation of change in tumor size with overall survival and time to progression (TTP). **Results:** Median survival was 10.6 months (range, 1-60 months) for the 125 patients who had died and median follow-up was 54 months (range, 45-57 months) for the 5 who remained alive. Median TTP was 4.2 months (range, 0.5-54 months). 32 patients had tumor growth by first follow-up scan (median 19% increase in tumor diameter, range 1%-49%). For the 98 with tumor regression, maximum regression over the course of therapy was 1-76% (median 27%). Maximum tumor regression correlated with overall survival (Spearman r = 0.46, p<0.0001) and with TTP (r = 0.69, p<0.0001). (For these correlations, % tumor growth at first follow-up scan was coded as "negative tumor regression".) Median overall survival was 15 months in patients with any tumor regression at first follow-up scan vs 5.9 months with any growth (p<0.0001), and for patients with RECIST confirmed PR (23% of patients), minor tumor regression (52% of patients), minor tumor growth (13% of patients) and PD (13% of patients) was 16.9, 13.6, 9.8 and 4.0 months, respectively (P<0.0001). **Conclusions:** Change in tumor size as a continuous variable correlated strongly with both overall survival and TTP in patients with advanced NSCLC receiving platinum-based therapy. Within the SD RECIST category, patients with minor tumor regression do better than patients with minor growth. Response as a continuous variable (% change in tumor size) warrants further assessment.

**8115 General Poster Session (Board #296), Sat, 1:15 PM-5:00 PM**

**Advanced NSCLC: Finding the right prescription for oncologist education.** *Presenting Author: Tara Herrmann, Medscape Education, New York, NY*

**Background:** Lung cancer is the leading cause of cancer related death in the United States. The objective of this study was to evaluate the impact of a personalized education curriculum on narrowing gaps in clinical practices of oncologists who care for patients with advanced NSCLC. **Methods:** A pre-education assessment tool designed to identify relevant knowledge and practice gaps in individual oncologist learners was made available online to healthcare providers without monetary compensation or charge. The assessment consisted of 10 knowledge and case-based multiple-choice questions. Upon completion of the survey, each oncologist learner was directed to a personalized learning plan, which included up to 5 distinct activities. Confidentiality of survey respondents was maintained and responses were de-identified and aggregated prior to analyses. The case vignettes and questions were based on current standards of care and evidence-base in the treatment of advanced NSCLC. The pre-assessment survey and corresponding activities launched on January 31, 2013 and participant responses were collected over the following 6 months. **Results:** In total, 92 oncologists completed their individualized educational curriculum. The intervention was associated with an effect size of 0.70, exceeding the recognized medium effect size standard of 0.45-0.50. After the education activity, there was a significant increase in the number of oncologists able to identify the rationale for determining the histological subtype of NSCLC (68% at baseline to 81% post education), prevalence of specific genetic abnormalities (76% to 97%, $P = 0.04$), and awareness of who should be considered for maintenance therapy (55% to 86%, $P = 0.01$). There was also a significant improvement in the identification of the most appropriate treatment regimen for squamous cell carcinoma (19% increase, P = 0.003) and adenocarcinoma (44% increase, $P< 0.001$). **Conclusions:** Our study demonstrates the feasibility of a personalized, targeted educational intervention for improving practice patterns of oncologists treating patients with advanced NSCLC. Novel personalized educational programs need to be developed to improve physician learning experience in an era of personalized medicine.

**8116 General Poster Session (Board #297), Sat, 1:15 PM-5:00 PM**

**Validation study of graded prognostic assessment (GPA) of non-small cell lung cancer (NSCLC) patients with brain metastasis (BM).** *Presenting Author: Eberechi Sandra Agwa, Cleveland Clinic Foundation, Cleveland, OH*

**Background:** NSCLC is the most common cause of BM and GPA is used as a prognostic index (PI) for BM. We evaluated its validity in a contemporary large cohort treated at a single tertiary care institution. Preliminary data was presented at ASCO 2013. **Methods:** IRB approved. NSCLC BM treated between 2000 and 2012 was identified from the Cleveland Clinic Brain Tumor and Neuro-Oncology Center's database. OS from the diagnosis of NSCLC BM was the primary end point.Cox proportional hazards models were used for data analysis. **Results:** 958 (54% male) patients were included for final analysis. Median age at BM diagnosis was 62 years (29-92). Karnofsky performance scale (KPS) was 90-100 in 345 (39%), 70-80 in 415 (47%) and <70 in 116 (13%) patients. Single BM was noted in 448 (47%), 2 BM in 169 (18%), 3 BM in 92 (10%), 4 BM in 49 (5%), 5 BM in 56 (6%) and >5 in 136 (14%) patients. Initial therapy included stereotactic radiosurgery (SRS) in 186 (20%) patients, whole brain radiation (WBRT) in 420 (44%), surgery (S) + WBRT in 132 (14%), WBRT + SRS in 138 (15%) and S + SRS in 23 (2%) patients, while 20 patients underwent only S, 11 patients received medical therapy alone, 17 were observed, 1 patient had S, WBRT + SRS. Median OS from diagnosis of BM was 7.8 months (95% C.I. 7.1-8.9).GPA for lung cancer is derived from KPS, number of BM, the presence/absence of extracranial metastases and age. GPA was prognostic for survival with very good separation between each of the groups (p<.0001). **Conclusions:** Even in the modern era GPA is still a valid PI for OS in NSCLC patients with BM.

| Factor | N (%) | Median survival (months) | P* |
|---|---|---|---|
| **KPS** | | | |
| **90-100** | 345 (39%) | 12.0 | <0.001 |
| **70-80** | 415 (47%) | 7.5 | |
| **< 70** | 116 (13%) | 2.8 | |
| **Number of brain metastases** | | | |
| **1** | 448 (46%) | 10.0 | <0.001 |
| **2-3** | 261 (27%) | 7.4 | |
| **>3** | 241 (25%) | 6.3 | |
| **Extracranial metastases** | | | |
| **No** | 434 (46%) | 12.1 | <0.001 |
| **Yes** | 502 (54%) | 5.6 | |
| **Age (years)** | | | |
| **<50** | 122 (13%) | 11.9 | <0.001 |
| **50-60** | 291 (30%) | 9.8 | |
| **>60** | 544 (57%) | 6.4 | |
| **GPA** | | | |
| **0 - 1.0** | 209 (24%) | 3.4 | <0.001 |
| **1.5 - 2.0** | 312 (36%) | 7.0 | |
| **2.5 - 3.0** | 275 (32%) | 13.0 | |
| **3.5 - 4.0** | 62 (7%) | 23.2 | |

*Proportional hazards model stratified by when brain metastases were diagnosed.

**8117 General Poster Session (Board #298), Sat, 1:15 PM-5:00 PM**

**Final overall survival results of WJTOG 3405, a randomized phase 3 trial comparing gefitinib (G) with cisplatin plus docetaxel (CD) as the first-line treatment for patients with non-small cell lung cancer (NSCLC) harboring mutations of the epidermal growth factor receptor (EGFR).** *Presenting Author: Hiroshige Yoshioka, Department of Respiratory Medicine, Kurashiki Central Hospital, Kurashiki, Japan*

**Background:** WJTOG3405 has proven that chemotherapy-naïve patients with postoperative recurrent or stage IIIB/IV NSCLC harboring activating *EGFR*mutation have longer progression free survival (PFS) when treating with G than treating with CD. (9.2 months (mos.) for G vs. 6.3 mos. for CD, hazard ratio (HR) 0.489, 95% confidence interval (CI): 0.336-0.710). (Mitsudomi et al., Lancet Oncol. 2010) Although we reported updated overall survival results of this study after 34 mos. median follow-up period, the impact on overall survival (OS) was still unclear because of lack of survival events. (Mitsudomi et al, ASCO 2012). **Methods:** Overall survival (OS) was re-evaluated using updated data (data cutoff, 30 Sep, 2013, median follow-up, 59.1 mos.) for 172 patients. **Results:** One hundred twenty-seven events had occurred (73.8%). Median survival time (MST) for G arm was 34.8 mos. (95% CI: 26.0 – 39.5) which was not significantly different from 37.3 mos. (95% CI: 31.2 – 45.5) for CD arm (HR 1.252, 95% CI 0.883-1.775). Multivariate analysis using Cox proportional hazards model revealed that postoperative recurrence or IIIB/IV significantly affected OS among assessed covariates (treatment arm, smoking status, sex, age, postoperative recurrence or IIIB/IV, and mutation type). The overall survival of patients with postoperative recurrence was better than that of those with IIIB/IV stage disease (HR 0.459, 95% CI 0.312-0.673, p < 0.001). In the CD arm, 8 patients (9%) never received EGFR-TKI in their whole courses of therapy, whereas 31 patients (36%) never received chemotherapy in the G arm. MST for the former and the latter group were 13.5 months (95% CI: 6.5 -) and 44.5 months (95% CI: 21.3 - 51.8), respectively. **Conclusions:** This five-year follow-up OS analysis confirmed that G for advanced NSCLC with *EGFR* mutation offers survival benefit of 3 years. There was no difference in OS whether the initial treatment was G or CD, probably due to high cross over rate. Clinical trial information: 000000539.

**TPS8118^ General Poster Session (Board #299A), Sat, 1:15 PM-5:00 PM**

**Galaxy-2 trial (NCT01798485): A randomized phase 3 study of ganetespib in combination with docetaxel versus docetaxel alone in patients with advanced lung adenocarcinoma.** *Presenting Author: Suresh S. Ramalingam, The Winship Cancer Institute of Emory University, Atlanta, GA*

**Background:** Hsp90 is a molecular chaperone recognized as a key facilitator of cancer cell growth and survival. Ganetespib is a resorcinolic Hsp90 inhibitor that has shown single-agent activity in patients with lung, breast, and other cancers after progression on standard treatments. Ganetespib in combination with docetaxel induces synergistic efficacy in human non-small-cell lung carcinoma (NSCLC) tumor xenografts. Ganetespib is well tolerated and has not shown severe liver or common ocular toxicities reported for other Hsp90 inhibitors. Transient diarrhea is the most common adverse event, and is manageable with appropriate supportive care. A large randomized Phase 2 study of ganetespib in combination with docetaxel in advanced NSCLC patients (GALAXY-1 Trial) indicated good tolerability of the combination, and improvement in efficacy, including OS. **Methods:** GALAXY-2 is a randomized (1:1), international, open-label Phase 3 study enrolling patients who received and progressed on 1 prior systemic platinum-based combination therapy for advanced NSCLC of adenocarcinoma histology, were diagnosed ≥6 months before study entry, and whose tumors are negative for both EGFR mutations and ALK translocation (Target Patient Population [TPP]). Patients (N=700 TPP) are prospectively stratified for ECOG PS, total screening LDH, and geographic region (North America and Western Europe vs Rest of World). The primary endpoint is OS in the TPP. Key secondary endpoints include PFS, ORR, DCR, and DOR in the TPP. OS will also be analyzed in 3 subpopulations of the TPP: mKRAS, elevated LDH, and elevated LDH5. Patients in the control arm are treated with docetaxel 75 mg/m$^2$ on Day 1 of a 3-week cycle. In the combination arm, ganetespib 150 mg/m$^2$ is given on Day 1 with 75 mg/m$^2$ docetaxel, and ganetespib 150 mg/m$^2$ alone is given on Day 15 of each 3-week cycle. Two interim analyses for OS will be performed. Tumor tissue and blood samples will be collected for planned translational studies. Clinical trial information: NCT01798485.

**TPS8119^ General Poster Session (Board #299B), Sat, 1:15 PM-5:00 PM**

**A single arm, open-label, phase II study to assess the efficacy of lucitanib in patients with *FGFR1*-amplified squamous NSCLC (sqNSCLC).** *Presenting Author: David R. Spigel, Sarah Cannon Research Institute, Nashville, TN*

**Background:** Lucitanib, a potent, oral inhibitor of the tyrosine kinase activity of Fibroblast Growth Factor Receptors 1/2 (FGFR1/2), Vascular Endothelial Growth Factor Receptors 1-3 (VEGFR1-3) and Platelet-Derived Growth Factor Receptors A/B (PDGFRA/B), is being developed for the treatment of lung cancer and breast cancer. *FGFR1*-amplification is a hallmark genomic alteration in sqNSCLC, observed at a frequency of 10-20%. As such, inhibition of the FGF-axis represents a promising potential target for therapy of sqNSCLC. **Methods:** The current study evaluates daily oral lucitanib monotherapy in patients (pts) with *FGFR1*-amplified sqNSCLC. This is an international, multicenter, open-label, single-arm study. The primary endpoint is objective response rate (ORR; RECIST1.1) with secondary endpoints of response duration, clinical benefit rate, progression-free survival, and safety evaluation. Exploratory objectives include volumetric assessment of tumor growth kinetics, serial circulating tumor DNA measurement, and identification of additional biomarkers of lucitanib activity including determination of FGFR1 or FGF ligand RNA or protein expression using *in-situ* hybridization or immunohistochemistry. A Simon's minimax two-stage design will be used to provide 80% power to test the hypothesis $H_0$: p ≤ 10% versus $H_1$: p ≥ 25%, with a type I error at 5% (one sided). A minimum of 22 and maximum 40 pts will be enrolled. Key inclusion criteria include: pts aged ≥ 18 years with stage IV sqNSCLC and tumor *FGFR1*-amplified, tumors that are not invading or abutting a major vessel and/or tumors that are not cavitary. *FGFR1* amplification will be assessed centrally by FISH but local *FGFR1* testing is sufficient for enrollment. Pts should have measurable disease and have had at least one previous treatment for advanced disease. This study will begin enrolling pts in the United States and Europe in early 2014 at a network of centers skilled in the identification of pts with relatively uncommon tumor characteristics. Clinical trial information: 2013-003874-29.

**TPS8120 General Poster Session (Board #300A), Sat, 1:15 PM-5:00 PM**

**Multiarm, nonrandomized, open-label phase IB study to evaluate FP1039/GSK3052230 with chemotherapy in NSCLC and MPM with deregulated FGF pathway signaling.** *Presenting Author: Pilar Garrido Lopez, Hospital Ramón y Cajal, Madrid, Spain*

**Background:** FP1039/GSK3052230 (GSK230) is a soluble fusion protein that acts as a ligand trap by sequestering fibroblast growth factors (FGFs) involved in tumor growth. FGF ligand-dependent signaling plays an important role in cancer development and growth through autocrine production of FGFs from cancer cells, or paracrine production of FGFs from local stroma, or by tumor overexpression of FGF receptors (FGFRs) or amplification of FGFR genes. *FGFR1* amplification has been identified in ~15-20% of squamous non-small cell lung cancers (NSCLC) and is associated with shorter disease-free and overall survival. Efficacy was observed with GSK230 + chemotherapy in *FGFR1* amplified in NSCLC xenograft models and in xenograft models of malignant pleural mesothelioma (MPM) where FGF2 mRNA levels were overexpressed. In a phase I study, no maximum tolerated dose (MTD) was identified and 20 mg/kg weekly was the maximum feasible dose (MFD) achieving the desired target concentration. Toxicities associated with small-molecule FGFR inhibition, namely hyperphosphatemia and retinal, nail, and skin changes, were not observed. **Methods:** This is a multi-arm, nonrandomized, open-label phase IB study designed to evaluate the safety and preliminary efficacy of GSK230 in combination with paclitaxel + carboplatin in previously untreated *FGFR1* amplified metastatic squamous NSCLC (Arm A), in combination with docetaxel in *FGFR1* amplified metastatic squamous NSCLC that has progressed after 1 line of chemotherapy (Arm B), or in combination with pemetrexed + cisplatin in patients with untreated and unresectable MPM (Arm C). Approximately 70 patients will be enrolled. Each arm involves a dose escalation phase utilizing the 3+3 design, followed by a cohort expansion phase of at least 12 patients treated at either MTD or MFD. GSK230 will be administered as a 30-minute intravenous infusion once a week in a 21-day cycle. The starting dose is 5 mg/kg and will be dose escalated until MTD or MFD in combination with chemotherapy is reached. Endpoints include the combination dose of GSK230 with chemotherapy, safety, response rates and their duration, and translational objectives (NCT01868022). Clinical trial information: NCT01868022.

**TPS8121 General Poster Session (Board #300B), Sat, 1:15 PM-5:00 PM**

**Phase I/II multicenter, randomized, open-label trial of the c-Met inhibitor MSC2156119J and gefitinib versus chemotherapy as second-line treatment in patients with MET-positive (MET+), locally advanced, or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor mutation (EGFRm+) and progression on gefitinib.** *Presenting Author: Yi-Long Wu, Guangdong Lung Cancer Institute, Guangdong General Hospital (GGH) and Guangdong Academy of Medical Sciences, Guangzhou, China*

**Background:** Resistance to EGFR tyrosine kinase inhibitors (eg, gefitinib) in EGFRm+ NSCLC patients (pts) is mainly caused by a secondary mutation in the EGFR (ie, T790M) or by activation of the c-Met/HGF signaling pathway (eg, protein overexpression and/or amplification). MSC2156119J, a highly selective small-molecule c-Met inhibitor, displayed promising antitumor activity in pts with advanced solid tumors in a Phase I trial (Falchook et al. *J Clin Oncol* 2013:31(Suppl):2506). This Phase Ib/II, multicenter, open-label trial investigates the antitumor activity of MSC2156119J + gefitinib in pts with MET+ advanced EGFRm+ NSCLC (NCT01982955). **Methods:** Primary objectives are determination of the recommended phase II dose (RP2D) for the combination (Phase Ib), and progression-free survival (PFS) per investigator read (Phase II). Secondary objectives include safety, pharmacokinetics, and antitumor activity of MSC2156119J (PFS per independent read, overall survival, objective response, and disease control). Adults with advanced NSCLC with activating EGFR mutation, ECOG status 0–1, and resistance on 1st-line gefitinib (Phase II only) are recruited in mainland China, South Korea, Taiwan, and other Asian countries. Patients must have confirmed MET+ status, defined as either strong or moderate protein overexpression by immunohistochemistry, or *MET* gene amplification by in situ hybridization. Main exclusion criteria: life expectancy <3 mo, or prior EGFR targeting therapy other than gefitinib (Phase II only). For the Phase Ib part (3+3 design), 15–18 pts are planned to receive 300 or 500 mg MSC2156119J p.o. + 250 mg gefitinib p.o./d (21-d cycle); for the Phase II part, up to 200 pts are planned to be enrolled into 2 predefined subgroups according to their T790M mutation status and subsequently randomized 1:1 to RP2D MSC2156119J p.o. + 250 mg gefitinib p.o./d or 500 mg/m$^2$ pemetrexed i.v. + 75 mg/m$^2$ cisplatin i.v. on day 1 (max. of six 21-d cycles). Enrollment for Phase Ib began on Dec 23, 2013. Clinical trial information: NCT01982955.

**TPS8122 General Poster Session (Board #301A), Sat, 1:15 PM-5:00 PM**

**A phase II cluster study of single agent AUY922, BYL719, INC280, LDK378, and MEK162 in Chinese patients with advanced non-small cell lung cancer (NSCLC).** *Presenting Author: Qing Zhou, Guangdong Lung Cancer Institute, Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China*

**Background:** Advanced NSCLC management has evolved toward individual tumor subtyping based on targetable oncogenic drivers. Most molecularly characterized lung adenocarcinoma patients (pts) could thus potentially benefit from targeted treatment. This study investigates the innovative paradigm of allocating pts to specific treatment arms based on their genetic profile. The targeted therapies AUY922 (HSP90 inhibitor[i]), BYL719 (PI3Ki), LDK378 (ALKi), INC280 (METi), and MEK162 (MEKi) will be evaluated in different pt subgroups with appropriate confirmed molecular aberrations, in a single cluster study. **Methods:** This Phase II, multiple arm, open-label study will enroll pts (aged ≥18 years, ECOG PS ≤2) with advanced (stage IIIB/IV) lung adenocarcinoma bearing different molecular alterations, who have failed prior treatment or are unsuitable for chemotherapy, and have received ≤2 prior lines of therapy. Pts must have locally obtained documentation of a relevant molecular alteration from either a new or the most recent archival tumor sample, using primary genetic profiling. Pts will be allocated to a specific treatment arm accordingly (AUY922, 70 mg/m$^2$ QW: activating *EGFR* mutation and resistant to EGFR inhibitors; BYL719, 350 mg QD: *PIK3CA* mutation/amplification [other PI3K pathway alterations may be eligible]; INC280, 600 mg BID: *MET*-positive tumors [by IHC or FISH]; LDK378, 750 mg QD: *ALK* or *ROS1* rearrangement; MEK162, 45 mg BID: *KRAS, NRAS* or *BRAF* mutation). Sample size was calculated based on a Bayesian approach using either a minimally informative prior (BYL719, INC280 and MEK162; N=20 for each) or an informative prior using relevant historical data (AUY922 [N=30] and LDK378 [N=25]). The sample size will allow detection with high likelihood, of statistically and clinically relevant antitumor activity. Each treatment arm is independent from one another and will be analyzed separately. Study treatment is given until disease progression or discontinuation. The primary endpoint is overall response rate; secondary endpoints are overall survival, progression-free survival, disease control rate, duration of response, safety, and pharmacokinetics.

**TPS8123 General Poster Session (Board #301B), Sat, 1:15 PM-5:00 PM**

**Clinical trials of MPDL3280A (anti-PDL1) in patients (pts) with non-small cell lung cancer (NSCLC).** *Presenting Author: Naiyer A. Rizvi, Memorial Sloan-Kettering Cancer Center, New York, NY*

**Background:** Blocking the PD-L1/PD-1 immune inhibitory signals can reinvigorate preexisting anticancer immunity and can lead to durable responses in NSCLC. MPDL3280A is a human anti-PD-L1 monoclonal antibody that contains an engineered Fc-domain. MPDL3280A targets PD-L1, preventing binding to its receptors PD-1 and B7.1, thus restoring tumor-specific T-cell immunity. MPDL3280A does not disrupt the PD-L2/PD-1 interaction, which is potentially implicated in autoimmune lung toxicity. In a Phase I study, MPDL3280A led to antitumor responses, with an overall response rate (ORR) of 23% (12/53) in previously-treated NSCLC pts, 46% (6/13) in those pts with a PD-L1 IHC score of 2 or 3 and 83% (5/6) in those pts with a PD-L1 IHC score of 3. Based on these results, we initiated a clinical program examining unselected and PD-L1-positive pts with locally advanced or metastatic NSCLC. Here, we describe the BIRCH and OAK trials. **Methods:** Both studies require pts aged ≥ 18 y with an ECOG status of 0 or 1 and measurable disease (RECIST v1.1). Pts receive MPDL3280A (1200 mg IV) q3w for up to 16 cycles (or 12 months) in the absence of overt toxicity or deteriorative progressive disease. Pts with autoimmune disease, active CNS metastases and/or prior immune checkpoint blockade are excluded. For BIRCH, a Phase II, single-arm study, ≈ 300 pts (3 cohorts; chemo-naive, single prior platinum-based regimen and ≥ 2 prior therapies) with PD-L1-positive tumors receive MPDL3280A. Chemo-naive pts with a sensitizing *EGFR* mutation or an *ALK* rearrangement are excluded. The primary end-point is ORR (RECIST v1.1). Recruitment is ongoing (NCT02031458). OAK is a global Phase III, multicenter, randomized, open-label, efficacy and safety evaluation of MPDL3280A compared with docetaxel after failure of a platinum-containing chemotherapy. Pts (≈ 850) receive docetaxel (75 mg/m$^2$ IV) or MPDL3280A. Eligible pts are enrolled regardless of PD-L1 status but stratified by PD-L1 expression levels. The primary objective is a comparison of OS. Secondary objectives include ORR, PFS and other efficacy criteria. Recruitment begins Q1 of 2014 (NCT02008227). Clinical trial information: NCT02031458, NCT02008227.

**TPS8124 General Poster Session (Board #302A), Sat, 1:15 PM-5:00 PM**

**A phase II/III randomized trial of two doses of MK-3475 versus docetaxel in previously treated subjects with non-small cell lung cancer.** *Presenting Author: Roy S. Herbst, Department of Medical Oncology, Yale University School of Medicine, New Haven, CT*

**Background:** Docetaxel is a standard second line treatment for patients with advanced non-small cell lung cancer (NSCLC). It yields a low response rate (~10.5%), limited 1-year survival rate (~37%), and median overall survival (OS) of ~ 7.5 months. MK-3475 is a highly selective anti-PD-1 monoclonal antibody exerting dual ligand blockade (DLB) of the PD-1 pathway, a major pathway hijacked by tumors to suppress immune control. Preclinical and clinical data suggest that this pathway plays an important role in NSCLC. Upon interaction with its ligands, PD-L1 and PD-L2, the activation of PD-1 may lead to suppression of antitumor immunity. This randomized phase II/III trial was designed to assess the clinical activity of MK-3475 monotherapy compared with standard docetaxel in patients with advanced NSCLC whose disease has progressed after platinum-containing therapy. **Methods:** Eligibility stipulates minimum age of 18 years; ECOG performance status of 0-1, and diagnosis of advanced PD-L1-positive NSCLC with documented progression after platinum-containing systemic therapy. Patients are stratified by ECOG performance status, geographic location of the site, and degree of PD-L1 expression and randomized in a 1:1:1 ratio to receive intravenous MK-3475 (2 mg/kg, every 3 weeks [Q3W] or 10 mg/kg, Q3W) or docetaxel (75 mg/m$^2$, Q3W) for 2 years or until disease progression, unacceptable toxicity, intercurrent illness or investigator decision. Response to treatment will be evaluated every 9 weeks by investigators using the immune-related response criteria (irRC) and centrally by RECIST 1.1. Adverse events (AEs) will be monitored throughout the trial. Primary objectives include OS and PFS per RECIST 1.1 in patients with strong expression of PD-L1, and safety, including incidence and time to first Grade 3-5 AE. Secondary objectives include OS, PFS and ORR per RECIST 1.1 in patients with PD-L1 positive tumors. Fifty of approximately 920 pts targeted for accrual have enrolled. Clinical trial information: NCT01905657.

**TPS8126 General Poster Session (Board #303A), Sat, 1:15 PM-5:00 PM**

**A phase 2 study of defactinib (VS-6063), a cancer stem cell inhibitor that acts through inhibition of focal adhesion kinase (FAK), in patients with KRAS-mutant non-small cell lung cancer.** *Presenting Author: David E. Gerber, The University of Texas Southwestern Medical Center, Dallas, TX*

**Background:** *KRAS* mutations have been associated with poor prognosis in NSCLC and resistance to epidermal growth factor (EGFR) tyrosine kinase inhibitors. FAK represents a therapeutic target in *KRAS* mutant NSCLC. The RHOA-FAK axis is a critical downstream mediator of RAS signal transduction and FAK inhibition results in growth suppression in *KRAS* mutant but not KRAS wild type (wt) cancers both in vitro and in vivo. Interestingly, loss of function of the tumor suppressors CDKN2A/INK4a/ARF (p16) and/or p53 appears requisite for efficacy of FAK inhibition in KRAS-driven cancers. Specifically, in vitro and in vivo studies in xenograft and transgenic *KRAS* mutant NSCLC adenocarcinoma models carrying *INK4a/Arf* and/or *p53* mutant genotypes demonstrated susceptibility to FAK inhibition evidenced by tumor inhibition and prolonged survival. Furthermore, treatment with FAK inhibitors reduces the proportion of cancer stem cells (CSCs) compared to treatment with standard chemotherapy which enriches for CSCs. Defactinib is an oral inhibitor of FAK and proline-rich tyrosine-kinase-2 currently in clinical development in a number of indications including mesothelioma and ovarian cancer. **Methods:** Pts with *KRAS* mutant advanced NSCLC ($>$ 1 prior platinum based doublet) are enrolled into 1 of 4 cohorts (A-D): wt *INK4a/Arf*, wt *p53* (A); *INK4a/Arf* mutation, wt *p53* (B); wt *INK4a/Arf*, *p53* mutation (C), or *INK4a/Arf* mutation, *p53* mutation (D). Defactinib is administered continuously at 400 mg PO BID in 21 day cycles until disease progression. The primary endpoint is the Progression Free Survival (PFS) rate at week 12. In the Simon 2 stage design, if $\geq$ 4 of 11 pts have PFS at week 12, enrollment in that cohort will be expanded to a total of 34 pts. PFS at 12 weeks of $\geq$ 50% will be deemed clinically important and $\leq$ 25% will be deemed not clinically valuable. Response rate (RR), PFS, overall survival (OS), and comparisons between Cohort A to B, C, and D will also be measured. Associations between pharmacodynamic biomarkers (including pFAK) and clinical outcomes (RR, PFS, OS) will be evaluated. The study is currently enrolling at 8 US centers. Clinical trial information: NCT 01951690.

**TPS8127 General Poster Session (Board #303B), Sat, 1:15 PM-5:00 PM**

**Open, phase II randomized trial of gefitinib alone versus olaparib (AZD2281) plus gefitinib in advanced non-small cell lung cancer (NSCLC) patients (P) with epidermal growth factor receptor (EGFR) mutations: Spanish Lung Cancer Group trial (NCT=1513174/GECP-GOAL).** *Presenting Author: Bartomeu Massuti, Hospital General de Alicante, Alicante, Spain*

**Background:** EGFR tyrosine kinase inhibitors (TKIs) are considered the treatment of choice for p with advanced NSCLC harboring EGFR mutations, with higher response rate (RR) and longer progression free survival (PFS). However, the majority of p develop resistance to TKIs via several mechanisms. Our previous experience in the EURTAC trial showed that high BRCA1 mRNA expression levels cause shorter PFS for erlotinib-treated p. Olaparib, a PARP-inhibitor, can reduce BRCA1 expression and could improve PFS in this subset of patients when added to an EGFR TKI. A phase IB study confirmed activity and tolerance of olaparib plus gefitinib in the absence of pharmacokinetic interactions. Recommended dose for the combination was gefitinib 250 mg daily + olaparib 200 mg TDS. **Methods:** Stage IV EGFR-mutated NSCLC p, previously untreated for metastatic disease, with PS 0-2 and evaluable disease (RECIST criteria) are randomly assigned in a 1:1 ratio to single agent gefitinib or gefitinib+olaparib. Primary planned endpoint is PFS. Secondary endpoints: Overall survival (OS), RR, toxicity (CTC criteria), detection of initial presence of T790M resistant mutation, influence of BRCA1 and EGFR mutations on PFS, parallel analysis of EGFR mutations in serum, and ancillary molecular analyses. Statistical hypothesis: Median PFS of 10 months (m) in the gefinitib arm could be increased to 16 m in the combination arm; two-sided alpha error = 0.05 and power 80%. One hundred and sixteen events are required to test the superiority hypothesis. Total planned number of inclusions: 186 p. Pre-planned interim analysis at 58 PFS events (progression or death). Current status: Study opened on July 2013 in 38 Spanish centers; recruitment ongoing. Fifty-nine p screened; 14 included. Clinical trial information: NCT1513174.

**TPS8128 General Poster Session (Board #304A), Sat, 1:15 PM-5:00 PM**

**A phase III, randomized, open-label trial of nivolumab (anti-PD-1; BMS-936558, ONO-4538) versus investigator's choice chemotherapy (ICC) as first-line therapy for stage IV or recurrent PD-L1+ non-small cell lung cancer (NSCLC).** *Presenting Author: David Paul Carbone, Ohio State University Wexner Medical Center, Columbus, OH*

**Background:** The majority of NSCLC patients (pts) present at the time of diagnosis with advanced disease. Subsets of pts are eligible for therapies targeted at mutated oncogene drivers; however, the majority of pts have few effective options beyond standard platinum-based chemotherapy. Preclinical data suggest that immune dysfunction, including T-cell downregulation through increased tumor expression of programmed death-1 ligand (PD-L1), plays a role in NSCLC. Nivolumab, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody, has shown clinical activity against several solid tumors including NSCLC. Preliminary data suggest that nivolumab's activity in first-line NSCLC is accentuated in pts with positive tumor PD-L1 expression (PD-L1+). This phase III, randomized, open-label trial will compare the clinical activity of first-line nivolumab monotherapy vs ICC in treatment-naïve pts with stage IV or recurrent NSCLC with PD-L1+ tumor expression. **Methods:** Chemotherapy-naïve pts with ECOG performance status $\leq$1 and without known EGFR mutations or ALK translocations will be randomized 1:1 to nivolumab (3 mg/kg IV Q2W) or ICC, and stratified by tumor PD-L1 expression level (Dako immunohistochemistry assay) and NSCLC histology. Pts randomized to ICC (maximum of six 3-week cycles) will receive gemcitabine 1250 mg/m$^2$ + cisplatin 75 mg/m$^2$, gemcitabine 1000 mg/m$^2$ + carboplatin AUC 5, or paclitaxel 200 mg/m$^2$ + carboplatin AUC 6 (squamous [sq]), or pemetrexed 500 mg/m$^2$ + either cisplatin 75 mg/m$^2$ or carboplatin AUC 6 (non-sq); with optional crossover to nivolumab. The primary objective is to assess progression-free survival (PFS) with nivolumab vs ICC in pts with strong PD-L1 expression. Secondary objectives are objective response rate and overall survival in strongly PD-L1+ pts, PFS in pts with any PD-L1 expression level, and disease-related symptom improvement. Exploratory objectives include safety, correlation of PD-L1 expression with PFS, pharmacokinetics, pharmacodynamics, pt-reported outcomes, and potential biomarkers. Clinical trial information: NCT02041533.

**TPS8129 General Poster Session (Board #304B), Sat, 1:15 PM-5:00 PM**

**Stimulating an immune response through bavituximab in a phase III lung cancer study.** *Presenting Author: David E. Gerber, The University of Texas Southwestern Medical Center, Dallas, TX*

**Background:** Escape from immune surveillance is a frequent mechanism of tumor initiation, proliferation, and resistance to treatment. Bavituximab is a chimeric monoclonal antibody with immune modulating properties. Bavituximab targets exposed phosphatidylserine (PS) on tumor vascular endothelium, tumor cells and tumor derived exosomes. Exposed PS in the tumor microenvironment suppresses immune and inflammatory responses by binding to PS receptors on myeloid derived suppressor cells (MDSC) and M2 macrophages, which leads to production of anti-inflammatory cytokines such as TGF-$\beta$ and IL-10which inhibits the development of an adaptive immune response. In preclinical models, PS-targeting antibodies counter these effects, resulting in production of pro-inflammatory cytokines such as TNF-$\alpha$ and IL-1$\beta$, maturation of dendritic cells and induction of tumor specific cytotoxic T lymphocyte immunity. Administration of docetaxel increases PS exposure within the tumor microenvironment and also suppresses MDSCs, thereby enhancing bavituximab's effects. In a double-blind Phase II clinical trial, bavituximab 3 mg/kg plus docetaxel was well-tolerated and demonstrated 60% improvement (11.7 vs 7.3 month) in median overall survival (OS) compared to control. **Methods:** In this randomized, double-blind, global Phase III clinical trial, approximately 600 pts with second-line stage IIIb/IV non-squamous NSCLC will be randomized 1:1 to receive up to six 21-day cycles of docetaxel 75 mg/m2 with placebo or bavituximab 3 mg/kg weekly until disease progression or unacceptable toxicity. Patients must have one progression on platinum doublet therapy for advanced disease. Prior maintenance or targeted therapy is allowed if only 1 progression occurred. Within each geographic region, patients will be stratified by disease stage and prior maintenance/targeted therapy. The primary endpoint is overall survivaland secondary endpoints include overall response rate (modified RECIST 1.1), progression free survival (PFS) and safety. Clinical trial information: NCT01999673.

**TPS8130 General Poster Session (Board #305A), Sat, 1:15 PM-5:00 PM**

**A randomized, double-blind, multicenter phase 2 trial of denosumab in combination with chemotherapy as first-line treatment of metastatic non-small cell lung cancer.** *Presenting Author: David R Spigel, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN*

**Background:** Non-Small Cell Lung Cancer (NSCLC) is a heterogeneous disease forwhich patients (pts) may benefit from targeted therapies. RANK ligand (RANKL) and its receptor RANK are expressed in a subset of NSCLC tumors (Branstetter, 2013). Results from preclinical models show that RANKL acts directly on RANK-expressing tumor cells to promote tumor progression and metastases (Gonzalez-Suarez, 2010; Tan, 2011). Denosumab is a fully human monoclonal antibody that binds RANKL, approved for the prevention of skeletal-related events in pts with solid tumors and bone metastases. In a study of pts with solid tumors receiving standard treatment, post hoc analysis of those with stage IV NSCLC (n = 702) showed that pts who received denosumab had improved median overall survival (OS) vs those who received zoledronic acid (ZA; HR [95% CI] 0.78 [0.65–0.94], p = 0.01; Scagliotti, 2012). The current trial will correlate tumor RANK and RANKL expression and OS in pts with metastatic NSCLC receiving denosumab in combination with standard chemotherapy vs those receiving chemotherapy alone. The trial is sponsored by Amgen Inc. and registered with ClinicalTrials.gov (NCT01951586). **Methods:** ~216 pts with untreated stage IV NSCLC will receive 4–6 cycles of standard of care chemotherapy and be randomized (2:1) to denosumab 120 mg or placebo SC Q3W or Q4W plus a loading dose on day 8. ZA or placebo IV may be offered in a blinded manner if requested. The sample size is powered to test the interaction between treatment effect and RANK or RANKL expression under various reasonable scenarios. Pts will receive calcium and vit D daily. Randomization will be stratified based on bone metastasis (yes or no), histology (squamous vs nonsquamous), and region (North America, Western Europe/Australia, rest of world). The primary endpoint is tumor RANK expression correlated with OS. Primary analysis will occur when ~149 deaths have occurred. Eligible pts will have ECOG status 0–1 and radiographically evaluable disease. Pts with known EGFR-activating mutations, EML-4-ALK translocations, or brain metastasis will be excluded. Pt screening and enrollment is planned or underway in ~10 countries. Clinical trial information: NCT01951586.

**TPS8131 General Poster Session (Board #305B), Sat, 1:15 PM-5:00 PM**

**NEJ009 trial: A randomized phase III study of gefitinib (G) in combination with carboplatin (C) plus pemetrexed (P) versus G alone in patients with advanced nonsquamous non-small cell lung cancer (NSCLC) with EGFR mutation.** *Presenting Author: Akira Inoue, Department of Respiratory Medicine, Tohoku University Hospital, Sendai, Japan*

**Background:** Based on the previous phase III studies including our NEJ002 study comparing G with platinum doublet, G alone has been accepted as the standard first-line treatment for patients with EGFR-mutated NSCLC. To improve the survival in this population, we had investigated subsequent randomized phase II study (NEJ005) that evaluate the efficacy and safety of two patterns of combined regimen with G, C, and P, and selected one regimen with concurrent use of G, C, and P according to the results of interim monitoring. **Methods:** This randomized phase III trial was designed to compare the efficacy and safety of G alone with combined regimen with G, C, and P in patients with advanced EGFR-mutated NSCLC. Eligible patients (N=340) have pathologically confirmed stage IIIB/IV NSCLC with activating EGFR mutation including exon 18 G719A, C, or S mutation, exon 19 deletion, exon 21 L858R, or L861Q mutation. Concurrent mutation in exon 20 T790M is ineligible. Patients must have radiologically measurable disease, ECOG PS 0–1 and no prior systemic therapy. Patients will be randomized (1:1) to receive G 250 mg alone once daily or same schedule of G with C (AUC 5.0) plus P (500 mg/m2) on day1, every 3 weeks, up to 4-6 cycles, followed by maintenance P with concurrent G. The primary endpoint is overall survival (OS) and secondary endpoints include progression-free survival, best overall response, toxicity profile, and quality of life. A minimum of 168 OS events is required for 80% power to detect a OS improvement of GCP regimen versus G alone using the intent-to-treat (ITT) analysis population (HR $\leq$0.7). A significant (0.025 significance level) 2-sided stratified log-rank test for OS at the final analysis will be indicative of a positive study outcome. An interim analysis is planned to assess safety and whether early discontinuation of the trial is required for futility. Clinical trial information: UMIN000006340.

**TPS8132 General Poster Session (Board #306A), Sat, 1:15 PM-5:00 PM**

**Metformin with a carbohydrate-restricted diet in combination with platinum-based chemotherapy in advanced-stage lung adenocarcinoma.** *Presenting Author: Benjamin Philip Levy, Mount Sinai Beth Israel Hospital, Icahn School of Medicine at Mount Sinai, New York, NY*

**Background:** Metformin (MTF), an oral biguanide, has recently demonstrated preventative and therapeutic effects in both preclinical and observational clinical studies in non-small cell lung cancer (NSCLC), with minimal toxicity. MTF's antineoplastic effects are mediated by inhibition of the "energy sensing" AMP kinase pathway (AKP) and reversal of hyperinsulinemia. Preclinical data suggest that carbohydrate restriction (CR) also inhibits cancer growth by down-regulation of the AKP as this strategy is currently being investigated in multiple tumor types (NCT01716468). In vivo studies suggest alterations in LKB1, an upstream kinase of the AKP, may predict sensitivity to MTF and is altered in up to 30% of lung adenocarcinoma. We seek to exploit the potential synergy of MTF and a CR diet on this novel pathway as a unique approach to the treatment of NSCLC. **Methods:** Two out of a planned 60 patients have been enrolled in this open label, single arm phase II trial. Advanced stage adenocarcinoma patients with measurable disease, ECOG $<$ 2, and preserved organ function are included. Exclusion criteria included weight less than 80% of ideal body weight (IBW), previous use of metformin, or history of lactic acidosis. Patients are treated with carboplatin (Cb) AUC 5, pemetrexed (P) 500mg/m2 IV every three weeks followed by maintenance P until disease progression or unacceptable toxicity. MTF is initiated at 500mg bid on day 1 of chemotherapy and dose escalated in 500mg increments every 7 days to a final dose of 1,000 mg bid. Patients receive an early referral to a registered dietitian to assess daily caloric needs based on height and weight, and subsequent counseling on a CR diet ($<$30% of the patient's caloric needs from carbohydrates). Patients are removed from the diet portion of the study if they lose more than 10% of their IBW. The primary endpoint of the study is PFS, and the study will be considered positive if PFS is 6.6 months, based on comparison to 4.4 months in historic controls. Secondary objectives include correlation of archival tissue LKB1 mutations assessed by next generation sequencing (Ion Torrent, Integrative Oncology) and changes in serum insulin levels with clinical outcomes (ORR and PFS). Clinical trial information: NCT02019979.

**TPS8133 General Poster Session (Board #306B), Sat, 1:15 PM-5:00 PM**

**NLG-0301: An open-label, randomized phase 2B active control study of second-line tergenpumatucel-L immunotherapy versus docetaxel in patients with progressive or relapsed non-small cell lung cancer (NSCLC).** *Presenting Author: Ramaswamy Govindan, Division of Oncology, Washington University School of Medicine, St. Louis, MO*

**Background:** Tergenpumatucel-L immunotherapy consists of allogeneic lung cancer cells that have been genetically modified to express the carbohydrate $\alpha$(1,3)Gal, to which humans have an inherent pre-existing immunity. It is $\alpha$Gal that is primarily responsible for the hyperacute rejection of foreign tissue via this potent immune defense mechanism in humans. Tergenpumatucel-L leverages this mechanism to educate the immune system towards components of the patients' own tumor cells. In a Phase 2 study of tergenpumatucel-L, patients with evidence of immune activation after therapy (11/18 patients with elevated IFN gamma via ELISPOT) had a median survival of 21.9 months. 16 of 28 patients went on to salvage therapy after progression and 9 of these 16 had objective responses (5PR, 4SD) to the post immunotherapy chemotherapy. This study is designed to further evaluate this potential chemo-sensitization effect of tergenpumatucel-L. **Methods:** This Phase 2B study is an open label, multi center randomized trial of single agent tergenpumatucel-L versus docetaxel. Eligible patients have pathologically confirmed NSCLC and may have previously undergone surgery, radiotherapy, and $\leq$ 2 prior chemotherapy regimens for this diagnosis. 240 patients will be randomized in a 2:1:1 manner to docetaxel (75mg/m$^2$ q3 weeks x 4 doses) versus tergenpumatucel-L (300 million cell intradermally weekly for 11 weeks and then q2 months for 5 additional doses) versus tergenpumatucel-L (300 million cell q2 weeks for 6 doses and then monthly for 10 months). Patients will be monitored and at progression may stay on study and receive gemcitabine or premetrexed if randomized to the docetaxel arm or docetaxel or gemcitabine or premetrexed if randomized to one of the tergenpumatucel-L arms. Patients randomized to immunotherapy may continue to receive tergenpumatucel-L while on salvage chemo until all 16 planned doses are administered. This design with the patients staying on trial after progression is intended to capture and evaluate the possible chemo-sensitization seen in previous trials. Primary endpoint is overall survival. Clinical trial information: NCT01774578.

**8135 General Poster Session (Board #220), Sat, 1:15 PM-5:00 PM**

**The *KRAS*-variant and treatment response in BATTLE-1.** *Presenting Author: Joanne B. Weidhaas, Yale School of Medicine, New Haven, CT*

**Background:** The program, "BATTLE: Biomarker-integrated Approaches of Targeted Therapy of Lung Cancer Elimination" was initiated to establish individualized targeted therapy for NSCLC patients for whom standard therapy had failed. This trial prospectively examined patient tumor biomarker profiles, and assigned them to corresponding targeted therapies (erlotinib, vandetanib, bexarotene+erlotinib, and sorafenib). The primary end-point was 8-week disease control (DC) rate, with a secondary endpoint of overall survival (OS). The *KRAS*-variant is a germ-line mutation that predicts increased NSCLC risk, as well as tumor biology across numerous cancer types. **Methods:** 161 patients from the BATTLE-1 clinical study with sufficient DNA available were tested for the *KRAS*-variant. Overall survival (OS) and progression-free survival (PFS) were estimated by the Kaplan-Meier method. Log-rank test was used to test the difference in survival distributions among groups. **Results:** Overall, 16 BATTLE patients had the *KRAS*-variant, 10.2% (11/107) without tumor acquired EGFR or KRAS mutations (WT), 4.3% (1/23) with tumor acquired EGFR mutations, and 9.7% (3/31) with tumor acquired KRAS mutations. For the primary objective of the study of 8-week DC, *KRAS*-variant patients faired worse (48.5% non-variant vs 28.6% *KRAS*-variant patients). For WT patients, the *KRAS*-variant predicted borderline worse OS (p=0.072) and significantly worse PFS (p=0.01). The impact of the *KRAS*-variant on outcome depended significantly on treatment type. *KRAS*-variant patients treated with Erlotinib had significantly worse PFS (p=0.001). *KRAS*-variants patients treated with Vandetanib had significantly worse OS (p=0.029). However, *KRAS*-variant patients treated with Sorafenib had borderline improved OS (p=0.056). For Sorafenib treated patients with tumor acquired KRAS mutations, those with the *KRAS*-variant had significantly improved PFS (p=0.045) vs non-variant patients. **Conclusions:** The *KRAS*-variant appears to be a predictive biomarker in NSCLC, regardless of tumor acquired KRAS and EGFR mutations. These findings will be further investigated in the BATTLE2 trial as well as RTOG 0617 to confirm the potential of the *KRAS*-variant to be employed to direct treatment for NSCLC patients. Clinical trial information: NCT00409968.

**8500 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Randomized phase 3 study of rituximab, cyclophosphamide, doxorubicin, and prednisone plus vincristine (R-CHOP) or bortezomib (VR-CAP) in newly diagnosed mantle cell lymphoma (MCL) patients (pts) ineligible for bone marrow transplantation (BMT).** *Presenting Author: Franco Cavalli, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland*

**Background:** R-CHOP is standard therapy for newly diagnosed, BMT-ineligible MCL pts. Bortezomib (V) is approved in the US for relapsed MCL. This study evaluated whether replacing vincristine with V in R-CHOP improves outcomes in newly diagnosed, BMT-ineligible MCL pts (NCT00722137). **Methods:** Adults with treatment-naive, measurable stage II–IV MCL and ECOG PS 0–2 were randomized 1:1 (stratified by IPI score and disease stage) to 6–8 21-d cycles of rituximab 375 mg/m$^2$, cyclophosphamide 750 mg/m$^2$, doxorubicin 50 mg/m$^2$, all IV d 1, and prednisone 100 mg/m$^2$ PO d 1–5, plus V 1.3 mg/m$^2$ IV d 1, 4, 8, 11 (VR-CAP) or vincristine 1.4 mg/m$^2$(max 2 mg) IV d 1 (R-CHOP). Primary endpoint was PFS by independent radiology review (IRC); secondary endpoints included TTP, TTNT, OS, response by modified IWRC criteria, and safety. 486 pts were planned for 295 total PFS events, to provide 80% power ($\alpha$=.05, 2-sided) to detect 40% PFS improvement with VR-CAP. **Results:** 487 pts were randomized (244 R-CHOP, 243 VR-CAP; median age 66 yrs, 74% male, 74% stage IV MCL, 54% IPI ≥3). Pts received a median of 6 cycles. After 40 mos' median follow-up (298 PFS events), median PFS by IRC was 14.4 (R-CHOP) vs 24.7 mos (VR-CAP) (ITT analysis: HR=.63* [.50, .79], *P*<.001**). Secondary efficacy data are below. Rates of grade ≥3 AEs were 85% (R-CHOP) vs 93% (VR-CAP), serious AEs 30% vs 38%, discontinuations due to AEs 7% vs 9%, and on-treatment drug-related deaths 3% vs 2%. **Conclusions:** VR-CAP significantly prolonged PFS and consistently improved secondary efficacy endpoints vs R-CHOP in newly diagnosed, BMT-ineligible MCL pts, with additional but manageable toxicity. Clinical trial information: NCT00722137.

| Median outcomes, mos | R-CHOP | VR-CAP | HR* | *P*** |
|---|---|---|---|---|
| **PFS** | | | | |
| Investigator | 16.1 | 30.7 | .51 | <.001 |
| **TTP** | | | | |
| IRC | 16.1 | 30.5 | .58 | <.001 |
| Investigator | 16.8 | 35.0 | .47 | <.001 |
| **TTNT** | 24.8 | 44.5 | .50 | <.001 |
| **OS** | 56.3 | NR | .80 | .173 |
| 4-yr OS, % | 54 | 64 | – OR‡ | – P§ |
| **CR+CRu, %** | | | | |
| IRC† | 41 | 48 | 1.4 | .075 |
| Investigator | 28 | 42 | 1.9 | .002 |

* Stratified Cox model (HR <1 favors VR-CAP). ** Stratified log-rank test. † Bone marrow and LDH verified. ‡ Stratified Mantel-Haenszel estimate (OR >1 favors VR-CAP). § Stratified Cochran-Mantel-Haenszel $X^2$ test.

**8501 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Increased rituximab (R) doses and effect on risk of elderly male patients with aggressive CD20+ B-cell lymphomas: Results from the SEXIE-R-CHOP-14 trial of the DSHNHL.** *Presenting Author: Michael Pfreundschuh, Saarland University Medical School, Homburg, Germany*

**Background:** Elderly male patients have significantly lower R serum levels, shorter exposure times and a worse outcome in RICOVER-60, RICOVER-noRTh, and Pegfilgrastim trials (Blood 2012, 119:3276; Blood 2014, 123:640-646). **Methods:** To test increasing R doses, male patients received 500 instead of 375 mg/m$^2$ in the SEXIE-R-CHOP-14 trial which also compared six cycles of CHOP-14 in combination with eight 2-week applications with eight upfront dose-dense applications of R (days -1, 0, 3, 7, 14, 21, 28, 42) in a randomized phase-II trial. 271 patients (61-80 years) were randomized, 268 patients are evaluable. 148 patients males received 500 mg/m$^2$, 120 females 375 mg/m$^2$R. **Results:** Protocol adherence was excellent with median relative doses of R and myelosuppressive drugs >98%. During the treatment period, the increased R dose in males resulted in slightly higher trough serum levels than in females; however, R levels dropped faster in males resulting in nearly identical serum levels thereafter and a very similar overall R exposure time. The increased R dose in males was not associated with increased toxicities. 3-year PFS was 74% in males and 68% in females (p=0.396), 3-year OS was 80% in males and 72% in females (p=0.111). In a multivariable analysis adjusting for IPI factors, male hazard was 0.9 (p=0.817) for PFS, and 0.8 for OS (p=0.317). In a historical comparison by multivariable analysis adjusting IPI risk factors and age >70 years, of 148 elderly males who received 500 mg/m$^2$ in SEXIE-R-CHOP-14 and 250 males who received 375 mg/m$^2$ in RICOVER-60, the increased dose of R was associated with a reduced risk for an event in PFS (HR=0.7; p=0.128) and 0.7 in OS (p=0.223). **Conclusions:** Increasing R dose by one third from 375 mg/m$^2$ to 500 mg/m$^2$ eliminated the increased risk of elderly males. That the increased R dose significantly improves outcome not only of elderly male patients, but also in young male and female patients who have a R pharmacokinetics similar to elderly males should be confirmed in a larger randomized study of these subpopulations with aggressive CD20$^+$ B-cell lymphomas. Supported by Roche and Deutsche Krebshilfe. Clinical trial information: NCT00290667.

**8502 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Prognostic value of PET-CT after frontline therapy in follicular lymphoma: A pooled analysis of central review in three multicenter studies.** *Presenting Author: Judith Trotman, Concord Hospital, University of Sydney, Sydney, Australia*

**Background:** The value of $^{18}$F-FDG PET-CT (PET) in response assessment after induction rituximab-chemotherapy for advanced stage symptomatic follicular lymphoma (FL) has recently been documented. To provide more precise survival estimates from a larger patient cohort with longer follow-up we conducted a pooled analysis of centrally reviewed scans in three studies. **Methods:** Patient data and conventional CT-based response assessment (IWC 1999) were recorded for all patients undergoing central PET review in the prospective multicenter GELA (PRIMA and PET Folliculaire), and FIL (FOLL05) studies. Scans were assessed independently by three reviewers applying the standardized Five-Point Scale (5PS). Postinduction PET status was compared with patient characteristics, CT-based assessment and survival endpoints of PFS and OS. **Results:** Of 246 scans performed at the end of the induction immunochemotherapy, 178 (27.6%) were positive with a cut-off ≥3 (FDG uptake >mediastinum), and 41 (16.7%) with a cut-off ≥4 (moderately >liver). Patient and baseline disease characteristics did not differ significantly between PET+ and PET- patients. With a median follow-up of 55 months, both PET cut-offs were highly predictive of PFS and OS, with a cut-off ≥4 being most reproducible and discriminatory. With this cut-off the HR for PFS and OS of PET+ vs. PET- patients was 3.9 (95% CI 2.5-5.9, P<.0001), and 6.7 (95% CI 2.4-18.5, P=0.0002) respectively. For PET+ patients 4 year PFS was 23.2% (95% CI 11.1-37.9%) vs. 63.4% (95% CI 55.9-70.0%) in those who became PET- (P<.0001). Four year OS was 87.2% (95% CI 71.9-94.5%) vs. 97.1% (95% CI 93.2-98.8%), (P<.0001). Conventional CT-based response (CR/CRu vs.PR) was weakly predictive of PFS (HR 1.7, p=0.02) but not OS. **Conclusions:** This large pooled analysis with longer patient follow-up and standardized central review of scans confirms PET status after first-line therapy is strongly predictive of survival in FL. PET-CT rather than contrast enhanced CT scanning should be considered the new gold standard for response assessment in clinical practice, and a platform for study of response-adapted therapy.

**8503 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Final results of a randomized phase II GELA/LYSA study of rituximab plus ACVBP or CHOP, using a PET-driven consolidation strategy, in patients with high-risk diffuse large B-cell lymphoma (DLBCL).** *Presenting Author: Rene-Olivier Casasnovas, Hôpital Le Bocage, Dijon, France*

**Background:** GELA standard for young patients (pts) with high-risk DLBCL (aaIPI 2-3) is R-ACVBP induction plus consolidative BEAM and autologous stem cell transplantation (ASCT). R-CHOP induction might be as efficient and possibly less toxic than R-ACVBP. Also, early PET-negative patients may not need first-line ASCT. A phase II randomized trial was designed in 2007 to test both induction regimen and a PET-driven consolidation strategy (NCT00498043). **Methods:** Eligible pts were 18-59 years with a previously untreated CD20+ DLBCL, an aaIPI 2-3. Pts were randomly assigned to 4 cycles of either R-ACVBP14 or R-CHOP14 induction. Consolidation treatment was driven by centrally reviewed PET assessment (IHP visual criteria) after 2 (PET2) and 4 (PET4) induction cycles. Pts classified as PET2-/PET4- received a sequential immuno-chemotherapy consolidation; PET2+/PET4- pts underwent ASCT; PET4+ pts were considered as induction treatment failure and eligible for a salvage therapy. Primary endpoint was to evaluate the complete response (CR) rate after 4 induction cycles according to IWG 07 criteria. **Results:** 222 pts (R-ACVBP: 114; R-CHOP: 108) with a median age of 46 yrs were included: 97% had stage III/IV, 95% elevated LDH, 24% ECOG≥2. After induction treatment, 47% of the R-ACVBP arm and 39% of the R-CHOP arm pts achieved a CR. PET2 and PET4 were negative in 30% and 53% of pts in the R-ACVBP arm, and 25% and 40% in the R-CHOP arm, respectively. PET2-/PET4- pts were 27% and 24% in the R-ACVBP and R-CHOP arms respectively. Due to more frequent PET4+, pts in the R-CHOP arm more often received salvage therapy as post-induction treatment (39%) than pts in the R-ACVBP arm (27%) (p = 0.048). With a median follow-up of 45 months, PFS and OS were similar in both arms (4y-PFS=75%; 4y-OS=83%). **Conclusions:** A PET driven treatment of high risk DLBCL pts is feasible in a multicenter trial setting. Based on PET visual criteria at 4 cycles, CR rate was higher in the R-ACVBP arm and salvage was more frequently used after R-CHOP, possibly explaining similar PFS and OS in the two induction arms. 25% of pts found to be PET2-/PET4- do not require ASCT. Clinical trial information: NCT00498043.

**8504 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Noninvasive monitoring of cellular versus acellular tumor DNA from immunoglobulin genes for DLBCL.** *Presenting Author: David Matthew Kurtz, Division of Oncology, Stanford University School of Medicine, Stanford, CA*

**Background:** In patients with diffuse large B cell lymphoma (DLBCL), tumor specific immunoglobulin genes can be detected in both the cellular and acellular compartments of blood (Green et al ASH 2013; Armand et al BJH 2013; Roschewski et al ASH 2013). Detection of these genes by high-throughput sequencing (Ig-HTS) has promise for monitoring minimal residual disease (MRD). We compared the performance of Ig-HTS in the cellular and acellular compartments of blood and related them to other measures of disease. **Methods:** We profiled 50 patients with DLBCL at time of diagnosis, therapy, remission, and relapse. Forty-two patients were treated at Stanford University with curative intent. Eight patients were from an Australian Phase 2 study (ALLG NHL21) for patients with poor risk treated with R-CHOP. Involved tissue was used to define clonotypic tumor heavy and light chains by Ig-HTS. Identified sequences were tracked in the cellular and acellular compartments of blood (Faham M et al Blood 2012). **Results:** We identified clonotypic sequences in 100% of fresh tissue but only 59% of FFPE (72% overall). Heavy chains were more frequent than light chains (86% vs 47%). For 36 cases with clonotypic sequences, we followed MRD with 216 tests on 98 blood samples. Within the cellular compartment of blood, we identified disease in 70% of patients at diagnosis, but only 20% at relapse. In the acellular compartment, we identified disease in 78% at diagnosis and 83% at relapse. In those achieving complete response, MRD became undetectable by cycle 2 and remained so while in CR. Only 1 of 46 assays revealed MRD in the cellular compartment while in CR; this in a patient with double-hit DLBCL and high relapse risk. Using radiographic assessment as gold standard, cellular Ig-HTS had 52% sensitivity and 97% specificity and acellular Ig-HTS had 67% Sn and 100% Sp. MRD level correlated with LDH ($R=0.76$, $p<0.0001$) and metabolic tumor volume (MTV) ($R=0.58$, $p<0.01$). **Conclusions:** Ig-HTS can detect tumor specific DNA in the blood of patients with DLBCL. Performance is superior in cell-free DNA from the acellular compartment of blood compared to the cellular compartment. Given its high specificity, Ig-HTS has potential clinical utility during surveillance after achieving CR.

**8505 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Interim analysis of a phase 1, open-label, dose-escalation study of SGN-CD19A in patients with relapsed or refractory B-lineage non-Hodgkin lymphoma (NHL).** *Presenting Author: Andres Forero-Torres, The University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL*

**Background:** CD19, a member of the immunoglobulin superfamily, is expressed in most patients with B-cell NHL. SGN-CD19A is a novel antibody-drug conjugate composed of a humanized anti-CD19 monoclonal antibody conjugated to the microtubule-disrupting agent monomethyl auristatin F (MMAF) via a maleimidocaproyl linker. **Methods:** This phase 1, open-label, dose-escalation study investigates the safety, tolerability, pharmacokinetics (PK), and antitumor activity of SGN-CD19A in patients with relapsed or refractory B-cell NHL with at least 1 prior systemic regimen (NCT01786135). Patients with DLBCL or follicular lymphoma grade 3 (FL3) must have received intensive salvage therapy. A modified continual reassessment method is used for dose allocation and maximum tolerated dose (MTD) estimation. SGN-CD19A is given by IV on Day 1 of 21-day cycles. **Results:** To date, 22 patients with a median age of 63 years (range, 33 to 81) with DLBCL (18), MCL (3), and FL3 (1) have been treated with SGN-CD19A. 50% of patients were refractory to their last treatment; 6 patients received prior autologous SCT. Patients have received a median of 2 cycles (range, 1 to 9) at dose levels from 0.5 mg/kg to 6 mg/kg. 11 patients remain on treatment and 11 have discontinued due to progressive disease (10) and patient decision (1). No dose-limiting toxicity (DLT) has been reported in 21 DLT-evaluable patients; the MTD has not yet been identified. Adverse events occurring in $\geq$10% of patients are fatigue (27%), blurred vision (27%), dry eye (23%), constipation (23%), dyspnea (14%), and keratitis (14%). Of the 20 patients evaluated, objective responses were observed in 8 patients (40%), 6 CRs (30%) and 2 PRs (10%); 3 patients had SD (15%) and 9 had PD (45%). SGN-CD19A ADC plasma exposures were approximately dose-proportional in preliminary PK analysis with mean terminal half-lives between 9-30 days. **Conclusions:** To date, SGN-CD19A has shown evidence of clinical activity with an objective response rate of 40% (8 of 20 patients) and an observed CR rate of 30% (6 of 20 patients). No DLTs have been reported in tested dose levels; enrollment is ongoing to identify the optimal dose of SGN-CD19A for future studies. Clinical trial information: NCT01786135.

**8506 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Starlyte phase II study of coltuximab ravtansine (CoR, SAR3419) single agent: Clinical activity and safety in patients (pts) with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL; NCT01472887).** *Presenting Author: Marek Trneny, Charles University Hospital, Department of Hematology, Prague, Czech Republic*

**Background:** CoR is an anti-CD19 antibody maytansinoid conjugate. CD19 is expressed in the majority of B cell lymphomas. Phase I program showed clinical activity in pts with both indolent and aggressive lymphomas. **Methods:** Pts withCD19+ R/R DLBCL after at least one standard treatment including rituximab and not candidate for transplantation were eligible. Primary refractory pts were excluded. Biopsy was required at baseline. CoR 55 mg/m$^2$ was administered weekly for 4 weeks then bi-weekly until disease progression or other study discontinuation criteria. The primary objective was to demonstrate an overall response rate (ORR) of at least 20% following Cheson 2007 criteria. Tumor assessments were done every 12 weeks. Secondary objectives were: safety, pharmacokinetics (PK), duration of response (DOR), progression free and overall survival (PFS, OS). Assessment of correlation between biomarkers (BM) status and disease outcome was an exploratory objective. **Results:** 41 pts were evaluable. Median age was 71 (39:85), 53.7% were male; 92.7% had ECOG performance status 0-1. 31.7% had received $\geq$ 3 prior regimens for DLBCL. The ORR was 43.9% (90% CI: 30.6% to 57.9%, p-value$<$0.0001) including 5 complete responses (12.2%). DOR, OS and PFS data are not mature (11 pts ongoing). The most common (>10%) all grades (gr) non-hematologic treatment-emergent adverse events (TEAEs) were nausea (23.0%), diarrhea (19.7%), fatigue and cough (18.0%), vomiting and decrease appetite (13.1%), asthenia, abdominal and back pain (11.5%). TEAEs led to treatment discontinuation in 4 pts. Only gr 1-2 eye disorders were reported, including 1 pt with unrelated gr 2 keratitis. Peripheral neuropathies were observed in 5 pts, all were gr 1-2. Hematological toxicity was moderate, with gr 3-4 neutropenia, thrombocytopenia and anemia in 26.4%, 9.9% and 6.6% pts respectively. PK assessment and investigations on BM expression are ongoing. **Conclusions:** CoR as single agent demonstrated significant activity in R/R DLBCL pts and reached its primary endpoint for ORR, with acceptable safety profile. Trial funded by Sanofi. Clinical trial information: NCT01472887.

**8507 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**A pilot phase II study with brentuximab vedotin followed by ABVD in patients with previously untreated Hodgkin lymphoma: A preliminary report.** *Presenting Author: Massimo Federico, Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy*

**Background:** In the majority of patients with relapsed or refractory Hodgkin Lymphoma (HL) Brentuximab vedotin (BV) has shown significant activity, with a manageable safety profile. We aimed to assess the role of 2 cycles of BV before starting the standard treatment with ABVD +/- RT in patients with previously untreated HL. **Methods:** Patients with previously untreated CD30-positive HL, stage IA or IIA or IIIA, absence of bulky disease, defined as a mediastinal mass greater than one-third of the maximum chest diameter, or any other mass greater than or equal to 10 cm, received 2 cycles of BV 1.8 mg/Kg intravenously every 3 weeks over 30 minutes, as an outpatient infusion, followed by 3-6 cycles of ABVD depending on stage. Decision on radiotherapy was at physician's discretion. The primary endpoint of the study was the response to BV assessed by FDG/PET, defined as reduction of Deauville score or, in case of no change in Deauville score, as any reduction in SUV intensity compared to basal SUV. PET results (baseline and after 2 cycles of BV) were assessed by a panel of three external independent reviewers. The sample size was fixed at 12 patients. The treatment was considered promising if 10 or more responses were observed (response rate 83%, 95%CI 52-98%). **Results:** Between April and October 2013, 12 patients with a median age of 36 years (age range: 19-70 years), eleven in stage II (Early favorable 7, early unfavorable 4, according to EORTC criteria) and one in stage III, were enrolled. BV was administered as scheduled and at the full dose in all patients. After the 2 cycles of BV, all patients but one (91%) responded, ten with complete (83%) and one (8%) with partial metabolic response. Of note, all seven patients with early favorable disease achieved a complete metabolic response. The only non responding patient had stage III and showed a new lesion at PET2. The only grade 3 adverse events were transient and asymptomatic increase in liver transaminases (n=3, 25%) and gamma glutamyl transpeptidase (n=2, 17%). **Conclusions:** Two cycles of BV induced a complete metabolic response in the majority of patients with previously untreated, limited stage HL, and warrant further studies in first line therapy.

**8508 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Activity of the mTOR inhibitor sirolimus and HDAC inhibitor vorinostat in heavily pretreated refractory Hodgkin lymphoma patients.** *Presenting Author: Filip Janku, Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Preclinical models suggested synergistic antineoplastic activity of HDAC and mTOR inhibitors in Hodgkin lymphoma by reducing the activity of AKT, mTOR and HDAC. **Methods:** We designed a phase I study to determine the safety of the mTOR inhibitor sirolimus (1mg-5mg PO daily q 28 days) and HDAC inhibitor vorinostat (100mg-400mg PO daily q 28 days) in advanced cancers with an expansion cohort at the recommended phase 2 dose (RP2D) of sirolimus 4mg and vorinostat 300mg for patients with refractory classical Hodgkin lymphoma. The expansion cohort included optional pre- and post-treatment tumor biopsies, peripheral blood mononuclear cells (PBMCs), plasma/serum collections for pharmacodynamic (PD) and pharmacokinetic (PK) endpoints. Upon identification of R2PD patients were allowed to be treated and registered off label if protocol spots were not available. **Results:** A total of 28 patients (men, n=15; women, n=13), median age 34 years, median of 6 prior therapies (including autologous SCT [n=23], autologous and allogeneic SCT [n=6]) were enrolled in dose escalation (n=1), RP2D (n=19) or registered off label (n=8). Per Cheson 2007 criteria the overall response rate was 57% with 9 CRs (32%) and 7 PRs (25%). At the median follow-up of 5.4 months, the median progression-free survival has not been reached. Also given successful induction of remissions 5 (18%) patients were referred for allogeneic SCT. Major grade 3-4 treatment-related toxicities included grade 3 thrombocytopenia (9 patients, 32%), grade 4 thrombocytopenia (8, 29%), grade 3 anemia (4, 14%), and grade 3 transaminitis (3, 11%). Treatment interruptions and/or dose modifications were needed in 19 (68%) patients. Ten (36%) patients had archival tissue available for targeted next-generation sequencing and one patient had a loss of *TSC2*, an abnormality that putatively activates mTOR (PR -56% for 8.4+ months). PD studies in pre- and post-treatment tumor biopsies, PBMCs and plasma as well as PK analysis are pending. **Conclusions:** The combination of sirolimus and vorinostat is well tolerated with encouraging activity in very heavily pretreated patients with Hodgkin lymphoma refractory to standard therapies. Clinical trial information: NCT01087554.

**8510^ Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**Panorama 1: A randomized, double-blind, phase 3 study of panobinostat or placebo plus bortezomib and dexamethasone in relapsed or relapsed and refractory multiple myeloma.** *Presenting Author: Paul G. Richardson, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Panobinostat (PAN) is a potent pan-deacetylase inhibitor that demonstrates synergistic antimyeloma activity when combined with bortezomib (BTZ) + dexamethasone (Dex). Early studies demonstrated durable responses in patients (pts) with relapsed (Rel) and relapsed/refractory (RR) multiple myeloma (MM) treated with PAN + BTZ + Dex. This initiated the PANORAMA 1 study, presented herein. **Methods:** Eligible pts had Rel or RR (excluding BTZ- and primary-ref MM) following 1-3 prior regimens. Pts received oral PAN (20 mg) or placebo (pbo) 3 ×/wk + IV BTZ (1.3 mg/m$^2$; D 1, 4, 8, 11) during wks 1-2 with oral Dex (20 mg) on the days of and after BTZ in treatment phase (TP) 1, eight 3 wk cycles. Pts demonstrating benefit could proceed to TP2, with PAN dosing maintained and BTZ/Dex less frequent. The primary endpoint was progression free survival (PFS) with response assessed by modified EBMT criteria. Other endpoints included overall survival (OS), overall response rate (ORR), near complete/complete response (nCR/CR) rate, duration of response (DOR), and safety. PFS/ORR was confirmed by an independent review committee. **Results:** A total of 768 pts (PAN + BTZ + Dex [n = 387]; pbo + BTZ + Dex [n = 381]) were randomized. Median age was 63 y (42% ≥ 65 y) and 48% received ≥ 2 prior regimens. Prior therapies included BTZ (43%), thalidomide (51%), lenalidomide (20%), and 25% received both prior BTZ + IMiDs. The primary endpoint was met with median PFS of 12 mo vs 8.1 mo ($P < .0001$; HR 0.63, 95% CI [0.52, 0.76]) for pts treated on the PAN vs pbo arm. In the PAN and pbo arms, ORR was 61% vs 55% and nCR/CR rate was 28% vs 16%, with DOR of 13.1 mo vs 10.9 mo, respectively. OS data is not mature. Adverse events (AEs) led to discontinuation in 36% in the PAN arm and 20% in the pbo arm. Common grade 3/4 lab abnormalities and AEs (regardless of study drug relationship) in the PAN vs pbo arms included thrombocytopenia (67% vs 31%), neutropenia (35% vs 11%), and diarrhea (26% vs 8%); these were generally manageable with dose reduction/supportive care. On-treatment deaths occurred in 8% and 5%, respectively. **Conclusions:** PAN + BTZ/Dex significantly improves PFS in pts with Rel or RR MM, with manageable toxicity. Clinical trial information: NCT01023308.

**8511 Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**E1A06: A phase III trial comparing melphalan, prednisone, and thalidomide (MPT) versus melphalan, prednisone, and lenalidomide (MPR) in newly diagnosed multiple myeloma (MM).** *Presenting Author: A. Keith Stewart, Mayo Clinic, Scottsdale, AZ*

**Background:** Melphalan, prednisone and thalidomide (MPT) is an accepted regimen in newly diagnosed MM. Early studies suggested that lenalidomide (R) might be substituted for thalidomide (T) with equal efficacy and less toxicity. We present E1A06, a randomized, multicenter phase 3 trial comparing MPT vs. MPR in pts with untreated, symptomatic, transplant ineligible MM. **Methods:** The primary objective was PFS differences between pts receiving MPT: M 9 mg/m$^2$ and P 100 mg p.o. each on days 1-4 with T 100 mg daily vs. MPR: M 5 mg/m$^2$and P 100 mg p.o. each on days 1-4 with R 10 mg p.o. on days 1-21. MPT or MPR therapy was continued for twelve 28 day cycles followed by T 100mg or R 10mg daily until relapse. Aspirin prophylaxis was required. Pts were stratified by ISS stage (I-II vs. III) and age (<65 vs. ≥65). Inferiority of MPR was defined as a PFS treatment hazard ratio (HR) of MPT/MPR ≤ 0.82. Secondary objectives included OS between the arms, toxicities, response rates, depth of response and quality of life (QoL) change. **Results:** 306 pts were enrolled. Treatment arms were balanced for age, ISS stage and other major prognostic factors. Median age was 75.7y. The median follow-up was 40.7 months (m). Median time on therapy was 12m, and 23m for the 46% of pts on maintenance therapy, with no differences by arm. Per protocol partial response rate was 62% (MPT) vs. 61% (MPR) with no difference in VGPR/CR rates (18.8% vs. 23%). Grade ≥3 toxicity was 71.6% (MPT) vs. 56.7% (MPR); p=0.008. By ITT, the median PFS was 21m on MPT and 18.7m on MPR; HR 0.84 [95%CI: 0.64, 1.09]. The null hypothesis of inferiority of MPR was not rejected. Three year OS was identical by arm at 63% and median OS was not significantly different; p=0.476. Second primary malignancies were observed in 17 (MPT) vs. 14 (MPR) pts with incidence rates of 3.47 and 2.01 (/100 person years). DVT/PE occurred in 8.8% vs. 6.7% of pts. QoL analysis favored MPR by induction end; p=0.007. **Conclusions:** This phase III trial compares the efficacy of MPT and MPR in elderly patients with newly diagnosed MM. Response rates, PFS and OS were similar between the two arms; however, there was significantly better QOL at 12m and lower toxicity with MPR. Clinical trial information: NCT00602641.

**8512 Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**A phase Ib dose escalation trial of SAR650984 (Anti-CD-38 mAb) in combination with lenalidomide and dexamethasone in relapsed/refractory multiple myeloma.** *Presenting Author: Thomas G. Martin, University of San Francisco, San Francisco, CA*

**Background:** SAR650984 (SAR) is a humanized IgG1 monoclonal antibody that binds selectively to a unique epitope on human CD38 receptor. SAR kills tumor cells via antibody-dependent cellular-mediated cytotoxicity, complement-dependent cytotoxicity, direct apoptosis induction without secondary crosslinking and allosteric inhibition on CD38 enzymatic activity. We present data on the dose escalation phase of the study (NCT01749969). **Methods:** Three dose levels (DL) of SAR 3, 5 and 10 mg/kg were evaluated in combination with lenalidomide (LEN) and dexamethasone (Dex). LEN 25 mg was given on days (d) 1 – 21 and D 40 mg on d 1, 8, 15 and 22 every 28 d's. SAR was given IV on d 1 and 15 and escalated using the classic 3+3 design. **Results:** 13 patients (pts) with RRMM were treated; median age 61 yrs (48 - 73); median prior treatment regimens 6 (2 - 12), 100% had received prior LEN (23% prior pomalidomide) and 92.3% previously received bortezomib (38.5% prior carfilzomib). The median time from diagnosis to first SAR dosing was 4.5 yrs (3 - 11). The maximum tolerated dose was not reached. The most frequent adverse events included nausea, cough (n = 6 each); fatigue, muscle spasm, infection (n = 5 each); vomiting, diarrhea, dehydration and insomnia (n = 4 each). Grade (G) ≥ 3 hematologic abnormalities were neutropenia (n = 4) and thrombocytopenia (n = 3). One pt discontinued therapy (cycle 1, d 1) due to an infusion reaction (bronchospasm G 3). The ORR (≥ PR), according to IMWG criteria, among 12 evaluable pts was 58 %. Responses occurred at each DL of 3mg/kg (1PR), 5mg/kg (1PR, 1 VGPR) and 10 mg/kg (1PR, 3 VGPR). Clinical benefit response (≥ MR) was 67 % with 1 MR at 3 mg/kg. Median time on treatment was 20.6 weeks (0 - 35) and 7 pts remain on therapy. PK showed non linearity at select dose levels, SAR plasma trough levels were above target for tumor eradication from preclinical data. **Conclusions:** The combination of SAR with LEN/Dex was tolerated and no DLT's were reported at any DL. SAR + LEN/Dex demonstrated encouraging efficacy in pts with heavily pretreated RRMM. An expansion cohort of 18 pts recently enrolled on the trial and the results will be reported at the meeting. Clinical trial information: NCT01749969.

**8513 Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**Dose-dependent efficacy of daratumumab (DARA) as monotherapy in patients with relapsed or refractory multiple myeloma (RR MM).** *Presenting Author: Henk M. Lokhorst, UMC Utrecht, Utrecht, Netherlands*

**Background:** Pts with RR MM received DARA for 9 wks in doses of 0.005-24mg/kg in the GEN501 dose-escalation part (Lokhorst: EHA 2013 abstract S576). The purpose of the GEN501 expansion part, which has completed enrollment, was to evaluate safety and efficacy of 2 doses of DARA for up to 24 mths using alternate dose schedules. **Methods:** Pts ≥18 yrs, RR to at least 2 prior lines of therapy, incl. IMiDs and proteasome inhibitors, and ineligible for ASCT were enrolled at 2 dose levels: A: 8mg/kg +/- pre-dose (10mg) wkly for the first 8 infusions.B: 16mg/kg without pre-dose with a 3-wk washout period between the first 2 doses followed by 7 wkly doses. Then all pts were dosed every 2nd wk for 16 wks followed by dosing every 4th wk until disease progression, toxicity or for max 24 mths. **Results:** Data from 30 pts in the 8mg/kg cohort and 15 pts in the 16mg/kg cohort recruited into the GEN501 expansion part are presented. Median age was 58.2 (35.1-76.9) and 64.1 (50.5-75.0) years, prior treatment lines were 5 (3-11), and 4 (2-8) and time since diagnosis was 5.5 (2.1-15.2) and 7.1 (0.4-13.3) years, respectively. Median number of DARA infusions was 10.5 vs 7.0, reflecting the more recent initiation of the 16mg/kg cohort. Infusion times were 3.5 vs 3.4 hours in the 8 and 16mg/kg groups, respectively. Safety: No dose-related increase in adverse events (AEs) was observed. Most common AEs reported (in ≥20% of all pts) were pyrexia, allergic rhinitis, fatigue, upper respiratory tract infection, diarrhea, dyspnea and cough. Only mild (Gr 1 and 2) infusion-related reactions (IRRs) were reported with 27% in the 16mg/kg group vs 20% in the 8mg/kg group. 2 SAEs, 1 in each group, were assessed as related to DARA (1 thrombocytopenia, 1 lymphocytopenia). One pt was withdrawn after 1st full dose due to thrombocytopenia Gr 3. Omission of the pre-dose increased neither the incidence nor the severity of IRRs. **Conclusions:** DARA monotherapy in RR MM pts resulted in high single agent activity when administered at 16 mg/kg (46% ORR). The safety profile was manageable. Full response data will be presented at the meeting incl. bone marrow assessments. Clinical trial information: NCT00574288.

| | PD | SD | MR | PR | VGPR | ORR[A] |
|---|---|---|---|---|---|---|
| **8 mg/kg n=30** | 9 | 14 | 5 | 2 | 0 | 7% |
| **16 mg/kg n=13[B]** | 3 | 3 | 1 | 3 | 3 | 46% |

[A] PR or better. [B] 2 pts only had 1st dose at data cutoff.

**8514 Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**Efficacy of siltuximab in patients with previously treated multicentric Castleman's disease (MCD).** *Presenting Author: Frits Van Rhee, Myeloma Institute for Research and Therapy, Little Rock, AR*

**Background:** Siltuximab is a chimeric anti−IL-6 monoclonal antibody under investigation for treatment of MCD.A randomized, double-blind, placebo-controlled study in MCD showed significant improvement in durable tumor and symptomatic response (34.0% vs 0.0% with placebo; $P = 0.001$), superior response in the secondary endpoints of tumor response rate, time to treatment failure, MCD symptom improvement, and no increased frequency of adverse events compared with placebo. A prespecified subanalysis evaluated the efficacy of siltuximab among patients who had received prior systemic therapy. **Methods:** Adults with confirmed symptomatic MCD were randomized 2:1 to siltuximab 11 mg/kg (n = 53) or placebo (n = 26) IV every 3 weeks and were stratified by corticosteroid use at randomization. All patients received best supportive care, and treatment was continued until treatment failure. **Results:** The majority (siltuximab, n = 29 [54.7%]; placebo, n = 17 [65.4%]) of patients had received prior systemic treatment for MCD. The most frequently used agents included corticosteroids 93.5%, cyclophosphamide 50%, vincristine 26.1% and rituximab 17.4%. Durable tumor and symptomatic responses were similar for pretreated and treatment naïve subgroups (34.5 % vs 0% and 33.3 % vs 0% respectively). Secondary endpoints consistently favored siltuximab in both subgroups as presented in the Table. Frequencies of adverse events (AE) and serious (S) AEs were similar across pretreated and treatment naive subjects. **Conclusions:** Siltuximab is an active agent in both newly diagnosed MCD and patients who have insufficient response to or failed other therapies. Clinical trial information: NCT01024036.

| | Pretreated MCD patients | | Treatment naïve MCD patients | |
|---|---|---|---|---|
| | Siltuximab | Placebo | Siltuximab | Placebo |
| **n** | 29 | 17 | 24 | 9 |
| **Durable tumor and symptom response by investigator** | 48% | 0% | 42% | 0% |
| **Median time to treatment failure** | Not reached | 184 days | Not reached | 177 days |
| **Hemoglobin increase > 1.5 g/dL in anemic subjects** | 59% (n = 17) | 0% (n = 7) | 64% (n = 14) | 0% (n = 4) |
| **Durable complete symptomatic response** | 17% | 0% | 33% | 0% |
| **Patients with AEs** | 100% | 100% | 100% | 89% |
| **Patients with SAEs** | 24% | 12% | 21% | 33% |

**8515 Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**Continuous treatment (CT) versus fixed duration of therapy (FDT) in newly diagnosed myeloma patients: PFS1, PFS2, OS endpoints.** *Presenting Author: Antonio Palumbo, Myeloma Unit, Division of Hematology, University of Torino, Torino, Italy*

**Background:** Continuous therapy significantly prolongs remission duration, resistant relapse may reduce the duration of subsequent remission which can negatively impact on OS. PFS1 defines the time from start of therapy to the occurrence of 1st relapse. PFS2 is defined as per EMA as the time from start of therapy to the occurrence of 2nd relapse, incorporating the duration of both 1st and 2nd remission. We evaluated PFS1, PFS2 and OS in newly diagnosed multiple myeloma (NDMM) patients who received CT or FDT. **Methods:** Patients were enrolled in 2 phase III randomized trials, comparing CT vs FDT (RVMM209: lenalidomide-based induction, consolidation, followed by maintenance [CT] vs lenalidomide-based induction, consolidation, no maintenance [FDT]; GIMEMA0305: bortezomib-based induction followed by maintenance (CT) vs bortezomib-based induction, no maintenance [FDT]). At diagnosis, in all randomized patients, we evaluated PFS1 (time: diagnosis followed by 1st relapse), PFS2 (time: diagnosis followed by 2nd relapse), and OS (time: diagnosis followed by death). In patients who experienced 1st relapse we tested 2nd PFS (time: 1st relapse followed by 2nd relapse) and survival from relapse (time: 1st relapse followed by death). **Results:** In the pooled analysis, 452 patients received CT and 461 patients received FDT. Median follow-up was 52 months [mo]. CT significantly prolonged PFS1 (median 35 vs 24 mo, HR 0.58; P<0.0001), PFS2 (median 63 vs 47 mo, HR 0.69, p=0.0001) and OS (median not reached [NR] vs 70 mo, HR 0.70, P=0.0019) in comparison with FDT. 2nd PFS and OS from relapse were similar among patients who received CT or FDT upfront. Results were similar in the single studies (Table). **Conclusions:** In NDMM patients, CT significantly improved PFS1, PFS2, and OS. Prolongation of PFS2 suggests that the clinical benefit observed during 1st remission is not cancelled by a shorter 2nd remission. PFS2 should be included in all CT vs FDT studies to evaluate the risk of tumor-resistance induced by CT. Clinical trial information: NCT01063179 and NCT00551928.

| | GIMEMA MM0305 | | | | RVMM209 | | | |
|---|---|---|---|---|---|---|---|---|
| | CT | FDT | | | CT | FDT | | |
| | (Median, mo) | | HR | P | (Median, mo) | | HR | P |
| **From diagnosis** | | | | | | | | |
| **PFS1** | 35 | 24 | 0.58 | <0.001 | 38 | 25 | 0.58 | <0.001 |
| **PFS2** | 59 | 42 | 0.69 | 0.003 | 63 | 49 | 0.69 | 0.015 |
| **OS** | NR | 60 | 0.70 | 0.01 | NR | NR | 0.68 | 0.047 |
| **From 1st relapse** | | | | | | | | |
| **PFS** | 14 | 12 | 1.1 | 0.61 | 17 | 19 | 1.09 | 0.61 |
| **OS** | 26 | 28 | 0.99 | 0.94 | 47 | 42 | 1.0 | 0.99 |

**8516^ Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**Health-related quality of life (HRQOL) in transplant-ineligible patients (pts) with newly diagnosed multiple myeloma (NDMM): Results from the first trial.** *Presenting Author: Michel Delforge, University Hospital Leuven, Leuven, Belgium*

**Background:** In the pivotal FIRST trial, continuous lenalidomide plus low-dose dexamethasone (Rd; [N = 535]) improved progression-free survival (PFS) and overall survival (OS) compared with 18 cycles of Rd (Rd 18; [N = 541] for and 12 cycles of melphalan-prednisone-thalidomide (MPT; [N = 547] for 72 weeks) (Facon, Blood 2013). This analysis evaluates HRQOL changes in these NDMM pts. **Methods:** HRQOL was assessed using the EORTC-QLQ-C30, QLQ-MY20, and EQ-5D validated questionnaires at baseline, end of cycle 1, then 3, 6, 12, 18 months (mos), and at study discontinuation. Cross sectional and longitudinal analyses were performed. Changes from baseline at each time-point were estimated with a focus on seven pre-selected and clinically-relevant domains (Global QOL, Physical Functioning, Pain, Fatigue, Disease Symptoms, Side Effects of Treatment, and Health Utility). **Results:** Questionnaire compliance was high (≥ 84%) at Cycle 1, 3 and 6 mos across treatment arms. At 12 and 18 mos, the compliance rates were lower in the MPT arm than the Rd arms, 81% vs. 91% and 67% vs. 89% respectively ($P \leq 0.002$). Statistically significant ($P \leq 0.05$) improvement from baseline in HRQOL scores was observed in all treatment arms, in 6 out of the 7 domains at most time-points. For the Side Effects domain, treatment with MPT showed a consistent and significant worsening from baseline at all the assessments. In addition Side Effects for MPT had a significantly worse score than continuous Rd at Cycle 1, 3 and 12 mos ($P \leq 0.05$). Progressive disease (PD) was associated with worsening in HRQOL scores for all domains across all 3 treatment groups ($P < 0.001$). **Conclusions:** In NDMM transplant ineligible pts, continuous Rd treatment resulted in improved PFS and OS thus improving clinically relevant HRQOL measurements over the course of treatment and better QOL related to treatment side effects than MPT. HRQOL improved with treatment and was generally maintained while subjects were progression-free. PD was associated with worsening HRQOL across evaluated domains. MPT therapy was perceived as having worse Treatment Side Effects as compared to Rd. Clinical trial information: 00689936.

**8517 Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

**Survival benefit and cost of autologous hematopoietic stem cell transplantation (Auto HSCT) in elderly patients with multiple myeloma (MM) using the SEER-Medicare database.** *Presenting Author: Gunjan L. Shah, Division of Hematology/Oncology Tufts Medical Center, Boston, MA*

**Background:** Medicare coverage for Auto HSCT for MM began in 10/2000. By 2009, MM was the leading indication for this treatment (CIBMTR, 2011). The survival benefit and cost implications of the rise in Auto HSCT are not well described in this population. Using SEER-Medicare data, we explored these implications for MM patients (pts) age 66+ by comparing them with pts not undergoing Auto HSCT. **Methods:** We used auto HSCT-specific ICD-9 or HCPCS codes to identify pts as having an Auto HSCT. We restricted the sample to pts age 66+ at time of MM diagnosis and used propensity score matching to create a cohort not receiving Auto HSCT. We calculated costs and survival for the first 100 days (d), year (yr), 3 yrs, and 5 yrs post-diagnosis using Kaplan-Meier curves stratified by patients receiving a transplant. We inflation-adjusted cost data to 2009 US dollars, using the medical care component of the Consumer Price Index. Patients were followed for up to 9 years. **Results:** We identified 10,832 pts diagnosed with MM from 1/2000 to 1/2008. Of these, 267 received Auto HSCT. We created a matched "control" sample of 267 pts not having Auto HSCT (c-statistic 0.83). The samples had a median age at diagnosis of 69.8 yrs, with 60% males and 90% Caucasians. The Charleson comorbidity index (CCI) was 0 for 62% of the Auto HSCT and 67% of the control pts (p=0.52), with the rest having a CCI of 1+. Median time to transplant was 250d. Median survival increased from 822 to 1,705 days with Auto HSCT (p=<0.001). Overall survival (OS) with Auto HSCT was higher at all time points: 99 vs 87% at 100d (p=<0.001); 95 vs 71% at 1 yr (p=<0.001); 73 vs 45% at 3 yr (p=<0.001); and 48 vs 30% at 5 yr (p=<0.001). Mean cost post diagnosis was $301,000 vs 124,000 with a life year gain of 2 years with Auto HSCT. The incremental cost-effectiveness ratio was $88,500/life year. **Conclusions:** Auto HSCT significantly increases OS in elderly patients with MM. While the cost of treating the transplanted patients was higher, the incremental cost effectiveness ratio is below the commonly accepted threshold for cancer treatment. Components of cost will be presented to describe the impact of novel agents.

**8518 Clinical Science Symposium, Sat, 1:15 PM-2:45 PM**

**A phase 1 dose-escalation study of the oral selective inhibitor of nuclear export (SINE) KPT-330 (selinexor) in patients (pts) with heavily pretreated non-Hodgkin lymphoma (NHL).** *Presenting Author: Martin Gutierrez, John Theurer Cancer Center, Hackensack, NJ*

**Background:** KPT-330 (Selinexor) is a SINE XPO1 antagonist that forces nuclear retention and activation of >10 tumor suppressor proteins (TSP) and associated with reduction in c-myc and Bcl-$X_L$. Anti-NHL activity was observed in murine models and in spontaneous canine aggressive lymphomas. **Methods:** Oral KPT-330 was given at 8-10 doses / 28-day cycle. XPO1 inhibition leads to rapid elevations in XPO1 mRNA, representing a pharmacodynamic (PDn) marker for KPT-330. Tumor biopsies were performed. Response evaluation was done in cycles 1, 2, and every 2 cycles. All pts had heavily pretreated NHL with progressive disease (PD) on study entry. **Results:** Thirty-two pts (18 M, 14 F; median age 68 yrs; ECOG PS 0/1: 9/23; median prior regimens: 3 range 1-11) received KPT-330 across 8 dose levels (3 to 60 mg/m$^2$). Dosing at 60 mg/m$^2$ twice weekly (BIW) is ongoing and MTD has not been reached. Cycle 1 (DLT period) Grade 3/4 events in >1 pt included thrombocytopenia (20%) and neutropenia (20%). The most common grade 1/2 AEs in cycle 1: anorexia (53%), nausea (50%), fatigue (50%), and vomiting (43%). Supportive care with appetite stimulants and anti-emetics diminished constitutional symptoms. Increases in XPO1 mRNA levels were observed at 4-48 hours, supporting BIW dosing. Tumor biopsies confirmed TSP nuclear localization, c-myc reduction, and apoptosis. Objective responses were observed in all histologies of NHL (Table). 5/16 pts have remained on therapy for an average of 9 months (>5-17) months without clinically significant toxicities. **Conclusions:** KPT-330 is generally well tolerated and can be administered over prolonged periods. The recommended phase 2 dose is ≥45 mg/m$^2$BIW. Durable single agent activity was observed in heavily pretreated NHL pts, and phase 2 studies in DLBCL and Richter's Syndrome are planned. Clinical trial information: NCT01607892.

**Response in 28 evaluable pts.**

| NHL | N | PR+SD (%) | PR (%) | SD (%) [%Change in LN Size] | PD |
|---|---|---|---|---|---|
| Follicular (FL) | 6 | 6 (100%) | 1 (17%) | 5 (83%) [-17% to -44%] | – |
| Mantle Cell | 2 | 2 (100%) | 1 (50%) | 1 (50%) [-36%] | – |
| DLBCL | 14 | 9 (64%) | 3 (21%) | 6 (43%) [-12% to -19%] | 5 (36%) |
| Transformed FL | 3 | 1 (33%) | 1 (33%) | – | 2 (67%) |
| Richter's | 3 | 3 (100%) | 1 (33%) | 2 (67%) [-22%] | – |
| Total | 28 | 21 (75%) | 7 (25%) | 14 (50%) | 7 (25%) |

**8519 Clinical Science Symposium, Sat, 1:15 PM-2:45 PM**

**Preliminary results of a phase II randomized study (ROMULUS) of polatuzumab vedotin (PoV) or pinatuzumab vedotin (PiV) plus rituximab (RTX) in patients (Pts) with relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL).** *Presenting Author: Franck Morschhauser, CHU Lille, Lille, France*

**Background:** PoV and PiV, antibody drug conjugates (ADC) containing the anti-mitotic MMAE targeting CD79b (PoV) and CD22 (PiV), showed clinical activity in Phase I. The current study aims to compare PoV and PiV + RTX in R/R DLBCL and R/R follicular lymphoma (FL). **Methods:** Pts were randomized to receive PoV or PiV + RTX (ADC 2.4 mg/kg + RTX 375 mg/m$^2$) every 21 days. Tumor assessments were performed every 3 months. **Results:** As of 8 November 2013, 58 received PoV + RTX (38 DLBCL; 20 FL), 63 PiV + RTX (42 DLBCL; 21 FL). Median prior therapies [DLBCL, 3 (1-10); FL, 2 (1-8)] were balanced between treatment arms; 46% were RTX refractory. Median treatment (tx) cycles in DLBCL: 5 for both ADC (1-15); FL: 8.5 PoV (3-15) and 6 PiV (1-13). Overall safety profiles of both regimens were similar. Tx-emergent adverse events (AE) >25%: fatigue (52%), diarrhea (42%), nausea (37%), peripheral neuropathy (PN) (32%), constipation (26%). Grade ≥ 3 AE >3%: neutropenia (21%), diarrhea (6%), dyspnea (4%), febrile neutropenia (4%), hyperglycemia (4%) and PN (4%). Serious AE reported in 36%. Thirty-eight discontinued tx for AE after median 5 doses (range 1-14), including 16 for PN. Tx delays and ADC dose reductions reported in 27% and 22%. Two of 7 deaths (sepsis, urosepsis) unrelated to NHL were attributed to PiV. Complete (CR) and partial (PR) responses, n (%) [% 95% CI] (see Table). **Conclusions:** PoV and PiV + RTX were generally well-tolerated with similar toxicity. Neutropenia, PN and diarrhea were principal toxicities. Similar efficacy was observed with both ADCs in heavily pretreated pts with DLBCL. The higher CR rate with PoV + RTX suggests greater clinical activity in R/R FL. Combination studies of R + PoV with chemotherapy and with ADC schedules to reduce PN are ongoing or in planning. Clinical trial information: NCT01691898.

| | PoV (CD79b) + RTX | PiV (CD22) + RTX |
|---|---|---|
| R/R DLBCL | N = 37 | N = 37 |
| ORR | 19 (51%) [34, 68] | 20 (54%) [37, 71] |
| CR | 5 (14%) [5, 29] | 7 (19%) [8, 35] |
| PR | 14 (38%) [23, 55] | 13 (35%) [20, 53] |
| R/R FL | N = 20 | N = 21 |
| ORR | 12 (60%) [36, 81] | 14 (67%) [43, 85] |
| CR | 6 (30%) [12, 54] | 1 (5%) [0.1, 24] |
| PR | 6 (30%) [12, 54] | 13 (62%) [38, 82] |

Pharmacokinetic profiles were similar for both ADCs across DLBCL and FL with no free MMAE accumulation.

**8520 Clinical Science Symposium, Sat, 1:15 PM-2:45 PM**

**Effect of lenalidomide combined with R-CHOP (R2CHOP) on negative prognostic impact of nongerminal center (non-GCB) phenotype in newly diagnosed diffuse large B-cell lymphoma: A phase 2 study.** *Presenting Author: Grzegorz S. Nowakowski, Mayo Clinic, Rochester, MN*

**Background:** The non-germinal center B-cell like (non-GCB) subtype of diffuse large cell lymphoma (DLBCL) is associated with a worse outcome when treated with RCHOP chemotherapy. Lenalidomide has significant single-agent activity in relapsed DLBCL and might be particularly active in non-GCB DLBCL. We have previously reported that lenalidomide can safely be combined with RCHOP (R2CHOP). This phase 2 study evaluated the efficacy of this combination in newly diagnosed DLBCL and analyzed the outcomes based on DLBCL subtype. **Methods:** Eligible patients were adults with newly diagnosed, untreated, stages II-IV CD20 positive DLBCL. Patients received oral lenalidomide 25 mg days 1-10 with standard dose R-CHOP every 21 days for 6 cycles. All patients received pegfilgrastim on day 2 of each cycle and aspirin prophylaxis throughout. DLBCL molecular subtype was determined by tumor immunohistochemistry (Hans algorithm) and classified as germinal center B-cell (GCB) vs non-GCB in the R2CHOP patients and 87 control DLBCL patients from the Mayo Clinic Lymphoma Database meeting the same inclusion criteria and treated with conventional RCHOP. **Results:** 64 DLBCL patients were enrolled. Median age was 65 years (22-87) and 34 patients (53%) had IPI intermediate-high or high. 60 were evaluable for response. The overall response rate was 98% (59/60) with 80% (48/60) complete response (CR). 24 month EFS and OS rates (95% CI) were 59% (48%-74%) and 78% (68-90%), respectively. In RCHOP patients, 24 months PFS and OS were 28% vs 64%, p<0.001 and 46% vs 78% p<0.001 in non-GCB patients vs GCB patients respectively. In contrast, there was no difference in 24 months PFS or OS for R2CHOP treated patients based on non-GCB and GCB subtype, 60% vs. 0.59%, p= 0.83 and 83% vs. 75%, p=0.61 at 2 years respectively. **Conclusions:** R2CHOP shows promising efficacy in DLBCL. The addition of lenalidomide to RCHOP appears to mitigate the negative impact of non-GCB phenotype on the outcome. A randomized phase 2 study of RCHOP vs. R2CHOP utilizing gene expression profiling classification of DLBCL subtype and led by the Eastern Cooperative Oncology Group (E1412) is currently ongoing. Clinical trial information: NCT00670358.

**8521 Poster Highlights Session (Board #1), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**CALGB 50803 (Alliance): A phase II trial of lenalidomide plus rituximab in patients with previously untreated follicular lymphoma.** *Presenting Author: Peter Martin, Weill Cornell Medical College, New York, NY*

**Background:** The CALGB 50401 randomized phase II trial demonstrated the safety and efficacy of lenalidomide plus rituximab in (pts) with previously treated follicular lymphoma (FL). CALGB 50803 was a multicenter phase II trial of lenalidomide plus rituximab in pts with previously untreated FL. **Methods:** Pts with grade 1-3a FL, stage 3-4 or bulky stage 2 (> 7 cm), FLIPI 0-2, and no prior systemic therapy were eligible to receive rituximab 375 mg/m$^2$ weekly x 4 during cycle 1 and day 1 of cycles 4, 6, 8, and 10, plus lenalidomide 20 mg on days 1-21 for a total of twelve 28-day cycles. Restaging was performed on weeks 10, 24, and 52, then q4 months for 2 years, and q6 months until progression for up to 10 years. The primary objective was to evaluate complete response (CR) rate based on 2007 IWG criteria. **Results:** From October 2010 to September 2011, 65 subjects were enrolled. Median age was 53 years; 34 were female; 14 had bulky disease; 20 were FLIPI 0-1, 41 FLIPI 2, 2 FLIPI 3; and 2 had insufficient data. Fifty pts completed 12 cycles of lenalidomide. Reasons for discontinuation included refusal/withdrawal (N=6), adverse events (N=4), progression (N=2), and extended treatment delay (N=1). Grade 3-4 hematologic toxicity included neutropenia (19%), lymphopenia (8%), and thrombocytopenia (2%). Febrile neutropenia occurred in 1 pt. Grade 3-4 non-hematologic toxicity occurring in at least 2 pts included rash (8%), infection (8%), pain (8%), fatigue (6%), tumor lysis (3%). The overall RR in evaluable subjects was 93% (53/57); the CR rate was 72%. There was no significant association between CR rate and FLIPI risk, histological grade, or bulky disease. The median time to CR was 10 weeks and 92% of PET-negative CRs occurred by 24 weeks. With a median follow-up of 2.3 years, the 2-year PFS is 89%. **Conclusions:** Lenalidomide plus rituximab was well tolerated and effective in pts with untreated FL. These data are similar to those reported with chemotherapy-based therapy and support evaluation of this regimen in randomized trials. Clinical trial information: NCT01145495.

**8522 Poster Highlights Session (Board #2), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Phase I study of ABT-199 (GDC-0199) in patients with relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL): Responses observed in diffuse large B-cell (DLBCL) and follicular lymphoma (FL) at higher cohort doses.** *Presenting Author: Matthew Steven Davids, Dana-Farber Cancer Institute, Boston, MA*

**Background**: The anti-apoptotic protein Bcl-2 is a highly expressed in NHL and contributes to chemotherapy resistance. ABT-199 is a selective, orally bioavailable, small molecule Bcl-2 inhibitor that is a promising agent for the treatment of patients (pts) with NHL. **Methods:** Objectives of this Phase I, dose-escalation study include evaluations of safety, pharmacokinetics (PK), and preliminary efficacy in pts with R/R NHL. ABT-199 was given on Week 1 Day -7 (W1D-7), followed by continuous, once-daily dosing from W1D1 until progressive disease or unacceptable toxicity. A 2 to 3 week lead-in period with stepwise dose titration was implemented. Final cohort doses of 200 - 900 mg have been evaluated. **Results:** As of December 4, 2013, 44 pts have been enrolled, 15 (35%) with mantle cell lymphoma (MCL), 11 (26%) with FL, 10 (23%) with DLBCL, 4 (9%) with Waldenström macroglobulinemia (WM), 2 (5%) with marginal zone (MZL), 1 (2%) with primary mediastinal B-cell lymphoma (PMBCL), and 1 (2%) with multiple myeloma (MM). The most common AEs (≥20% of pts) were nausea (34%), upper respiratory tract infection (27%), diarrhea (25%), and fatigue (21%). Grade (G) 3/4 AEs occurring in >3 pts were anemia (14%), neutropenia (11%), and thrombocytopenia (9%). G 3/4 thrombocytopenia was not dose-dependent or dose-limiting. Two of 10 pts in cohort 5 experienced a DLT (G3 febrile neutropenia and G4 neutropenia) at the target dose of 600 mg. G3 laboratory tumor lysis syndrome was seen after the initial dose in 1 pt with bulky MCL (elevations in phosphate and potassium only) and 1 pt with DLBCL (elevations in phosphate and uric acid only). For the 40 pts evaluable for efficacy, the overall response rate was 48%, 9/12 MCL (1 CR); 3/11 FL; 3/9 DLBCL (1 CR); 3/4 WM (1 CR); 1/2 MZL; 0/1 PMBCL; 0/1 MM. All responses in DLBCL and FL pts were observed at doses ≥600 mg; 3/8 DLBCL (38%) and 3/6 FL (50%). **Conclusions:** ABT-199 monotherapy showed anti-tumor activity across the range of ABT-199 cohort doses for several NHL subtypes, most notably in MCL and WM. In DLBCL and FL, responses were observed at higher doses. Dose escalation is continuing to determine the MTD and RP2D. Clinical trial information: NCT01328626.

**8523 Poster Highlights Session (Board #3), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**U.S. Intergroup phase II trial (SWOG 1108) of alisertib, an investigational aurora A kinase (AAK) inhibitor, in patients with peripheral T-cell lymphoma (PTCL; NCT01466881).** *Presenting Author: Paul M. Barr, James P. Wilmot Cancer Center, University of Rochester Medical Center, Rochester, NY*

**Background:** AAK is a serine/threonine kinase that regulates the G2-M transition and centrosome separation during mitosis. Alisertib (MLN8237) is an oral AAK inhibitor active in aggressive lymphoma, with 4 of 8 T cell lymphoma pts responding in a phase II trial (Friedberg JCO 2013). This phase II study was conducted to further investigate the efficacy of alisertib in PTCL. **Methods:** Eligible pts with histologically confirmed relapsed/refractory PTCL had normal organ function, ANC ≥1500/mm$^3$ and platelets ≥75,000/mm$^3$. Pts received alisertib 50mg BID for 7d on 21d cycles. Tumors were evaluated for expression levels of AAK, ABK, Myc, Bcl2, PI3Kδ, and Notch1 and quantified by image analysis. **Results:** Of 42 pts accrued, 37 eligible pts had a median age of 62 (range 22-86). Histologies included PTCL not otherwise specified (NOS)(13), angioimmunoblastic (AITL)(9), transformed mycosis fungoides (MF) (7), adult T-cell lymphoma (ATLL) (4), anaplastic large cell (ALCL) (2) and extranodal NK/T-cell (NK/T) (2). With a median number of 3 (range 1-18) prior therapies, 3 pts had undergone a prior stem cell transplant and 20 were refractory to prior therapy. Grade 3 and 4 AEs in ≥ 5% of pts included neutropenia (30%), anemia (27%), thrombocytopenia (24%), febrile neutropenia (14%), mucositis (11%) and rash (5%). 6 pts discontinued therapy and 9 were dose reduced due to AEs. Treatment was discontinued most commonly for PTCL progression. 2 complete responses and 7 partial responses were observed for a response rate (ORR) of 24% (95%CI: 12-41%). Among the most common subtypes, (PTCL NOS, AITL and ALCL), the ORR was 33% (95%CI: 16-55%). Of 27 pts with available biopsies, 0 and 6 expressed AAK and ABK respectively. **Conclusions:** Alisertib has antitumor activity in PTCL, including heavily pretreated pts. Toxicities to date were manageable and reversible. An international randomized phase III trial is comparing alisertib to investigator's choice in PTCL. Support: NIH/NCI Cooperative Group Grants CA32102 and CA38926; CA21115; CA21946; and Takeda Pharmaceuticals. Clinical trial information: NCT01466881.

| Histology | PTCL NOS | AITL | Transformed MF | ATLL | ALCL | NK/T |
|---|---|---|---|---|---|---|
| N | 13 | 9 | 7 | 4 | 2 | 2 |
| CR/PR | 1/3 | 0/3 | 0/0 | 1/0 | 0/1 | 0/0 |
| SD | 1 | 2 | 2 | 0 | 1 | 1 |
| PD | 8 | 4 | 5 | 3 | 0 | 1 |

**8524 Poster Highlights Session (Board #4), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**A phase I trial of ublituximab (TG-1101), a novel glycoengineered anti-CD20 monoclonal antibody (mAb) in B-cell non-Hodgkin lymphoma patients with prior exposure to rituximab.** *Presenting Author: Owen A. O'Connor, Columbia University Medical Center/New York Presbyterian Hospital, New York, NY*

**Background:** Ublituximab (UTX) is a novel mAb targeting a unique epitope on the CD20 antigen, glycoengineered for greater ADCC than rituximab (RTX). A prior Phase I/Ib trial with UTX monotherapy in patients (pts) with relapsed/refractory (R/R) CLL reported an ORR of 45%. Herein we report the results of a Phase I/Ib trial of UTX in pts with RTX R/R B-cell lymphoma (BCL). **Methods:** Eligible pts have R/R BCL that was previously treated with RTX containing regimens, with ECOG PS < 3. 3+3 dose-escalation evaluated cohorts of 450, 600, 900, and 1200 mg. Select expansion cohorts have included R/R NHL and CLL pts. UTX is administered weekly x 4 doses in Cycle 1 for NHL pts and on days 1, 8, 15 in Cycles 1 & 2 for CLL pts (cycle = 28 days), with maintenance for all pts. Primary endpoints: Maximum Tolerated Dose (MTD) and Dose Limiting Toxicities (DLT). Secondary endpoints: PK/PD and Efficacy. **Results:** 32 pts were enrolled. 17 M/15 F with: Median age 68 yr (range 45-88); ECOG 0/1/2: 12/18/2; Median prior Tx = 3 (range 1-9); 72% with > 2 prior RTX therapies; and 41% were RTX refractory. No DLTs have been observed. Gr 3/4 AE's at least possibly related to UTX have been reported in 6/32 pts (19%) and include: neutropenia, anemia, weakness, and fatigue. Infusion related reactions requiring interruption occurred in 8/32 pts (25%); however, all pts received all planned infusions with an ave infusion time of ~90 min for dose 4 and later. PK/PD analysis is ongoing. As of Jan 2014, 29/32 pts are evaluable for response (Table). Median ALC depletion in CLL pts was 93% after 2 UTX infusions. Median PFS for all pts is 34 weeks (95% CI: 19, NA) with no observed progression in 16/29 pts (range 4 - 18 mo). **Conclusions:** Single agent UTX is well tolerated and active in RTX exposed patients. Responses were observed in 67% of CLL and 67% MZL pts with median PFS not reached for each group. 86% of pts achieved at least SD, including 100% of CLL, MZL and DLBCL pts. Studies are ongoing with UTX in combination with novel targeted agents (PI3K-δ and BTK inhibitors). Clinical trial information: NCT01647971.

| Type | Pts (n) | CR (n) | PR (n) | ORR (%) | PD (n) | % pts > SD for 12 wks |
|---|---|---|---|---|---|---|
| FL | 11 | 1 | 2 | 27% | 2 | 82% |
| CLL | 6 | - | 4 | 67% | - | 100% |
| MZL | 6 | 2 | 2 | 67% | - | 100% |
| MCL | 5 | - | - | - | 2 | 60% |
| DLBCL | 1 | - | 1 | 100% | - | 100% |
| Total | 29 | 4 | 8 | 41% | 4 | 86% |

**8525 Poster Highlights Session (Board #5), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**A phase 1b study in cutaneous T-cell lymphoma (CTCL) with the novel topically applied skin-restricted histone deacteylase inhibitor (HDAC-i) SHP-141.** *Presenting Author: Youn H. Kim, Stanford Cancer Institute, Stanford, CA*

**Background:** The efficacy of HDAC-i as systemic therapy in CTCL is well-established although adverse effects limit use. The topical hydroxamic acid HDAC-i SHP-141 is intentionally designed to maximize activity in skin but limit systemic exposure by rendering the drug inactive via endogenous serum esterases. **Methods:** A phase 1b multi-center, double-blind, placebo (PBO)-controlled, randomized trial in stage IA-IIA CTCL was conducted in the USA to assess safety, pharmacokinetic (PK), pharmacodynamic, and preliminary efficacy with SHP-141 applied twice daily to index lesions (maximum 5% BSA) for 28 days; last assessment was 42 days after start of drug. Eighteen patients were enrolled: 6 patients (5 SHP-141:1 PBO) at each escalating dose level (0.1%, 0.5%, 1.0%). In SHP-141 arms there were 3 patients with stage IA, 11 IB, and 1 IIA; PBO arm with 2 stage IA and 1 IB. **Results:** No DLTs, early discontinuations, serious adverse events (AEs) or systemic AEs were recorded; SHP-141 related events were predominantly CTCAE Grade 1 and limited to skin (Skin, SHP-141: 4/15, PBO: 1/3; 1 CTCAE Grade 2 dermatitis in SHP-141). Only SHP-141 patients had clinical objective response (OR; >50% improvement by CAILS) and incremental weekly CAILS improvement through dosing period (see Table). Time to OR occured as early as Day 7; 2 others at Day 21 with the last at Day 42. Based on CAILS subscore a significant reduction in lesion thickness for SHP-141 groups was measured. Skin biopsy histology confirmed increased dermal actetylation by staining with a specific acetyl–lysine antibody. PK results confirmed lack of SHP-141 peripheral blood exposure. **Conclusions:** This is the first skin-optimized topical HDAC-i with evidence of early clinical activity and without systemic HDAC-i related toxicity. Patients responded after few weeks of treatment; rapidity is not a typical feature of approved topical drugs for CTCL. SHP-141 may address an important unmet medical need in early stage CTCL by feasibly offering clinical benefits of a HDAC-i without safety concerns. Clinical trial information: NCT01433731.

| | SHP-141 | Placebo |
|---|---|---|
| Objective response at day 42 | 4(28%) | 0 |
| Reduction in thickened lesions at day 42 | 89% | 0% |
| Incremental improvement to day 28 | 6(40%) | 0 |

**8526 Poster Highlights Session (Board #6), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Preliminary findings from a phase I, multicenter, open-label study of the anti-CD37 antibody-drug conjugate (ADC), IMGN529, in adult patients with relapsed or refractory non-Hodgkin lymphoma (NHL).** *Presenting Author: Anastasios Stathis, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland*

**Background:** IMGN529 is a CD37-targeting ADC comprising a CD37-binding antibody conjugated to the maytansinoid anti-mitotic, DM1. CD37 is present on the surface of normal and malignant B lymphocytes. In preclinical studies, IMGN529 exhibits potent antitumor activity against NHL cells via direct inhibition, effector function and delivery of the maytansinoid payload. **Methods:** Study objectives are: determine the maximum tolerated dose/recommended phase 2 dose of IMGN529 in adult patients (pts) with relapsed or refractory NHL, and evaluate safety, pharmacokinetics, pharmacodynamics, and evidence of preliminary efficacy. IMGN529 is given intravenously on Day (d) 1 of each 21d cycle (C). **Results:** To date, 22 pts have been enrolled across four dose levels ranging from 0.1 to 0.8 mg/kg. NHL subtypes enrolled: 10 Follicular lymphoma (FL), 7 Diffuse large B-cell (DLBCL), 5 other. A reduction in lymphocyte count seen early after dosing (d 2) in the majority of pts suggests a CD37-mediated reduction in lymphocytes. One pt with DLBCL treated at 0.4 mg/kg, and 1 pt with FL treated at 0.2 mg/kg achieved partial remission in C 3 and C 5 respectively. Dose limiting toxicities (DLTs) consisted of grade (G) 4 neutropenia > 7 days (1pt) and G2 peripheral neuropathy (1pt) at 0.8 mg/kg and G3 febrile neutropenia (2 pts) at 0.4 mg/kg. Adverse events (AEs) of G3 or higher occurred in 8 pts; those reported in more than 1 pt were: neutropenia (5 pts) and febrile neutropenia (2pts). Four of these pts experienced transient, early onset (C1d2-4) G3 neutropenia which may be a manifestation of cytokine release. The protocol was amended to provide peri-infusional steroids as a prophylactic regimen and dose re-escalation is ongoing; 3 patients treated at 0.4 mg/kg have completed C 1 with no DLTs. Clinical trial enrollment is ongoing with additional data expected. Preclinical studies to investigate the mechanism of the transient neutropenia are underway. **Conclusions:** IMGN529, a CD37-targeting ADC, has demonstrated early evidence of clinical activity and has the potential to be a novel therapeutic for B-cell lymphoproliferative malignancies. Clinical trial information: 01534715.

**8527 Poster Highlights Session (Board #7), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**G-PCNSL-SG-1 randomized phase III trial of high-dose methotrexate with or without whole brain radiotherapy for primary central nervous system lymphoma: Long-term follow-up.** *Presenting Author: Agnieszka Korfel, Department of Hematology and Oncology, Charité Campus Benjamin Franklin and Mitte, Berlin, Germany*

**Background:** The role of whole brain radiotherapy (WBRT) in first-line therapy of primary CNS lymphoma (PCNSL) has been increasingly questioned. This is the final report of the G-PCNSL-SG-1 trial evaluating WBRT in primary therapy of PCNSL after a median follow-up (MFU) of 81.2 months. **Methods:** G-PCNSL-SG-1 (www.clinicaltrials.gov NCT00153530) had randomised immunocompetent patients with newly diagnosed PCNSL to high-dose methotrexate (HDMTX) - based chemotherapy (CHT) followed by WBRT or CHT alone. We hypothesized that the omission of WBRT from first-line treatment would not compromise overall survival (OS; primary endpoint), using a non-inferiority design with a margin of 0.9. **Results:** Of 551 patients who entered the study 524 fulfilled the eligibility criteria (primary eligibility population), 410 entered the post-HDMTX phase (intention-to-treat, ITT population), and 320 were treated per protocol (PP). OS with *versus* without WBRT was different neither in the ITT (HR 0.997, 95%CI 0.79-1.26, p=0.98) nor in the PP population (HR 1.03, 95%CI 0.79-1.35, p=0.82). In the ITT population CR patients experienced neither a progression-free survival (PFS) benefit from the last HDMTX-based CHT (PFS-2) (HR 0.84, 95% CI 0.60-1.19, p=0.33) nor an OS benefit (HR 1.13, 95% CI 0.77-1.66, p=0.53) with WBRT. In CR patients of the PP population, WBRT conferred a benefit for PFS-2 (HR 0.68, 95%CI 0.46-1.01, p=0.059), but no OS benefit (HR 1.06, 95%CI 0.69-1.63, p=0.78). In non-CR patients of the ITT population, a benefit of PFS-2 (HR 0.58, 95%CI 0.44-0.77, p<0.001), but not of OS (HR 0.86, 95%CI 0.64-1.16 p=0.32) was found with WBRT; in non-CR patients of the PP population, WBRT conferred a benefit of PFS-2 over CHT alone (HR 0.41, 95%CI 0.29-0.57, p<0.001) and a trend for OS, too (HR 0.76, 95%CI 0.54-1.08, p=0.12). **Conclusions:** Despite improvement in PFS, particularly in patients without CR to HDMTX-based CHT, no significant difference in OS was found when WBRT was omitted from primary therapy in this long-term follow-up. The PFS afforded by WBRT has to be balanced against its long-term toxicity. Clinical trial information: NCT00153530.

**8528 Poster Highlights Session (Board #8), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**10-year remission rates following rituximab (R) and FND chemotherapy (fludarabine, mitoxantrone, dexamethasone) with interferon (IFN) maintenance in indolent lymphoma: Results of a randomized study.** *Presenting Author: Loretta J. Nastoupil, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Between 1997-2002, we conducted a randomized trial for patients (pts) with previously untreated stage IV small lymphocytic (SLL), marginal zone (MZL), or follicular lymphoma (FL), with the primary aim to compare concurrent FND+R versus sequential FND followed by R. This is the final analysis with mature data. **Methods:** Patients were randomized to 6 doses of R given during the first 5 of 8 courses of FND, or monthly during IFN maintenance following FND. We now report response rates, progression free survival (PFS), overall survival (OS), and adverse events (AE) including secondary malignancy with nearly 12 years of follow up. **Results:** Of the 157 pts, 18% had SLL, 11% MZL, and the remaining 71% had FL. 80 pts received concurrent FND+R, 77 sequential. Pts on the 2 arms were comparable in terms of prognostic features (FLIPI components). Median age for all pts was 54 years, 54% were female, 90% had bone marrow involvement, 80% had intermediate or high FLIPI score, 68% had high tumor burden. With a median follow up of 11.8 years, response rates, PFS, and OS were similar between the two groups and are included in the table below. Most AEs were hematologic, grade ≥3 neutropenia in 76%, thrombocytopenia 24%, and anemia in 13%. There was slightly more neutropenia with FND+R, but no excess infection or neutropenic fever. Non-hematologic AEs were mostly grade 1/2: 46% fatigue, 33% nausea, 31% alopecia, 18% neuropathy, and 18% infection (8% grade ≥3 infection). Six pts (4%) developed MDS/AML. **Conclusions:** With mature data, this large frontline study of FND with either concurrent or sequential R, and IFN maintenance in advanced stage indolent lymphoma demonstrated high complete response rates, robust PFS and OS. Determining the curative potential for this highly effective therapy will require further follow up. Concerns about tolerability and the incidence of secondary malignancy may impact treatment decisions. Clinical trial information: NCT00577993.

| | All patients N=157 | FND+R N=80 | FND->R N=77 |
|---|---|---|---|
| CR/CRu | 90% | 93% | 87% |
| 10-yr PFS estimates | 55% | 53% | 56% |
| Median OS | NR | NR | NR |
| 10-yr OS estimates | 76% | 74% | 78% |
| Events | 63 | 35 | 28 |

**8529 Poster Highlights Session (Board #9), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Randomized, phase 3 trial of inotuzumab ozogamicin plus rituximab (R-InO) versus chemotherapy for relapsed/refractory aggressive B-cell non-Hodgkin lymphoma (B-NHL).** *Presenting Author: Nam H. Dang, University of Florida, Gainesville, FL*

**Background:** InO is an anti-CD22 antibody conjugated to calicheamicin; R-InO has shown activity in pts with relapsed/refractory aggressive B-NHL in a phase 1/2 study (Fayad, *J Clin Oncol* 2013; 31, 573-583: ORR, 74% and 20% for relapsed and refractory pts, respectively). **Methods:** This randomized, phase 3 trial (NCT01232556) compared efficacy and safety of R-InO (R 375 mg/m$^2$ IV–day [d] 1; InO 1.8 mg/m$^2$ IV–d 2 [each cycle]; 28 d cycles) vs investigator's choice (IC: R-bendamustine [R-B: R 375 mg/m$^2$ IV–d 1, B 120 mg/m$^2$–d 1 and d 2 each cycle] or R-gemcitabine [R-G: R 375 mg/m$^2$ IV–d 1, 8, 15, 22 cycle 1, d 1 all other cycles; G 1000 mg/m$^2$–d 1, 8, 15 each cycle]) in adults with relapsed/refractory CD22+ aggressive B-NHL; not candidates for high-dose chemotherapy. Endpoints were OS (primary), PFS, ORR (CR + PR); safety. A planned interim analysis based on 108 events (~40% of planned OS events) was conducted in May, 2013 when enrollment was stopped for futility. We present preliminary results for all enrolled pts. **Results:** 338 pts were enrolled (age ≥65 y, 68%; DLBCL, 91%; sIPI [≥4], 24%; best prior response of progressive disease [PD], 28%; previous time-to-progression ≥12 mo, 32%). See Table for efficacy results. Most common AEs (R-InO vs IC): thrombocytopenia (59% vs 37%), neutropenia (32% vs 47%), nausea (29% vs 33%), fatigue (33% vs 25%), and leukopenia (21% vs 31%). 2 R-InO pts had venoocclusive disease (VOD) on study treatment (1 additional pt had VOD after an allotransplant and ~13 mo after 1 R-InO dose). Treatment-related death occurred in 6 pts (4 R-InO, 2 IC). Among R-InO vs IC pts, 28% vs 15% discontinued due to AEs; 53% vs 57% due to PD. **Conclusions:** Although R-InO activity was observed, there was no statistical difference in ORR, PFS, or OS between R-InO vs IC treated pts. R-InO was not superior to IC among subgroups analyzed to date (to be presented). Poorer outcomes in this phase 3 study vs the phase 1/2 study may reflect more refractory pts in this study. Clinical trial information: NCT01232556.

**Efficacy (95% CI).**

| | R-InO (n=166) | IC (n=172) |
|---|---|---|
| **ORR, %** | 41 (33.4–48.9) | 44 (36.6–51.9) |
| **CR** | 15 | 19 |
| **PR** | 26 | 26 |
| **Median, mo** | | |
| **DOR** | 11.6 (7.8–NR) | 6.9 (4.6–10.8) |
| **PFS** | 3.9 (2.9–5.0) | 3.6 (2.8–4.9) |
| **OS** | 8.6 (6.7–11.8) | 9.3 (7.5–13.9) |
| | HR = 1.13; p = 0.80 | |

**8530 Poster Highlights Session (Board #10), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Updated results of the FOLL05 phase III trial from the Fondazione Italiana Linfomi comparing R-CVP, R-CHOP, and R-FM in patients with advanced follicular lymphoma.** *Presenting Author: Stefano Luminari, Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy*

**Background:** The final results of FOLL05 for the initial therapy of advanced stage follicular lymphoma (FL) were recently reported with a median follow–up of 34 months. This trial showed that R–CHOP and R–FM were superior to R–CVP in terms of 3–year time to treatment failure (TTF), the primary study endpoint, and that R–CHOP had a better risk/benefit ratio compared with R–FM. Here, we present the 5–year follow–up analysis of progression free survival (PFS) of the 504 patients included in the study. **Methods:** Patients were 18–75 year old, with untreated stage II–IV FL, ECOG performance status of 0–2, and active disease according to the Italian Society of Hematology guidelines. They were randomly assigned to receive 8 doses of rituximab associated to 8 cycles of CVP, or 6 cycles of CHOP or FM. Maintenance was not admitted. **Results:** The median follow–up was 56 months (range 1–90). The overall 5–year TTF was 52% (95%CI, 47–56%). R–CHOP and R–FM had a better TTF compared to R–CVP (56% and 56% vs 43% at 5–years; p= 0.007 and p=0.017, respectively). Regarding PFS a total of 215 events were recorded, thus determining a 5–year PFS of 56% (95%CI, 52-61%). Compared to initial report 31 additional events for PFS were observed and were mainly represented by lymphoma relapses (80%). Better PFS rates were observed for R–CHOP and R–FM compared to R–CVP (62% and 60% vs 47% at 5–years). After adjustment by FLIPI, and using R–CVP as reference, HRs for PFS were 0.66 for R–CHOP (95%CI, 0.47–0.92; p=0.013), and 0.71 for R–FM (95%CI, 0.52–0.98; p=0.035); the HR between R–FM and R–CHOP was 1.08 (95%CI, 0.76–1.52; p=0.677). Considering additional events reported during the follow–up, 27 second malignancies were recorded in all treatment arms: four in R–CVP, 9 in R–CHOP and 14 in R–FM (p=0.062; R–CVP vs R–CHOP, p=0.169; R–CVP vs R–FM, p=0.018). Finally with 47 recorded deaths the 5–year overall survival rate was 91% (95%CI, 87–93%). **Conclusions:** The 5–year update of the FOLL05 study, with mature data on PFS, confirms that R–CHOP has the best efficacy profile compared to R–CVP and R–FM for the initial treatment of patients with advanced FL. Clinical trial information: NCT00774826.

**8531 Poster Highlights Session (Board #11), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Long-term results of the phase III GITMO/FIL trial of CHOP-R versus R-HDS plus autograft in high-risk follicular lymphoma (FL) at diagnosis.** *Presenting Author: Corrado Tarella, Hematology Univ. Div. and Cellular Therapy, A.O. Ordine Mauriziano-Umberto I, Torino, Italy*

**Background:** Early results of a randomized phase III GITMO/FIL study (www.clinicaltrials.gov NCT00435955) comparing CHOP-R vs. R-HDS + ASCT as primary treatment in134 FL pts, aged ≤60 yrs with aaIPI>1/IIL score>2, showed superior disease control with R-HDS but no OS advantage (Ladetto et al, Blood 2008). We here present an updated analysis from July 2013 at a median follow-up (MFU) of 9.5 yr including 125 pts of 134 originally randomized pts (61 CHOP-R/64 of R-HDS). **Methods:** Clinical features (CF) and treatment schedules have been already reported. Briefly, median age was 51 yrs. (22-60), M/F ratio 74/51, aaIPI 2-3 90%, retrospective FLIPI >2 60%, high LDH 49%, bulky disease 62%, B-symptoms 45%, BM+ 86%. CF were balanced among the two arms. Analysis was intention to treat and EFS the primary endpoint. Minimal residual disease was done by nested and RQ-PCR. **Results:** CR rate was 70.4% (57% with CHOP-R and 83% with R-HDS, p < .001); 64% patients achieved a Molecular Remission (MR). At MFU, 88 patients (70.4%) are alive. 19 pts died of lymphoma (CHOP-R:11; R-HDS: 8), 9 of second cancer (CHOP-R: 3; R-HDS: 6) and 9 for other causes, including 4 early toxic deaths. OS is 78% and 70% at 5 and 10 yrs, respectively. There was no difference in OS, with 5 and 10 yrs projections respectively of 75% and 70% for CHOP-R and 81% and 70% for R-HDS (p=0.96). Response to primary treatment had a major impact on OS, with 5 and 10 yr survival projections respectively of 90% and 80% for patients achieving CR, and of 49 and 43 for those with less than CR (p < .001). Similarly, MR achievement was associated with prolonged OS, with 5 and 10 yr survival projections respectively of 89% and 83% for patients achieving MR vs 76% and 57% for those remaining PCR-positive(p = .03). **Conclusions:** our results indicate that: i) 70% of high-risk FL now experiences a prolonged survival, being alive at 10 yrs; ii) the superior disease control of R-HDS does not translate in any OS advantage, iii) achieving CR and MR is crucial for long-term OS; iv) progression remains the major cause of death, though a major toll is paid to secondary neoplasms, particularly AML. Clinical trial information: NCT00435955.

**8532 Poster Highlights Session (Board #12), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**A phase I trial of SAR650984, a CD38 monoclonal antibody, in relapsed or refractory multiple myeloma.** *Presenting Author: Thomas G. Martin, University of San Francisco, San Francisco, CA*

**Background:** SAR650984 (SAR) is a naked humanized IgG1 monoclonal antibody that binds to the CD38 receptor. SAR kills tumor cells via ADCC, CDC, direct apoptosis without secondary crosslinking and allosteric inhibition on CD38 enzymatic activity. Data on relapsed /refractory multiple myeloma (RRMM) patients (pts) in the dose escalation phase of the study are reported. (NCT01084252). **Methods:** SAR was given IV weekly (QW) or every 2 weeks (Q2W). Dose levels (DL) 0.3, 1, 3, 5, 10 and 20 mg/kg Q2W and 10 mg/kg QW using the classic 3+3 design were evaluated. **Results:** 35 pts with RRMM were treated; median age 64 yrs (40-76); median lines of therapy were 6 (2-14), 34/35 received an IMiD and a proteasome inhibitor (57% had carfilzomib (C) and/or pomalidomide (P). MTD was not reached at any DL. Adverse events in ≥ 10% of pts at all DL, regardless of causality, were fatigue (48.6%), nausea (34.3%), pyrexia (28.6%), anemia (28.6%), cough (25.7%), headache (25.7%), upper respiratory infection and chills (22.9%), dyspnea (20%), constipation (17.1%), diarrhea and vomiting (14.3%) and bone pain, chest discomfort, muscle spasms, thrombocytopenia and hypokalemia in 11.4% of pts. SAR related ≥ G 3 adverse events included pneumonia (n = 3), with hyperglycemia, hypophosphatemia, pyrexia, apnea, fatigue, thrombocytopenia and lymphopenia in 1 pt each. Investigator assessment by EBMT response criteria (ORR ≥ PR) among 34 evaluable pts was 24% (CR n = 2, PR n = 6). Responses occurred at all DL ≥ 1 mg/kg. Clinical benefit response (≥ MR) was 29% with 41% SD. In the ≥10 mg/kg cohort ORR was 33% (n =6/18) and CBR was 39% (n =7/18). The time to response was 4.6 weeks and time on treatment was 9.9 weeks (2-81). 10 pts remain on treatment. The expansion cohort dose was selected based on efficacy, safety, and receptor occupancy data. **Conclusions:** The MTD of SAR was not reached. SAR demonstrates encouraging and durable single agent efficacy in heavily pretreated RRMM pts, including those with prior (C) and (P) and warrants further evaluation. Clinical trial information: NCT01084252.

| Response EBMT * | All DL (n=34) | DL ≥10mg/kg (n=18) |
|---|---|---|
| **ORR** | (8) 24% | (6) 33% |
| **CBR** | (10) 29% | (7) 39% |
| **PD** | (10) 29% | (4) 22% |
| **SD** | (14) 41% | (7)39% |
| **MR** | (2) 6% | (1) 5% |
| **PR** | (6) 18% | (4) 22% |
| **CR** | (2) 6% | (2) 11% |

*Investigator assessment of response as of Dec 31, 2013.

**8533 Poster Highlights Session (Board #13), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Safety and efficacy of daratumumab with lenalidomide and dexamethasone in relapsed or relapsed, refractory multiple myeloma.** *Presenting Author: Torben Plesner, Vejle Hospital, Vejle, Denmark*

**Background:** Daratumumab (DARA) (HuMax-CD38), a human IgG1κ monoclonal antibody effectively mediates destruction of CD38-expressing malignant plasma cells. In the first-in-human dose-escalation study, 42% of heavily pretreated patients with relapsed or relapsed, refractory (RR) multiple myeloma (MM) treated with DARA alone (≥4mg/kg) achieved partial response (PR) and 25% had minimal response (MR) (modified IMWG guidelines). In preclinical studies, DARA + lenalidomide (LEN) enhanced killing of MM cells in vitro.We evaluated safety, pharmacokinetics (PK) and efficacy of DARA + LEN + dexamethasone (DEX) in patients with relapsed or RR MM. **Methods:** In this ongoing phase I/II open-label multicenter dose-escalation (part 1) study, patients (≥ 18 years old) with life expectancy ≥3 months and ECOG status 0, 1 or 2 received DARA+LEN+DEX: (DARA [2-16 mg/kg] per week [8 wks], twice a month [16 wks], then, once monthly until disease progression, unmanageable toxicity or ≤24 months; LEN [25 mg]; DEX [40 mg] once weekly). Cohort expansion (part 2) study explores testing of maximum DARA dose determined in part 1. **Results:** Data from 12 patients (10 men, 2 women), median age 62 years (48-76) are evaluable to date. Median prior therapies: 4 (2-4); median ECOG status: 0.5 (0-1); median DARA infusions: 14.5 (1-23); median infusion time: 6.6 (5.9-7.3) hours. One patient (2 mg/kg dose) withdrew from study due to recurrent grade 1 QT prolongation and hypokalemia. Most frequent (>40% patients) adverse events were neutropenia and diarrhea; 17 were ≥ grade 3 with 70% hematological (neutropenia, thrombocytopenia, anemia). MTD was not reached. DARA+LEN+DEX PK-profile was similar to DARA alone suggesting LEN and DEX do not affect the DARA PK-profile. Available efficacy data from 11 patients demonstrated marked decrease in M-protein in all patients; 8/11 patients achieved PR or better, 5/11 with VGPR, 2/11 with MR. Median time to response was 4.1 weeks (2.1-4.3). **Conclusions:** DARA+LEN+DEX has favorable safety profile with manageable toxicities in relapsed and RR MM. Encouraging early activity is seen with marked reduction in M-protein and 8/11 patients (72%) achieving PR or better. Part 2 data will be presented. Clinical trial information: 2011-005709-62.

**8534 Poster Highlights Session (Board #14), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Preliminary safety and efficacy of TH-302, an investigational hypoxia-targeted drug, and dexamethasone (dex) in patients (pts) with relapsed/refractory multiple myeloma (RR MM).** *Presenting Author: Jacob Laubach, Dana-Farber Cancer Institute, Boston, MA*

**Background:** While alkylators, IMiDs and proteasome inhibitors are current standard treatment for pts with MM, the presence of hypoxia in the diseased bone marrow (Colla, *Leukemia* 2010) presents a new therapeutic target for MM. TH-302 is a novel 2-nitroimidazole prodrug of the DNA alkylator bromo-isophosphoramide mustard that is selectively activated under hypoxia. Synergistic induction of apoptosis in MM cells by TH-302 and bortezomib was shown in MM models *in vivo* and *in vitro* (Hu et al, *Mol Cancer Ther* 2013). An ongoing Phase 1/2 study investigates TH-302 with dex in RR MM. In the dose-escalation stage of the study, the maximum tolerated dose (MTD) of biweekly TH-302 was established at 340 mg/m$^2$ and preliminary activity was reported based on the modified IMWG guidelines (Ghobrial et al., ASH 2013). The 340 mg/m$^2$ plus dex expansion arm is ongoing. **Methods:** The Phase 1/2 open-label multicenter study investigates IV TH-302 (240-480 mg/m$^2$) plus PO dex (40 mg) on Days 1, 4, 8 and 11 of a 21-day cycle. At the MTD, a Simon two-stage minimax design was implemented to pursue a regimen with ≥25% response rate or discontinue if ≤5% (90% power, 10% alpha). **Results:** 16 pts (11 male, 5 female) were enrolled through completion of the initial stage of the Simon design, including 9 at the MTD. Median prior therapies was 6 (3 – 11) and median age 60 years (53 – 86). All had previously received both bortezomib and lenalidomide/thalidomide containing regimens and an alkylating agent. The most common ≥Gr 3 AEs were thrombocytopenia (44%) and leukopenia (38%). Dose limiting Gr 3 stomatitis was only reported in the 480 mg/m$^2$ cohort. 7 pts had SAEs, 6 of which were related to TH-302, including 3 pts with pneumonia. The pre-specified target for response for the initial 9-pt Simon stage at the MTD was achieved with 1 PR, 2 MRs, 4 SDs, 1 PD and 1 NA. To date, 15 of 24 pts have been enrolled to evaluate safety and efficacy at the MTD. **Conclusions:** TH-302 can be administered at 340 mg/m$^2$ biweekly with dex. Preliminary clinical activity has been noted in pts with heavily pre-treated RR MM. Data from pts in the Simon two-stage treated at the MTD will be updated and presented at the meeting. Clinical trial information: NCT01522872.

**8535^ Poster Highlights Session (Board #15), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**A phase I study of carfilzomib, lenalidomide, vorinostat, and dexamethasone (QUAD) in relapsed and/or refractory multiple myeloma (MM).** *Presenting Author: David H. Vesole, John Theurer Cancer Center, Hackensack, NJ*

**Background:** Carfilzomib in combination with an immunomodulatory agent has proven efficacy in NDMM and RRMM. There is also synergistic activity of the combination of a proteasome inhibitor and a histone-deacetylase inhibitor **Methods:** To determine the toxicity and activity of the quadruplet using carfilzomib with lenalidomide, vorinostat and dexamethasone. The primary objectives were to determine the maximum tolerated dose (MTD) and the safety/tolerability of QUAD. Secondary objectives included ORR, DOR, TTP and TTNT. All patients had relapsed or RRMM after at least one line of Tx. Tx consisted of 28-d cycles of lenalidomide d 1-21, vorinostat d 1-7 and 15-21, IV carfilzomib d 1, 2, 8, 9, 15 and 16 and IV/po dexamethasone 40 mg q wk. A standard 3+3 dose escalation schema to determine DLTs occurring in Cycle 1. AEs were graded using the NCI-CTCAE v3. Response was assessed by the modified IMWG criteria. **Results:** As of January 20, 2014, 21 pts have been enrolled: 1 patient was replaced due to inability to complete Cycle 1 due to AE. Pt characteristics included: median age 61 yrs (range 48-71), 57% male, median # of prior regimens: 3 (range 1-9), median time from Dx: 4 years. All pts had prior autotransplant, 20 bortezomib, 20 lenalidomide and 4 vorinostat. AEs were experienced by 100% of pts including: anemia (16), fatigue (11), thrombocytopenia (14), neutropenia (12), muscle cramping (10) and diarrhea (9). 15 pts experienced ≥ grade 3 AEs: neutropenia (9), anemia (7), thrombocytopenia (9), infection (2), electrolyte imbalances (2), hyperglycemia (3), fatigue (1) constipation (1) and 1 death from progressive disease (PD). No DLTs were observed. The ORR was 53% and the CBR was 82%. 2 patients had PD as best response. 9 pts discontinued due to PD, 1 pt choice and 1 pt due to toxicity. 3 pts have completed 18 cycles. **Conclusions:** QUAD is well tolerated in both relapsed and RRMM pts with no DLTs identified. The safety profile is manageable. The ORR of 53% and CBR of 82% are encouraging; the PFS is 12 months and OS not reached. Clinical trial information: NCT01297764.

| Cohort | Pts | Car | Len | Vor | Dex | ORR |
|---|---|---|---|---|---|---|
| 1 | 4 | 15 | 15 | 300 | 40 | 3 SD 1 NE |
| 2 | 3 | 20 | 15 | 300 | 40 | 3 PR |
| 3 | 3 | 20 | 25 | 300 | 40 | 1 VGPR 1 PR 1 SD |
| 4 | 4 | 20/27 | 25 | 300 | 40 | 1 VGPR 2 PR 1 PD |
| 5 | 3 | 20/27 | 25 | 400 | 40 | 1 PR 1 SD 1 PD |

**8536 Poster Highlights Session (Board #16), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Phase I trial of pomalidomide (P) in patients (pts) with relapsed and/or refractory (R/R) Waldenström's macroglobulinemia (WM).** *Presenting Author: Sheeba K. Thomas, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Thalidomide, and its analog, lenalidomide have shown activity in WM, when combined with rituximab. However, neuropathy and anemia respectively, have limited their use. P is a newer generation IMID® which has demonstrated efficacy and tolerability in R/R multiple myeloma. These results provided the rationale for a phase I study of P in pts with R/R WM. **Methods:** Eligible pts had WM that was R/R to ≥ 1 prior therapy. All pts received daily oral P (28d cycles), starting at a 1mg dose level. Following a 3+3 statistical design, the dose was increased by 1 mg increments until the MTD was reached. Overall response was assessed as per International WM Working Group Response Criteria. **Results:** Between 10/2010-01/2014, 9 pts (7 males, 2 females) were treated. Median age at enrollment was 64 yrs (range 51-85), median time from 1$^{st}$ therapy was 6.1 yrs (range 2.0-16.3), and median prior therapies was 2 (range 1-5). With a median f/u of 30 mos. (range: 6-36), 8 pts remain alive, and 1 continues to receive therapy. At 1 mg, no DLTs were seen, and pts received a median of 6 cycles (range: 4-12+). At 2 mg, 2 pts experienced DLTs, including dizziness (Gr 4) and syncope (Gr 3) in 1 pt and grade 4 neutropenia in 1 pt. A 3$^{rd}$pt withdrew after experiencing mild fever, headaches and blurred vision starting on day 4 of cycle 1. Fever and headache resolved with stopping P; blurred vision resolved after plasma exchange. Other grade 3-4 adverse events (AEs) included neutropenia (3 pts) and infection (knee joint, 1 pt). Gr 1-2 AEs include fatigue (6), rash (5), diarrhea (4), nausea/emesis (4), edema (3), myalgias (3), blurred vision (2), peripheral neuropathy (2), dyspnea (2), constipation (2), headache (2), dizziness (2), mucositis (1), infection [otitis media (1);URI –(3)], rash(1), pruritus (1), and night sweats (1). Among 8 evaluable pts, 2 had minor responses, 3 had stable disease (SD), and 3 had progressive disease as best response. **Conclusions:** The MTD of single agent P is 1 mg/day in pts with R/R WM. P provided ≥ SD in 63% of pts, suggesting that combinations with other effective agents should be studied. Abbreviated dosing schedules, such as d1-21 q28d may permit recovery of cytopenias between cycles, facilitating such combinations. Clinical trial information: NCT01198067.

**8537 Poster Highlights Session (Board #17), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Optimizing induction and pretransplant consolidation for myeloma: Results of Myeloma XI, a phase III trial comparing different IMiDs.** *Presenting Author: Charlotte Pawlyn, Centre for Myeloma Research, Institute of Cancer Research, London, United Kingdom*

**Background:** Treatment with immunomodulatory agents (IMiDs) and proteasome inhibitors (PIs) has dramatically increased response rates and survival for myeloma patients over the last decade. Triplet drug combinations are more effective than doublets or single agents. The more recently developed IMiD lenalidomide, with a different spectrum of effects to thalidomide, is an excellent option for induction therapy due to its oral administration and lack of significant peripheral neuropathy (PN) when compared with bortezomib and thalidomide. **Methods:** Myeloma XI, a phase III randomised trial for newly diagnosed patients of all ages, compared induction treatment with cyclophosphamide/lenalidomide/dexamethasone (CRD) to cyclophosphamide/thalidomide/dexamethasone (CTD) given to max. response or intolerance. To evaluate the role of pre-transplant consolidation with a PI we randomised patients achieving <VGPR to additional cyclophosphamide/bortezomib/dexamethasone (CVD) vs nothing. Fit patients went on to receive melphalan+ASCT. Recruitment is now complete. **Results:** Results are available for a total of 1939 patients, 1104 intensive pathway (540 CRD vs 564 CTD, median age 61 yrs, range 28-75) + 835 non-intensive (411 CRDa vs 424 CTDa, median 74 yrs, range 51-89). 274 patients received additional bortezomib. The pre-planned ITT analysis of combined CR+VGPR rates shows a significant difference between CRD and CTD treatment on multivariate analysis in favour of CRD with odds ratio 1.27 (95% CI 1.06-1.52, p = 0.009). This is due to different CR rates (CRD: CR 25%, VGPR 30%, PR 26% vs CTD: CR 15%, VGPR 33%, PR 31%). Additional bortezomib therapy for those with a suboptimal response upgraded response in 51% demonstrating that PI therapy can be effective in patients intrinsically resistant to IMiDs. Treatment with both IMiDs was well tolerated. Patients on lenalidomide had lower rates of PN (≥ grade II CRD 1.9% vs CTD 6.3%, p<0.001) but higher rates of grade III/IV cytopenias. **Conclusions:** We have demonstrated an important difference in response between the IMiDs thalidomide and lenalidomide however further follow up is required to see whether this translates into prolonged PFS and OS. Clinical trial information: NCT01554852.

**8538 Poster Highlights Session (Board #18), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Randomized phase III trial of busulfan plus melphalan versus melphalan alone for multiple myeloma.** *Presenting Author: Muzaffar H. Qazilbash, Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** High-dose melphalan at 200 mg/m$^2$ (Mel) is the standard for autologous hematopoietic stem cell transplantation (auto-HCT) for multiple myeloma. Two recent retrospective analyses suggested that a combination of busulfan and melphalan (Bu-Mel) may be associated with a longer progression-free survival (PFS). In this randomized phase III trial we compared the safety and efficacy of Bu-Mel vs. Mel. **Methods:** Patients were randomized to either Bu-Mel or Mel. In the Bu-Mel arm, Bu 130 mg/m$^2$ was infused daily for 4 days, either as a fixed dose, or to target an average daily area under the curve of 5000 $\mu$mol-min, followed by 2 daily doses of Mel at 70 mg/m$^2$. The primary endpoint was day +90 CR (IMWG criteria) rate. Secondary endpoints were 100-day treatment-related mortality (TRM) and grade 3-4 non-hematologic toxicity. Log-rank test was used to compare PFS and OS by treatment arm. **Results:** Ninety-two patients (Bu-Mel: 49, Mel: 43) were enrolled between October 2011 and August 2013. Median ages at auto-HCT were 58.4 and 58.5 years in Bu-Mel and Mel arms, respectively (p=0.75). Ten (20%) and 11 (26%) patients had high-risk chromosomal abnormalities in Bu-Mel vs. Mel, respectively (p=0.62). Forty-four (90%) and 40 (93%) patients received bortezomib-based induction therapy in the Bu-Mel and Mel, respectively (p=0.71). At the time of auto-HCT, 8/0 (18%) and 7/3 (23%) patients were in CR/near (n)CR in Bu-Mel and Mel arms, respectively (p=0.44), Grade 3-4 non-hematologic toxicity was seen in 41 (84%) and 20 (47%) patients in Bu-Mel and Mel, respectively (p=0.0003). There was no 100-day TRM in either arm. At day 90, 8 (18%) and 15 (35%) patients had achieved a CR (p=0.05), and 13 (27%) and 20 (47%) patients had achieved a CR + nCR (p=0.05) in Bu-Mel and Mel, respectively. All 49 patients in Bu-Mel and 43 in Mel had started maintenance therapy after day 90. Median follow up was 11.7 months (range 0.7-24.6), One-year PFS was 93% and 82% (p=0.26), and 1-year OS was 100% and 100% in Bu-Mel and Mel arms, respectively. **Conclusions:** Bu-Mel was associated with a significantly lower day 90 CR rate and a significantly higher rate of grade 3-4 non-hematologic toxicity, compared to Mel. A longer follow up is needed to evaluate the impact of Bu-Mel on PFS. Clinical trial information: NCT01413178.

**8539 Poster Highlights Session (Board #19), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Individualized therapy of relapsed or refractory myeloma with targeted agents.** *Presenting Author: Christoph Johann Heuck, Myeloma Institute for Research and Therapy, Little Rock, AR*

**Background:** Diagnostic and therapeutic advances have improved the outcomes for multiple myeloma (MM) patients (pts). However, pts who are refractory to or relapse after therapy with immune modulatory drugs and proteasome inhibitors remain a therapeutic challenge. Next generation sequencing (NGS) studies of MM cells have revealed multiple targetable mutations that were previously unexploited in MM. We now report on the use of NGS to individualize MM therapy. **Methods:** Between 4/2013 and 12/2013 we performed genomic profiling of 115 pts who had failed at least 3 lines of therapy. Cancer associated genes were sequenced to an average depth >500x using a clinical NGS-based assay (FoundationOne). Pts with activating mutations of KRAS, NRAS or BRAF were considered for therapy with the targeted agents trametinib (TMTB), dabrafenib (DBFB) or vemurafenib (VMFB). **Results:** Among the 115 pts we identified 44, 24 and 12 with activating mutations of KRAS, NRAS and BRAF, respectively. 32 pts were treated with TMTB, 2 with DBFB and one with VMFB. The median age was 63 and pts had a median of 4 lines of prior therapy (range 1-11). 23 of 35 pts had prior treatment with Total Therapy. Prior to starting targeted therapy 23 pts had GEP defined high-risk disease (mean GEP70 0.94) and 10 had PET defined extra medullary disease (EMD). 20 pts were administered drugs as single agent and 15 received the in combination with other drugs. Treatment was interrupted due to drug related adverse events (AE) in 4 pts and resumed with dose reduction in 3/4. Seven discontinued therapy because of progressive disease and 2 due to AE unrelated to targeted therapy. Treatment resulted in SD in 10, PR in 5 and CR/nCR in 3 of the 35 pts. For pts with available GEP data, treatment resulted in an average reduction of the GEP70 score by 0.33. For patients with evaluable PET data treatment resulted in complete resolution of bone or EMD lesions in 8/20 and 3/10 cases, respectively. **Conclusions:** Targeted therapy guided by NGS genomic analysis of cancer associated genes in this heavily pretreated population of MM patients resulted in an unexpectedly high objective response rate. Observation of CR with single agent therapy alone support further investigation of this individualized approach to MM therapy.

**8540 Poster Highlights Session (Board #20), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Ikaros expression levels to predict response and survival following pomalidomide and dexamethasone in multiple myeloma (MM).** *Presenting Author: Yuan Xiao Zhu, Mayo Clinic, Scottsdale, AZ*

**Background:** Cereblon (CRBN) binding mediates immunomodulatory drug (IMiD) action in MM. **Methods:** We identified CRBN binding proteins in the presence or absence of IMiD and examined the clinical significance of binding proteins. **Results:** The abundance of 46 CRBN binding proteins deceased after IMiDs and the most downregulated proteins include Ikaros transcription factors IKZF1 and IZKF3 (recently identified as rapidly downregulated subsequent to cereblon-IMiD interaction). We then explored the clinical significance of IKZF1/IKZF3 in MM. IZKF gene expression was similar across all MM stages or subtypes however on western blot in a subset of IMiD resistant cell lines IKZF1 is substantially lower. Genetic mutation in *IZKF1/3* is observed in < 1% of MM patients however 6/69 MM cell lines (8.7%) have nonsynonymous SNVs including a L208R substitution and codon deletion in the FR4 cell line which has very low levels of IZKF1 and is highly IMiD resistant. Recurrent SNV at Q156K (XG1 and H1112) and at G158R in OCI-MY7 all occur within the critical binding domain of IZKF1/ IZKF3 to CRBN. The significance of the Q156K SNV is unknown as XG1 cells are sensitive to IMiDs. Next, we analyzed *IKZF1* and *IKZF3* expression levels in 55 refractory MM patients in whom gene expression was measured prior to pomalidomide and dexamethasone therapy on phase II clinical trials. Responders were defined as ≥ PR after 2 cycles of treatment. We determined the quartile cut-off points for *IKZF1* expression (for all MM patients) to be 7.6, 8.1 and 8.48, respectively. Response rate was 6% in the lower quartile of *IKZF1* expression vs. 39% in the highest 3 quartiles ($P$ = 0.02). *IKZF3*, *IKZF4* and *IKZF5*, had no difference in expression in responding patients. We demonstrate that *IZKF1* levels also correlate with significant differences in progression free survival (3.0 vs. 13 months (m), p < 0.005) with the longest PFS in the highest expression cohort. The median OS for patients with highest 2 quartile *IZKF1* expression was 46.6 m and 31.7 m respectively, whereas patients in the lowest quartile had only 7.2 months median OS (p=0.002). **Conclusions:** IKZF1 binds CRBN and measured prior to pomalidomide therapy is a biomarker for response, PFS and OS.

**8541 Poster Highlights Session (Board #21), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Utility of restaging bone marrow biopsy (BMB) in PET-negative patients with diffuse large B-cell lymphoma (DLBCL) with bone marrow involvement.** *Presenting Author: Amie Elissa Jackson, Mayo Clinic, Rochester, MN*

**Background:** Less than 10% of DLBCL patients have stage IV disease with BM involvement at diagnosis. For these patients, restaging BMB is required to document complete remission (CR). In addition to cost, BMB is a potential source of anxiety and pain for patients. PET-CT is the standard for response assessment in DLBCL and may accurately detect BM involvement at diagnosis (Khan 2013). This raises the question of whether BM assessment on restaging PET-CT could obviate the need for repeat BMB. **Methods:** This was a single institution, retrospective cohort study. After IRB approval, patients with DLBCL and a positive BMB at diagnosis were identified from the Mayo Clinic Lymphoma Data Base. The concordance of BM status on restaging histopathology and PET-CT reports and the positive (PPV) and negative predictive value (NPV) of PET-CT were determined. Findings were validated in a prospective cohort of 68 DLBCL patients treated on an ongoing phase II clinical trial of frontline lenalidomide and RCHOP (R2CHOP). **Results:** Between 2004 and 2013, 1080 patients with DLBCL were evaluated. Of those, 69 (6%) had DLBCL involving the BM at diagnosis. Forty-six patients completed frontline chemoimmunotherapy; 8 were lost to follow-up; and 15 did not complete therapy because of death or progression. Of 46 patients completing therapy, 31 had restaging PET-CT and BMB and were included in the analysis. The concordance between BMB and PET-CT was 100%. Thirty patients had a negative BM by PET-CT and BMB (29 CR; 3PR; 1PD). One patient had persistent BM involvement by biopsy and PET-CT. Thus, restaging PET-CT had 100% PPV and 100% NPV for assessing residual BM disease. In the validation cohort, four patients (6%) had DLBCL involving the BM at diagnosis. All had a negative BM by both restaging BMB and PET-CT. **Conclusions:** Compared with the gold standard of BMB, PET-CT had a 100% NPV to exclude residual BM disease in DLBCL patients after frontline therapy. These findings are being further studied in ECOG1412 testing RCHOP vs R2CHOP in untreated DLBCL. If further validated, DLBCL practice guidelines and response criteria could be modified so BMB is no longer required to document CR if the restaging PET-CT is negative.

**8542 Poster Highlights Session (Board #22), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Net antitumoral immunity and the predictive power of conventional prognosticators in diffuse large B-cell lymphoma.** *Presenting Author: Colm Keane, Princess Alexandra Hospital, Brisbane, Australia*

**Background:** Immunity represents a balance between immune-effectors and immune-checkpoints. In DLBCL, circulating lymphocyte:monocyte ratios are prognostic, implicating them as surrogate immune-effectors and immune-checkpoints within the tumor microenvironment (TME). Detailed assessment of blood would enable identification of the optimal TME immune-effector and monocyte/macrophage-checkpoints to assist sub-stratification of conventional prognosticators. **Methods:** Blood from 140 R-CHOP treated DLBCL patients in the NHL21 Australasian Leukaemia and Lymphoma Group trial were analysed. A circulating immune-effector: monocyte-checkpoint signature segregating interim-PET/CT positivity was identified. Intratumoral applicability was tested in two independent R-CHOP treated DLBCL cohorts, with cell-of-origin (COO) and international prognostic index (IPI) as co-variates. **Results:** Patient monocytes suppressed T-cell proliferation and NK-cell rituximab-ADCC. Both $CD14^{+}$ $HLA\text{-}DR^{lo}$ monocytoid-myeloid derived suppressor cells (moMDSC) and arginase activity were elevated ($P<0.0001$ and $P=0.0005$ respectively) and correlated with CD163 ($r=0.4$, $P<0.0001$ and $r=0.45$, $P=0.002$ respectively). $CD8^{+}$:$CD163^{+}$moMDSC ratios were highest in interim-PET/$CT^{-ve}$ patients ($P\leq0.0001$). Digital bar-coding in 191 DLBCL tissues demonstrated co-clustering of CD8 with immune-checkpoints (CD163/PD1/PDL1/PDL2/TIM3/LAG3, all $P<0.0001$), indicating an adaptive immune-checkpoint response to immune-effector activation. In 128 R-CHOP treated patients (median FU 3.9yrs), CD8:CD163 ratios (net anti-tumoral immunity) were prognostic, independent of IPI and COO. Combining CD8:CD163 ratio with the germinal centre B cell marker LMO2 (LMO2/CD8:CD163) strengthened the predictive ability. Results were externally validated in 233 R-CHOP patients, separating good-risk (0-2) IPI into two categories of 85% and 48% ($P=0.0003$), and poor-risk (3-5) IPI into 66% and 36% 4 year survival ($P=0.0007$). **Conclusions:** Net anti-tumoral immunity within the TME is a powerful new prognosticator, independent of IPI and COO in DLBCL. LMO2/CD8:CD163 adds to the predictive ability of IPI.

**8543 Poster Highlights Session (Board #23), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Role of surveillance imaging in the management of peripheral T-cell lymphomas.** *Presenting Author: Tiffany Pool Ling Tang, Weill Cornell Medical College, New York, NY*

**Background:** The role of routine surveillance imaging (RSI) in patients with peripheral T-cell lymphoma (PTCL) in first complete remission (CR1) is unclear. RSI offers the theoretical advantage of detecting asymptomatic relapses so that second line therapy may be initiated earlier. We investigated the proportion of PTCL relapses detected by RSI and those by clinical findings (C) such as abnormal symptoms, signs or raised LDH, and compared outcomes of these two groups. **Methods:** PTCL patients were identified through prospectively maintained T-cell lymphoma databases from the National Cancer Centre Singapore/Singapore General Hospital and Weill-Cornell Medical College. PTCL subtypes included were PTCL-NOS, AITL, ALCL (ALK positive and negative), EATL, GDT, HSTL and ATLL. Patients with leukemias, indolent, composite and cutaneous lymphomas were excluded. Patients who achieved CR1 and then relapsed were retrospectively reviewed and stratified according to whether the relapse was detected by RSI or by C. Fisher exact and Mann Whitney U test was used to compare the baseline characteristics such as age, stage, PTCL subtype, IPI and treatments between the 2 groups. Progression-free survival (PFS) and overall survival (OS) were compared using the log-rank test. **Results:** There were 427 patients in the combined database and 341 were included in the study. Of these, 145 patients achieved CR1 and 64 relapsed. Relapses were detected by C in 51, RSI in 9 and unknown in 4 patients. Regardless of method of detection, 93% had symptoms, 87% had signs and 76% had raised LDH at relapse. Three patients had no clinical evidence of relapse: 2 had AITL and 1 had NKTL. A median of 2 scans were performed in the first 12 months of CR1. Baseline characteristics and median RSI numbers were similar in both groups. After a median follow-up of 37 months (range 5-402), the median PFS was 19.6 months (range 5-381) in the C group and 14.5 months (range 8-38) in the RSI group ($p=0.740$). The median OS was 65 months (95% CI 36-88) in the C group and NR (95% CI 16-NR) in the RSI group ($p=0.652$). **Conclusions:** Our data suggests that most patients with PTCL in CR1 have abnormal symptoms, signs or raised LDH at relapse and RSI does not impact the detection. RSI does not appear to affect survival outcomes.

**8544 Poster Highlights Session (Board #24), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Value of surveillance studies for patients (pts) with stage I-II diffuse large B-cell lymphoma (DLBCL) in the rituximab (R) era.** *Presenting Author: Susan M. Hiniker, Stanford University Medical Center, Stanford, CA*

**Background:** The role of surveillance studies in early-stage DLBCL in the R era has not been well defined. The goal of this study is to evaluate the use of imaging (CT and PET-CT) scans and LDH in surveillance of patients with stage I-II DLBCL. **Methods:** A retrospective analysis was performed of pts who received definitive treatment (Rx) at Stanford from 2000-2013, using Kaplan-Meier analysis to compute estimates of overall survival (OS) and freedom from progression (FFP). **Results:** 162 pts with stage I-II DLBCL were treated with R-chemotherapy, radiation (RT), or combined modality therapy (CMT). 5-year OS and FFP were 80.7% and 81.5% respectively. 94/162 pts (58%) achieved a complete metabolic response on PET scan after completion of chemotherapy, and this was associated with superior FFP (HR 3.06, $p=0.003$). 128/162 pts (79%) were followed with at least one surveillance PET scan beyond end-of-treatment scans. 18/162 pts relapsed after initial response to Rx. Of these, 9 relapses were detected initially by surveillance imaging studies (8 PET, 1 CT), and 9 were detected clinically (5 by pt-reported symptoms, and 4 by both symptoms and physical exam). No relapses were detected by surveillance LDH. At the time of relapse, LDH was found to be elevated in 3/13 pts, all of whom had relapse detected clinically. Median duration from initiation of Rx to relapse was 14.3 mos (range 7.8 – 121.1 mos) among pts with relapses detected by imaging, and 59.8 mos (9.3 – 123.3 mos) among pts with relapses detected clinically ($p=0.077$). There was no significant difference in OS from date of first Rx or OS following relapse between pts whose relapse was diagnosed by imaging vs clinically. 13/18 pts were successfully salvaged; salvage Rx included chemotherapy alone (10 pts), hematopoietic cell transplant (4 pts), CMT (3 pts) and RT alone (1 pt). **Conclusions:** A complete response on PET scan immediately after initial chemotherapy is associated with superior FFP in stage I-II DLBCL. Use of PET scans as post-treatment surveillance imaging is associated with earlier diagnosis of relapse, but no OS advantage. LDH is not a sensitive marker for relapse. Our results argue for limiting the use of post-Rx surveillance studies in asymptomatic pts.

**8545 Poster Highlights Session (Board #25), Fri, 1:00 PM-4:00 PM and 4:30 PM-5:45 PM**

**Frontline bortezomib and rituximab for the treatment of newly diagnosed high tumor burden (HTB) indolent non-Hodgkin lymphoma (iNHL): A multicenter phase II study.** *Presenting Author: Andrew M. Evens, Tufts Medical Center, Boston, MA*

**Background:** There is a deficiency of published data examining non-cytotoxic options for the frontline treatment of HTB iNHL. In addition, few HTB iNHL series have reported outcomes with long-term follow-up (ie, >3-4 years). **Methods:** All patients (pts) were required to have HTB by GELF criteria. Treatment in this multicenter phase II study consisted of 3 induction cycles of bortezomib (1.6 mg/m$^2$ weekly x 4) and rituximab (4 weeks cycle 1; 1 dose cycles 2 + 3) administered q35 days. This was followed by an abbreviated consolidation (ie, each drug once q 2 months x 4). All outcomes were analyzed by intent-to-treat. **Results:** 42 pts were enrolled and all were evaluable. Histologies were follicular lymphoma (FL) (n=33, 79%), marginal zone lymphoma (n=6, 12%), small lymphocytic lymphoma (n=2, 7%), and Waldenstroms (n=1, 2%). Pt characteristics included median age 62 years (40-86); 38% bulky disease (>7cm); 19% malignant effusions; 91% advanced-stage; and the median FLIPI was 3. Therapy was well tolerated with few grade 3/4 toxicities and minimal neurotoxicity. Grade 3 adverse events (AE) were fever (5%), infusion reaction (5%), infection (5%), cardiac (5%), fatigue (5%), diarrhea, hypokalemia and bowel obstruction (2% each); the only grade 4 AEs were neutropenia (5%) and thrombocytopenia (2%). There was no motor neuropathy noted, no grade 3 or 4 sensory neuropathy, and the rates of grade 1 and 2 sensory neuropathy were 14% and 2%, respectively. Overall response rate (ORR) at end of therapy was 70% with a 40% complete remission (CR) rate (FL: ORR 76%, CR 44%). With 50 month median follow-up, 4-year progression-free survival (PFS) was 44% with 4-year overall survival (OS) of 87% (FL: 44% and 97%, respectively). Four-year PFS for FLIPI 0-2 vs 3-5 were 60% vs 26%, respectively ($P$=0.02), with corresponding OS rates of 92% and 81%, respectively ($P$=0.16). Interestingly, 4-year OS was superior for FL compared with non-FL histologies (97% vs 43%, respectively, $P$=0.003). **Conclusions:** Altogether, bortezomib/rituximab is a targeted therapeutic regimen that was very well tolerated and resulted in long-term survival rates approximating prior HTB FL rituximab/chemotherapy series. Clinical trial information: NCT00369707.

**8546 General Poster Session (Board #233), Mon, 1:15 PM-5:00 PM**

**Chemotherapy or combined modality therapy for early-stage Hodgkin lymphoma: A comparative, population-based study.** *Presenting Author: Rajesh Shrestha, Memorial Hospital of Rhode Island, Pawtucket, RI*

**Background**: The choice between chemotherapy alone (Ct) and combined modality therapy (Ct with radiation, CMT) in early-stage Hodgkin lymphoma (HL) remains controversial. Identifying patients (pts) who could omit radiotherapy is an important research goal. We compared the two strategies using the National Cancer Data Base, which captures >70% of incident cancer cases in the United States. **Methods**: We extracted data on 20,600 pts with stage I-II classical HL treated between 2003 and 2011. We studied factors predicting the use of Ct or CMT using logistic regression. Treatment selection bias was addressed by balancing groups with a propensity score, immortal time bias by landmark analysis, missing data bias by multiple imputation, with a sensitivity analysis for unobserved confounding. Overall (OS) and relative survival (RS, a surrogate for disease-related mortality) were then compared using proportional hazard models. **Results**: Administration of CMT (50.5%) rather than Ct (49.5%) was significantly influenced by clinical factors (B symptoms, histology and comorbidities, all $P$<.0001), but also by demographic ones: age/sex (odds ratio, OR .85, $P$=.0007 for women vs. men <30 years old), race (OR .83, $P$=.0007 for black vs. white pts), lack of insurance (OR .71, $P$<.0001), treatment in an academic center (OR .81, $P$=.0001) or after 2006 (OR .63, $P$<.0001). After bias adjustment, CMT was associated with a better OS (hazard ratio, HR 0.56, 95% CI 0.49-0.64) and RS (HR 0.37, 95% CI 0.29-0.47) than Ct. The 5-year OS was 94.0% for CMT and 88.7% for Ct. There was no evident heterogeneity of the CMT benefit in subgroups defined by age, sex, histology, B-symptoms, stage, anatomical origin or hospital type (all $P$>.20). **Conclusions**: Treatment selection in early-stage HL is influenced by sociodemographic factors, which may lead to outcome disparities. In this comprehensive dataset, CMT was associated with the same survival advantage as in the prior meta-analysis (Herbst et al., *Haematologica* 2010, HR .41). No clinical factors (including some defining "early unfavorable" stratum) could identify subsets without advantage from CMT, so CMT should remain a standard of care pending further prospective studies.

**8547 General Poster Session (Board #234), Mon, 1:15 PM-5:00 PM**

**Pharmacokinetics and tolerability of doxorubicin in newly diagnosed lymphoma patients with hepatic impairment.** *Presenting Author: Catherine Lai, NIH/NCI, Bethesda, MD*

**Background:** Doxorubicin (dox) is critical for the curative treatment of DLBCL. Principally metabolized in the liver, early studies showed significantly decreased clearance (cl) in patients (pts) with hepatic impairment, leading to empiric dox reduction in pts with elevated bilirubin. No studies have analyzed dox pharmacokinetics (pk) and clinical toxicity in lymphoma pts with hepatic impairment. **Methods:** Pts with newly diagnosed aggressive lymphoma received 6 to 8 cycles of DA-EPOCH +/-R at the NCI. Of 70 pts studied, 61 had normal and 9 had elevated bilirubin (> 1.2mg/dL). All pts received full dose dox (40 mg/m$^2$) over 96-hours on cycle 1. Blood samples were collected for dox and doxorubicinol (doxor) pk at 0, 22 and 96 hours after infusion began. **Results:** The median (range) dox cl in pts with elevated versus normal bilirubin was 393ml/min/m$^2$ (294-610) vs. 630 ml/min/m$^2$(262-1596) (p= 0.0036). Median (range) plasma dox steady state concentrations (Css) at 96 hours were 0.031 (0.020-0.042) vs. 0.021 (<LLQ-0.045) $\mu$M (p=0.0036) and doxor Css were 0.025 (0.008–0.052) vs. 0.010 (<LLQ–0.021)$\mu$M (p=0.0028) in elevated versus normal bilirubin. Neutropenia was lower and thrombocytopenia (tcp) was higher in pts with elevated bilirubin (see table below). Response rates (RR) were similar: Complete response (CR) was achieved in 78% (7/9) versus 82% (50/61) and PR in 0% (0/9) vs 7% (4/61) of pts with elevated vs normal bilirubin. **Conclusions:** Pts with elevated bilirubin had reduced cl of dox, but was within the range of normal. Importantly, there were no differences in febrile neutropenia - tcp was higher in pts with elevated bilirubin but was not clinically meaningful. RR were similar between the 2 groups. Our results do not support the empiric dose reduction of dox in pts with aggressive lymphomas receiving potentially curative treatment.

| Characteristics | Elevated bilirubin | Normal bilirubin |
|---|---|---|
| Median age (yrs) | 44 (24-62) | 46 (21-75) |
| IPI (int hi/hi risk) | 67% (6/9) | 28% (17/61) |
| ANC nadir < 500/mm$^3$ (% pts C1) | 33% (3/9) | 52% (32/61) |
| TCP nadir < 25x103/mm$^3$ (% pts C1) | 89% (8/9) | 0% (0/61) |
| Febrile neutropenia (% pts C1) | 22% (2/9) | 16% (10/61) |
| G3/4 GI and neuro tox (% pts C1) | 33% (3/9) | 11% (7/61) |

**8548 General Poster Session (Board #235), Mon, 1:15 PM-5:00 PM**

**Survival of patients with different AIDS-related lymphoma subtypes.** *Presenting Author: Marcus Hentrich, Harlaching Hospital, Department of Hematology, Oncology and Palliative Care, Munich, Germany*

**Background:** Previous data indicated that the overall survival (OS) of patients (pts) with AIDS-related Burkitt lymphoma (BL) is inferior to that of diffuse large B-cell lymphoma (DLBCL), and that the OS of pts with plasmablastic lymphoma (PBL) is inferior to that of BL and DLCBL. We aimed to analyse the OS of pts with these lymphoma subtypes enrolled in the German AIDS-related Lymphoma (ARL) Cohort Study. **Methods:** The prospective observational cohort study includes all adult HIV-infected pts with biopsy proven ARL diagnosed in 31 participating German centers since January 2005. Data on HIV-infection and lymphoma characteristics, treatment and outcomes were recorded until December 2012. OS was calculated from the date of ARL diagnosis until death of any cause or last follow-up. **Results:** Of 291 pts included in the analysis 154 (53%) had DLBCL, 103 (35%) BL, and 34 (12%) PBL. The mean CD4-count at ARL diagnosis was significantly higher in pts with BL (349/$\mu$l) compared to DLBCL (209/$\mu$l) or PBL (205/$\mu$l) ($P$ < 0.001 and $P$ = 0.008, respectively). After a median follow-up of 1.3 years there was no significant difference in the 2-year OS rates (2yOS) between pts with BL (69% [95%CI 59-79]) and DLBCL (63% [55-71]) ($P$ = 0.65). By contrast, the 2yOS of PBL was significantly lower (43% [23-63]) compared to that of DLBCL and BL ($P$ = 0.024). The OS rates for pts with low risk vs. intermediate/high risk international prognostic index (IPI) were 82% (70-95) vs. 52% (40-63) for DLBCL ($P$ = 0.001), 87% (74-101) vs. 60% (47-73) for BL ($P$ = 0.011) and 83% (60-105) vs. 20% (-2.8-42.6) for PBL ($P$ = 0.003), respectively. Pts with DLBCL and CD4 cells >100/$\mu$l had significantly better OS than those with CD4 cells ≤100/$\mu$l (66% [55-77] vs. 51% [36-66], $P$ = 0.022). However, this was not true for pts with BL (OS 74% [63-85] vs. 51% [24-77], $P$ = 0.069) and PBL (36% [12-59] vs. 63% [32-93], $P$= 0.459). Prior AIDS defining illnesses did not adversely impact OS of each lymphoma subtype. **Conclusions:** In contrast to previous data the present study showed no significant difference in the 2yOS rates between DLBCL and BL while the OS of pts with PBL remains poor. The improvement in survival of BL may be explained by the widespread use of antiretroviral therapy and the more frequent use of intensive chemo-immunotherapy regimens.

**8549 General Poster Session (Board #236), Mon, 1:15 PM-5:00 PM**

**Utility assessment of interim FDG-PET/CT in frontline therapy of patients with diffuse large B-cell lymphoma (DLBCL).** *Presenting Author: Scott F. Huntington, Division of Hematology/Oncology, University of Pennsylvania, Philadelphia, PA*

**Background:** FDG-PET/CT (PET/CT) is part of standard pre-treatment staging and post-treatment response assessment in patients undergoing first line therapy for DLBCL. While many providers obtain interim PET/CT (I-PET) during the course of therapy, the role of these scans remains unclear. We investigated the clinical utility of interim and end of treatment PET/CT (E-PET) in patients with DLBCL. **Methods:** All patients with biopsy confirmed DLBCL undergoing first line therapy at our institution between January 1, 2008 and June 1, 2012 were screened for this retrospective study. Patients who received immunochemotherapy and underwent at least one I-PET were included for analysis. Scan results were interpreted as positive or negative based on consensus criteria from the International Harmonization Project. Results from I-PET and E-PET were analyzed and clinical outcomes were recorded. **Results:** Of 101 patients with DLBCL undergoing first line treatment at our institution, 94 patients underwent at least one I-PET. The median age was 58.5 years (range 20-91), 55% were male, and median follow-up time was 32.2 months. The majority (61%) of patients had at least one negative I-PET and a total of 133 I-PETs and 84 E-PETs were obtained. The positive predictive value (PPV) and negative predictive value (NPV) of I-PET for predicting primary refractory disease were 40.5% (95% CI:25-58%) and 100% (95% CI: 92-100%) respectively. The PPV and NPV of I-PET for predicting primary refractory or relapsed disease were 51.4% (95% CI: 35-68%) and 86.8% (95% CI: 74-94%). Obtaining at least one negative I-PET was strongly associated with improved progression-free survival (PFS) and remained an independent prognostic factor in a bivariate Cox model with revised-IPI (negative I-PET: HR 0.31, p=0.002; R-IPI: HR 2.4, p=0.02). **Conclusions:** Negative I-PET predicted superior clinical outcomes in our DLBCL patient cohort. All patients with negative I-PET were in remission at end of treatment and E-PET offered little clinical utility in this patient subset. Therefore, I-PET may offer an approach of early prediction of treatment outcome and obviate the need for end of therapy imaging in a majority of patients with DLBCL.

**8550 General Poster Session (Board #237), Mon, 1:15 PM-5:00 PM**

**Differences in disease characteristics, treatment patterns, and outcomes between men (M) and women (W) with follicular lymphoma (FL): Prospective evaluation of 2,650 U.S. patients (pts).** *Presenting Author: Chadi Nabhan, The University of Chicago, Chicago, IL*

**Background:** Differences in disease presentation, characteristics, treatment patterns, and outcomes between sexes among pts with FL have not been well-described. **Methods:** Using the National LymphoCare Study, a prospective registry sponsored by Genentech, that enrolled newly diagnosed FL pts (2004–2007), we analyzed differences in baseline characteristics and outcomes by gender. Associations of gender with disease characteristics, treatment, R dose intensity, and overall response (OR) were assessed using Pearson $\chi^2$tests. For pts receiving R-based induction, median progression-free survival (PFS), overall survival (OS), and lymphoma related mortality (LRM) by gender, age, and treatment regimen were estimated using Kaplan-Meier method. Adjusted Cox modeling for baseline factors and treatment regimens assessed gender differences in PFS, OS, and LRM. **Results:** 1,276 M and 1,374 W were prospectively enrolled (median F/U 6.9 yrs). More W had poor-risk FLIPI (36% vs 32%; P=0.05), which was likely due to anemia (27% vs 15%; P<0.0001) without other differences. Treatment varied by gender (P=0.002) with more W receiving R-monotherapy (15% vs 11%). R-containing regimens were given to 62% M and 61% W respectively with no differences in dose intensity (P=0.428). ORs were similar for M and W across regimens and age groups but in M and W, R-chemotherapy provided superior OR to R-monotherapy. After adjusting for baseline factors and treatment, W receiving R-based induction had superior PFS (HR 0.82, 95% CI 0.71–0.95; P=0.009) and OS (HR 0.73, 95% CI 0.58–0.90; P=0.003). Comparisons to pts who did not receive R-treatment were not performed due to low pt numbers. There were no significant difference in LRM overall (HR 0.86, P=0.35), but W had superior LRM in the pts ≤60. W had superior PFS and OS across all age categories (Table). **Conclusions:** This is the first prospective report to show that PFS and OS of W with FL are superior to M in the modern era. Clinical trial information: NCT00097565.

| | W vs M | | |
|---|---|---|---|
| | ≤60 yrs | 61–80 yrs | >80 yrs |
| PFS | 0.79 (0.62–1.00) | 0.91 (0.73–1.12) | 0.58 (0.37–0.91) |
| OS | 0.61 (0.38–0.99) | 0.87 (0.66–1.14) | 0.47 (0.29–0.78) |
| LRM | 0.41 (0.20–0.87) | 1.07 (0.71–1.61) | 0.90 (0.39–2.07) |

**8551 General Poster Session (Board #238), Mon, 1:15 PM-5:00 PM**

**A phase 1 multicenter clinical trial of alemtuzumab and CHOP chemotherapy for peripheral T-cell lymphomas.** *Presenting Author: Rena Buckstein, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*

**Background:** Alemtuzumab is an anti CD52 monoclonal antibody with single agent activity in relapsed peripheral T cell lymphomas (PTCL), but the optimal dose/schedule to combine with chemotherapy is unknown. **Methods:** The primary objectives of this phase 1 study were to establish the maximally tolerated dose (MTD) and pharmacokinetics (PK) of alemtuzumab combined with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) q21days. The MTD with highest trough levels would define the recommended phase II/III dose. Patient eligibility included: > age 18, untreated CD52+ PTCL, stage 2-4, measurable disease and adequate organ function. Alemtuzumab was given subcutaneously in 1 of 4 schedules using a 3+3 design with CHOP chemotherapy: 1) 10 mg day 1; 2) 10 mg weekly days 1, 8, 15; 3) 30 mg day 1; 4) 60 mg day 1. Trough PK were measured on day 1 of each 21d CHOP cycle. **Results:** 20 patients were enrolled; histology: AILD (n=7), PTCL NOS (n=6), ALK 1–ALCL (n=3), subpanniculitic (n=2), hepatosplenic (n=1) and enteropathy associated (n=1). DLT's necessitated dose expansion of dose level 2 (fatal TB reactivation) and 4 (grade 4 thrombocytopenia). The MTD was not reached. The most common hematologic toxicities were lymphopenia (65% grade 3-4), neutropenia (55% grade 3-4) and febrile neutropenia (25%). Ten (50%) patients developed asymptomatic CMV reactivations at a median of 39 days (range 4-99) treated with valganciclovir. Two patients developed fungal pneumonias. Of 18 evaluable for response, the overall response rate was 65% (CR/Cru (n=7), PR (n=6)). With a median f/u of 28 months (range 1.3-77.4), 10 patients (52%) have relapsed or progressed and 4 (21%) have died. Median OS has not been reached and median PFS is 23 months. Peripheral blood CD3+ T cells declined by 80-100% from baseline and recovered in 55% of patients at a median time of 15 mos. Mean trough alemtuzumab levels by dose level were 1) 57, 2) 464, 3) 124 and 4) 501 ng/ml. **Conclusions:** Weekly SC alemtuzumab 10 mg achieves trough levels comparable with 60 mg q21d when given with CHOP. With close monitoring, toxicity was manageable and CMV disease was not seen. These doses with CHOP should be tested in patients with peripheral T cell lymphoma. Funded by NCIC grant#16398. Clinical trial information: NCT00363090.

**8552 General Poster Session (Board #239), Mon, 1:15 PM-5:00 PM**

**Extranodal natural killer T-cell lymphoma, nasal-type—A new staging system from CSWOG—A multicenter study.** *Presenting Author: Tongyu Lin, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China*

**Background:** Extranodal NK/T-cell lymphoma, nasal type (ENKTL), is a rare and high aggressive disease with poor prognosis. The Ann Arbor staging system had been unable to define ENKTL staging in specific way. This study conduct a new staging system specified for ENKTL, which can identify poor prognostic patients who need more aggressive therapy. **Methods:** Based on the primary studied of one single center consecutive patients diagnosed as ENKTL treated with CHOP-like regimens on ASCO meeting 2008, the new staging system was established as stage I: lesions confined within nasal cavity or nasopharynx without local invasiveness (paranasal sinuses or bony or skin invasion); stage II: localized disease with local invasiveness; stage III: localized disease with regional lymph node involvement (cervical lymph nodes); stage IV: disseminated disease (lymph nodes on both sides of diaphragm, multiple extranodal site). We further undertaken two multicenter study, one retrospective analyzed the patients treated with CHOP-like to confirm the new system and the other prospective validate the new system in current treatment modality containing L-asp-based chemotherapy in ENKTL. **Results:** A total of 821 patients with final diagnosis of ENKTL (ranging 9-90 years old) were included. Among them 588 were retrospective studied between Jan 2000 and Jun 2008, and 233 were prospective studied from Jul 2008 to Dec 2012. The distribution of all patients using the new system compared with Ann Arbor system were stage I: 19.6% vs 56.9%; stage II: 38.1% vs 20.1%; stage III: 17.8% vs 7.2%; stage IV: 24.5% vs 15.8%, respectively. In the retrospective study, the 5-year OS rate of stage I to IV using the new system were 63%, 51%, 38% and 29% compared with 55%, 45%, 15% and 29% using the Ann Arbor system, respectively. For prospective study, the 5-year OS rate of stage I to IV of the new system were 82%, 73%, 67% and 54%, respectively, while stage IV was better than stage III (74% vs 47%) when the Ann Arbor system was adopted. **Conclusions:** The new staging system with a more balanced distribution and a superior prognostic discrimination as compared with the Ann Abor staging system is more suitable for ENKTL and should be recommended used in the future.

**8553 General Poster Session (Board #240), Mon, 1:15 PM-5:00 PM**

**The Bruton's tyrosine kinase (BTK) inhibitor ONO-4059: Single-agent activity in patients with relapsed and refractory non-GCB-DLBCL.** *Presenting Author: Martin Dyer, Leicester Royal Infirmary, Leicester, United Kingdom*

**Background:** Bruton's tyrosine kinase (BTK) is a critical kinase involved in B-cell receptor signal transduction. ONO-4059, a highly potent and selective oral BTK inhibitor has demonstrated anti-tumour activity in pre-clinical models (Yasuhiro et al, AACR 2013) and in the clinic in both NHL and CLL patients (Salles et al, ASH 2013; Rule et al, ASH 2013). Here, we present data from non-GCB DLBCL patients enrolled in the ongoing Phase I study ONO-4059POE001. **Methods:** Thirteen patients with relapsed (n=8) or refractory (n=5) non-GCB-DLBCL were administered ONO-4059 as monotherapy, given once daily (QD) at doses ranging from 160-480mg, to determine safety, pharmacokinetics and pharmacodynamics, as well as any preliminary efficacy. Patients had a median age of 65yrs [range 30-72], median of 4 prior therapies [2-8], and a median baseline tumour burden of 2,504mm$^2$ [619-15,750mm$^2$]. All 13 patients had prior exposure to a rituximab-containing regimen and 5/13 patients (38%) had prior ASCT. **Results:** Thirteen patients were evaluable for safety - ONO-4059 was found to be well tolerated with a total of twenty seven (27) ONO-4059 related adverse events reported in 5/13 patients (CTCAE-V4.0 G1 [n=20 in 4 patients] and G2 [n=5 in 3 patients]). Two ONO-4059-related G3 events reported in two patients were: drug reaction and lymphopenia, with drug reaction reported as an SAE. The pharmacokinetics of ONO-4059 reflects a half-life of ~5-7 hours with sustained inhibition of BTK observed in PBMCs up to 24 hours from first dose. Eight patients are currently evaluable for efficacy - Six patients experienced reductions in lymphadenopathy within the first treatment cycle. Responses occurred at doses of 160mg (n=6) and 320mg (n=2), including 2 refractory patients, with a best overall response rate of 75% (6/8) with 6 PR (median reduction of lymph nodes was 81.5% [52.4-86.6%]) and 2 PD. Of note, no CD79b mutations were identified (n=7 evaluable). **Conclusions:** ONO-4059 showed a favorable safety profile along with promising preliminary efficacy in this difficult-to-treat non-GCB-DLBCL patient population. The study is ongoing with additional dose escalation cohorts underway. Clinical trial information: NCT01659255.

**8554 General Poster Session (Board #241), Mon, 1:15 PM-5:00 PM**

**Retrospective analysis of treatment patterns and outcomes with subcutaneous (SQ) bortezomib (BTZ) in patients (pts) with relapsed mantle cell lymphoma (MCL).** *Presenting Author: Vijayveer Bonthapally, Millennium: The Takeda Oncology Company, Cambridge, MA*

**Background:** Intravenous (IV) BTZ was approved in the US for the treatment of relapsed MCL in 2006 based on the phase 2 PINNACLE study (Fisher, JCO 2006). In 2012, SQ BTZ was approved based on the phase 3 MMY-3021 study (Moreau, Lancet Oncol 2011), which showed non-inferior efficacy and an improved safety profile with SQ vs IV BTZ in relapsed multiple myeloma. There are limited data on SQ BTZ in relapsed MCL. **Methods:** In this retrospective observational study, data on relapsed MCL pts aged ≥18 years with ≥1 SQ BTZ dose during 2010–2013, either as a single agent or in combination therapy, were collected from an oncology electronic medical records (EMR) database and patient medical charts (Altos Solutions, Inc). Analyses of treatment patterns and outcomes, including best response, PFS, OS, and AEs, were conducted. **Results:** Of 37,996 lymphoma pts in the database, 806 had MCL; 42 had ≥1 SQ BTZ dose, of whom 30 had ≥1 prior therapy identified. Of these 30 pts median age was 68.7 years, 70% were male, and 53% had stage IV MCL. Pts had a median of 3 lines of prior therapy (range 1–6). Median time from diagnosis to SQ BTZ was 2.5 years. 97% of pts received SQ BTZ in 2012–2013. Median treatment duration was 2.3 months (range 0.03–19.4); 13 (43%) had single-agent SQ BTZ and 17 (57%) had combination therapy (8 with rituximab [R], 6 with R+bendamustine, 1 each with R+lenalidomide, methotrexate, and dexamethasone). Overall response rate was 37% (11/30 pts; 3% CR). After a median follow-up of 8.8 months, median PFS was 10.5 months (IQR 3.8–29.3), median OS was not reached (1-year OS 72%). Common AEs included 57% fatigue, 27% neutropenia, 27% anemia, 27% neuropathy, 20% thrombocytopenia, and 20% nausea. Local redness/tenderness were seen in 10%/7%. Common grade 3/4 AEs were 10% neuropathy and 7% infection. Outcomes with single-agent SQ BTZ (n=13) were similar to overall data but with only 2 grade 3/4 AEs: 8% neuropathy, 8% diarrhea. **Conclusions:** SQ BTZ was active and well tolerated in relapsed MCL. These data are consistent with the non-inferior efficacy and improved safety profile of SC BTZ in multiple myeloma. As data mature, additional analyses will further evaluate treatment outcomes and safety profile.

**8555 General Poster Session (Board #242), Mon, 1:15 PM-5:00 PM**

**The outcome of patients with "nodal" peripheral T-cell lymphomas in a complete response following standard chemotherapy.** *Presenting Author: Jean-Michel Lavoie, British Columbia Cancer Agency, Vancouver, BC, Canada*

**Background:** The outcome of peripheral T-cell lymphomas (PTCLs) treated with anthracycline-based chemotherapy (CHT) regimens is poor. Previous studies have suggested a benefit of high dose chemotherapy and autologous stem cell transplant (HDC/ASCT) in first complete remission (CR). However, in the absence of a randomized trial, the benefit is unclear. We evaluated the outcome of patients in CR following CHOP (like) CHT to provide a comparison to outcomes with HDC/ASCT. **Methods:** The BCCA Lymphoid Cancer database was searched to identify all cases of 'nodal' PTCLs between 16 and 67 y with stage 3/4, or stage 1/2 with B symptoms, bulky (>10cm) or extensive disease, that were in a CR by clinical assessment and imaging at the end of curative intent combination CHT and did not undergo consolidative transplant. Charts were reviewed to confirm response assessment. **Results:** Between October 1980 and January 2014, 103 cases were identified to be in a CR (6 by PET scan): PTCL-NOS = 39/94 (45%); ALK-positive (ALK-pos) ALCL = 29/34(85%); ALK-negative (ALK-neg) ALCL = 17/34 (50%); AITL= 17/37 (46%). All patients received CHOP (like) CHT. The median age at diagnosis for non-ALK-pos vs. ALK-pos patients was 57 y (23-67 y) and 29 y (17-65), respectively. Patients with ALK-pos ALCL more often had low risk disease (IPI 0, 1 48% vs. all others 23%) (P=0.036) and patients with AITL commonly had bone marrow (bm) involvement. (41%, P=0.01). With a median follow-up for living patients of 9.0 years (1.75-24.0 years), the 5 y OS for ALK-pos ALCL was 79% vs. 57% for all other subtypes (P=0.0048) and the 5 y PFS was 65% vs. 42% (P=0.010). The 5 y OS by subtype was 69%, 67% and 46% for ALK-neg, AITL and PTCL-NOS respectively (P=0.006) and the 5 y PFS was 62%, 50% and 30%, respectively (p=0.001). Interestingly, the IPI and bm involvement were not prognostic for either PFS or OS in any subtype. **Conclusions:** The majority of patients with PTCL-NOS ultimately relapse despite achieving a CR at the end of standard CHT. In contrast, patients with ALK-neg ALCL have an excellent outcome if a CR is achieved with comparable survival rates to patients treated with HDC/ASCT. These data support separation of these entities for the evaluation of novel treatment regimens.

**8556 General Poster Session (Board #243), Mon, 1:15 PM-5:00 PM**

**Results of a phase I study of bendamustine in combination with ofatumumab, carboplatin, and etoposide (BOCE) for refractory or relapsed aggressive B-cell non-Hodgkin lymphomas (NHL).** *Presenting Author: Sameh Gaballa, Department of Medical Oncology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA*

**Background:** No salvage regimen has shown clear superiority in relapsed NHL. Bendamustine has single agent activity in relapsed aggressive NHL. We conducted a phase I trial using a novel RICE-like salvage regimen in which ofatumumab was substituted for rituximab and bendamustine replaced ifosfamide, combined with carboplatin and etoposide (BOCE) **Methods:** Patients (pts) with relapsed or refractory aggressive B NHL were eligible. The design was a standard 3+3 design using escalating doses of bendamustine [70, 90, and 120 mg/m$^2$ D1-2] with ofatumumab (cycle 1: 300 mg D1, 1000 mg D3, cycle 2 and 3: 1000 mg D1), carboplatin AUC 5 D2 and etoposide 100mg/m$^2$ D1-3. **Results:** Eleven pts were enrolled (7M/4F). Median age was 62 (range 53-75), 5 pts (45%) had diffuse large B NHL, 4 pts (36%) had grade 3 follicular NHL, 1 pt (9%) had mantle cell NHL, and 1 pt (9%) had transformed CLL. Five pts (46%) had refractory disease and 6 pts (56%) had relapsed disease. All pts with refractory disease were refractory to rituximab. All pts had stage III or IV disease. sAAIPI was: low-int 55%, high-int 36%, high risk 9%. ORR was 64% [CR: 5 pts (46%); PR: 2 pts (18%)]. Two pts (18%) had progressive disease and 1 pt (9%) had stable disease. Five pts (46%) subsequently underwent an allogeneic transplant. Four pts (36%) died, all of progressive disease. After a median follow-up of 6 months, the estimated 12-months OS is 63.5% DLT was not reached. Grade III-IV toxicity included neutropenia (82%), thrombocytopenia (64%), anemia (64%), lymphopenia (27%), febrile neutropenia (27%), hyponatremia (18%), and hypophosphatemia (18%). Six serious adverse events were reported in 4 pts including acute kidney injury, urinary tract infection, pleural effusion, GI bleeding, thromboembolic event and febrile Infusion related reactions occurred in 27% of pts (all grade I-II). **Conclusions:** The BOCE regimen is well tolerated in pts with relapsed or refractory aggressive NHL. A phase II trial with bendamustine at the dose of 120mg/m2 is ongoing. The advantage of this regimen over other commonly used salvage strategies is that it can be administered safely in the outpatient setting. Clinical trial information: NCT01458366.

**8557 General Poster Session (Board #244), Mon, 1:15 PM-5:00 PM**

**Post-treatment PET scan is highly predictive of outcome (PFS and OS) in MCL pts treated with R-Hyper-CVAD in the frontline setting regardless of MIPI score.** *Presenting Author: Anthony R. Mato, John Theurer Cancer Center, Hackensack, NJ*

**Background:** MIPI score (age, LDH, WBC, ECOG PS) defines 3 distinct risk groups in MCL pts. Though MIPI has been validated in series with dose intensive (DI) strategies and rituximab, a number of other prognostic factors have been reported that affect MCL survival. There remains a need to further stratify pts in each MIPI risk category despite optimal treatment approaches. We previously identified (Mato et al, Cancer 2012) FDG PET-CT as an important prognostic marker for survival in MCL pts following R-HyperCVAD completion. We examined here the additive prognostic utility of post-treatment PET-CT imaging to baseline MIPI scores. **Methods:** Primary endpoints were PFS and OS. PET-CT images were dichotomized using IHP response criteria (Juweid et al, JCO 2007). Reviewers were blinded to outcomes. MIPI scores were calculated as described by Hoster et al (Blood, 2008). Utilizing KM methods, we compared outcomes stratified by post-treatment PET-CT status and MIPI risk groups. Utilizing Cox regression, we tested the association between PET-CT + MIPI and survival. **Results:** 140 MCL pts (med age 60, 95% stage IV) treated with 1st line R-HyperCVAD were identified in our MCL outcome database. Of these, 58 pts had a post-treatment PET-CT available for review. MIPI scores were 44% low, 34% intermediate and 22% high risk. Post treatment PET-CTs were 18% (+) and 82% (-). Med PFS and OS estimates were 56 and 108 mo respectively (med follow up 35.2 mo). Both MIPI (HR 1.9 CI: 1.1-3.2 p=.012) and PET-CT (HR 7.1 CI:2.9-17.1 p=.001) independently correlated with PFS and OS MIPI (HR 3.3 CI: 1.5-7.3 p=.04) and PET-CT (HR 9.2 CI: 2.5-33.0 p=.001). The following defines a model, which includes baseline MIPI and PET-CT status: Low MIPI (HR=1), Int MIPI (HR=2.1), High MIPI (HR=3.5), PET-CT (-) (HR=1), PET-CT (+) (HR=7.1). **Conclusions:** Post treatment FDG-PET status and MIPI are validated independent predictors of survival in MCL pts treated with R-HyperCVAD. Outcomes are extremely poor in PET (+) patients regardless of MIPI risk group: Low risk / PET (+) had similar PFS as high risk / PET (-). Our results may identify MCL patient candidates for novel maintenance / consolidation approaches after 1st line therapy.

**8558 General Poster Session (Board #245), Mon, 1:15 PM-5:00 PM**

**Utility of surveillance imaging in patients with non-Hodgkin lymphoma.** *Presenting Author: Rangaswamy Chintapatla, Mount Sinai St. Luke's Hospital, Mount Sinai Roosevelt Hospital, Icahn School of Medicine at Mount Sinai, New York, NY*

**Background:** The optimal surveillance imaging in the management of patients (pts) with non-Hodgkins lymphoma (NHL) remains undefined. Unnecessary scans increase health care costs and radiation related health hazards. A recent report (Thompson, C.A. et.al; ASCO 2013) suggests that routine surveillance scans did not add much value to follow up of pts treated for NHL. We reviewed our hospital's patient charts to further explore the effectiveness and cost of surveillance imaging. **Methods:** We retrospectively studied the records of 218 pts (118 male, 100 female) with NHL managed at our institution from 2008 to 2012. Pts with high-grade (HG) NHL treated to complete remission, and pts managed for low-grade (LG) NHL were included. Patients with HIV-related NHL were analyzed separately. Primary CNS lymphoma was excluded. Data were analyzed to determine if re-treatment decisions at relapse, as well as decisions to initiate therapy in pts with LG NHL, were based on clinical features (physical exam, laboratory abnormalities) or findings noted on scans. **Results:** Of 218 pts, 115 (53 %) pts had HG NHL, and 103 (47 %) had LG NHL. Patients were managed with observation, radiation therapy, rituximab, and/or immunochemotherapy as appropriate. Median age was 60 years (Range: 24 - 97) and median follow-up was 31 months. Median overall survival was not reached. Forty -six pts had disease relapse or progression warranting treatment initiation: 38 were detected by symptoms and 8 were diagnosed by imaging alone. A total of 834 surveillance scans were done including 373 PET/CT scans with an estimated total cost of over USD 750,000. (Medicare reimbursement prices 2014). Of the 218 pts, 32 (15 %) had HIV-related NHL. Eleven of these patients had disease relapse, all detected by symptoms. HIV patients averaged 2.9 scans/pt compared to 3.9 scans/pt in non-HIV pts (p: 0.156). HIV-NHL pts had a higher relapse rate compared to non-HIV pts, which did not reach statistical significance. (34% vs 19% (p: 0.059). **Conclusions**: Disease relapses were mostly diagnosed due to a change in patient's clinical status. Only 8 of the 46 cases of relapse were detected by surveillance imaging alone. We plan to further explore whether the outcomes were different for patients with relapse detected by imaging.

**8559 General Poster Session (Board #246), Mon, 1:15 PM-5:00 PM**

**First-in-human study of 4SC-202, a novel oral HDAC inhibitor in advanced hematologic malignancies (TOPAS study).** *Presenting Author: Bastian von Tresckow, Department I for Internal Medicine, University Hospital of Cologne, Cologne, Germany*

**Background:** 4SC-202 is a specific inhibitor of protein deacetylases HDAC1, 2 and 3 and lysine specific demethylase LSD1 (KDM1A). Enzymatic inhibition leads to transcriptional repression of Wnt and Hedgehog signaling. 4SC-202 provokes the inhibition of stemness-related properties of cancer cells and affects their viability. **Methods:** Patients with advanced hematological malignancies including AML, ALL, CLL, MM, MDS or lymphoma were orally dosed either once daily (QD) or twice daily (BID) from days 1 to 14, or BID continuously, in a 21-day cycle. Dose escalation followed a 3+3 design. Study objectives include safety, tolerability and pharmacokinetics (PK), determination of MTD and DLT as well as optimization of dosing. Biomarker program includes measuring of HDAC inhibition, total lysine acetylation and gene expression profiling. Additionally, the anti-tumor effect of 4SC-202 was evaluated. Dose escalation part is completed and data allow for reliable evaluation. Further patients will be enrolled to establish the MTD at prior dose levels. **Results:** 24 patients were treated at 7 dose levels of 25/50/100/200/400mg QD and 200mg BID (N=3, each), and 200mg BID continuous dosing (N=6). Treatment was very well tolerated by heavily pre-treated patients up to the highest dose group. Possibly drug-related AE were less frequent, e.g. low-grade GI complaints such as nausea. Higher-grade hematological toxicity e.g. leading to treatment changes was not observed. Elevation of liver enzymes was observed at 200mg BID during continuous dosing. Two objective responses (PR & CR, unconfirmed) were observed. 75% of patients went into follow-up treatment due to stable disease. Median time on treatment was 98 days with 3 patients treated > 400 days. Plasma exposure reached one digit $\mu$M concentrations over 24h. Modulation of Wnt pathway gene-signature was observed in blood samples, as well as HDAC inhibition and lysine acetylation. **Conclusions:** 4SC-202 could be safely administered up to 200mg BID. Anti-cancer activity could be demonstrated by two patients achieving PR and CR, respectively, and long term stabilization of several patients. The mode of action of 4SC-202 is demonstrated by biomarker response. Clinical trial information: NCT01344707.

**8560 General Poster Session (Board #247), Mon, 1:15 PM-5:00 PM**

**A multicenter study of 66 patients with spinal cord compression at diagnosis of B-cell non-Hodgkin lymphoma.** *Presenting Author: Isabelle Fleury, AP-HP at Saint-Louis Hospital, Paris Diderot- Sorbonne University, Paris, France*

**Background:** Spinal cord compression (SCC) in non-Hodgkin lymphoma (NHL) is rare but associated with an increased risk of central nervous system (CNS) relapse. Our objective was to retrospectively analyze the outcome of patients with SCC caused by B-cell NHL and their CNS relapse risk. **Methods:** Patients with SCC at diagnosis of B-cell NHL from six centers in France were eligible. Burkitt and HIV-related lymphoma were excluded. Intradural extension on spine imaging was centrally reviewed. The primary endpoints were progression-free survival (PFS) and relapse site. Survival functions were estimated by the Kaplan-Meier method and compared by the log-rank tests. **Results:** We identified sixty-six patients treated between 1987 and 2012. Median age was 61,5 years. Histology was: diffuse large B cell (DLBCL) (71%), follicular (19%), small lymphocytic (6%), marginal zone (3%) and B-cell unclassified (3%) lymphomas. An intradural extension of lymphoma was detected in 29% (10/35) of the patients and cytological analysis of cerebrospinal fluid (CSF) revealed an infiltration in 9% (5/58) of the patients. Twenty-eight (42%) patients were managed by a surgical decompressive procedure before chemotherapy. All but two patients received CHOP or CHOP-like regimen and 61% received rituximab. Forty-six patients received CNS prophylaxis based on intravenous methotrexate and/or intrathecal therapy. At a median follow-up of 53 months, 5-year OS was 64% and 5-year PFS was 53%. CNS relapses occurred in 4 (6%) patients with DLBCL, all involving the cerebellum. Non-CNS relapse occurred in twenty (30%) patients. Neither CSF involvement nor intradural extension influenced PFS ($p = 0.5544$ and $p = 0.3399$ respectively). Initial decompressive surgery did not influence PFS or OS ($p = 0.4231$, and $p = 0.1823$ respectively). The use of at least 3 g/m$^2$ of MTX or the lack of any CNS prophylaxis modality did not influence PFS ($p = 0.1414$ and $p = 0.8221$ respectively). **Conclusions:** SCC at diagnosis of B-cell NHL carries a low risk of CNS relapse. Outcomes were not improved by CNS prophylaxis. Benefit from CNS prophylaxis according to intradural extension needs prospective evaluation.

**8561 General Poster Session (Board #248), Mon, 1:15 PM-5:00 PM**

**Stage migration and survival in DLBCL patients before and after the approval of positron emission tomography (PET) scan: Population-based analysis using the U.S. National Cancer Data Base (NCDB).** *Presenting Author: Anusha Reddy Madadi, Gundersen Lutheran Medical Center, La Crosse, WI*

**Background:** PET scan was approved by the US Medicare for diagnosis and staging of NHL in July 2001. We studied the DLBCL stage distribution and overall survival (OS) before and after introduction of PET scan. **Methods:** We identified DLBCL patients diagnosed in 1998 to 2011 from the NCDB. We obtained data pertaining to stage and OS. We grouped patients into 2 cohorts: pre (1998-2001) and post (2002-2005) PET approval. To minimize bias in improvement of OS due to new treatments, year 2005 cut-off was chosen as rituximab was approved by the US Food and Drug Administration for treatment of B-cell NHL in 2006. **Results:** There were 202,294 patients with DLBCL. Of these, 30.5% had extra-nodal disease presentation. The stage distribution over time is shown in table 1. Overall, early stage disease (I/II) remained relatively stable over time (35.1% in 1998 to 38.3% in 2011). Advanced stage disease (III/IV) increased from 30.7% to 51.8%. In contrast, patients with unknown stage decreased from 34.2% to 9.4%. We observed similar stage migration in both nodal and extra-nodal DLBCL subgroups.The median OS was significantly better (all P values $< 0.001$) in the post-PET approval era for all stages: combined (64.5 vs. 38.4 months), I/II (not reached (NR)[mean 103.8 months]) vs. (NR [mean 75.3 months]), III/IV (28.2 vs. 13.0 months), and unknown (57.2 vs. 39.9 months). **Conclusions:** Since the approval of PET scan for NHL diagnosis and staging in 2001, there has been a substantial change in the stage distribution among DLBCL patients. This is predominantly due to a migration from unknown stage into advanced stage disease. The OS has improved across all stages but most marked among patients with advanced stage disease. The latter may be in part due to stage migration.

| Stage (%) | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I | 20.2 | 21.7 | 21 | 20.2 | 19.8 | 21.6 | 20.9 | 20.3 | 19.9 | 19.4 | 21 | 20.9 | 20.7 | 20.9 |
| II | 14.9 | 14.9 | 15.3 | 15.4 | 15.8 | 16.4 | 17 | 17 | 16.2 | 16.6 | 17.8 | 18.4 | 18.1 | 17.3 |
| III | 10.6 | 10.6 | 11 | 11.3 | 11.7 | 13.2 | 13.6 | 14.8 | 14.8 | 14.9 | 16.6 | 16.8 | 17 | 17.9 |
| IV | 20.1 | 21 | 21.4 | 21.6 | 22.7 | 26.8 | 26.9 | 27.9 | 28.2 | 28.3 | 31.3 | 32.5 | 33.5 | 34.5 |
| Unknown | 34.2 | 31.8 | 31.3 | 31.5 | 30 | 22 | 21.6 | 20 | 20.9 | 20.8 | 13.3 | 11.4 | 10.7 | 9.4 |

**8562 General Poster Session (Board #249), Mon, 1:15 PM-5:00 PM**

**Early negative circulating EBV DNA as prediction of survival in extranodal NK/T-cell lymphoma, nasal type (ENKL).** *Presenting Author: Chaoyong Liang, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China*

**Background:** Predictive tumor markers are essential for extranodal NK/T cell lymphoma, nasal type (ENKL), which pursues an aggressive clinical course with poorer prognosis. This prospective study was conducted to evaluate the dynamic monitoring value of circulating EBV DNA concentration for the prediction of ENKL. **Methods:** From Jan 2006 to Aug 2012, plasma samples from 113 ENKL pts were collected before and/or every 2 cycles of chemotherapies for circulating EBV DNA measurement by a real-time PCR assay. **Results:** The positive rate of circulating EBV DNA was 61.9% (70/113) with a median concentration of $1.21\times10^3$copies/ml. After two cycles of chemotherapies, 45 pts were tested circulating EBV-DNA and 53.33% (24/45) pts became negative EBV-DNA candidates. There were 87.5% (21/24) pts obtained complete remission at the end of the treatment, comparing as 42.86% (9/21) in the still positive EBV-DNA groups(P= 0.002). There was a tendency that the pts whose circulating EBV-DNA became negative after two cycles would have better prognosis (5-year OS: 75% vs 46%, P=0.074). The similar situation of CR rate and OS happened in the EBV-DNA detection of completion of total chemotherapies. The more advance of the stage, the higher concentration of EBV-DNA was found. When divided the positive group as low and high-dose ones by the cut-off value as $2\times10^4$copies/ml, the CR rate of the high-dose group was much lower and the 5-year OS was significantly better than the low-dose group and the negative group.7 of 13 relapsed pts of $>1\times10^3$copies/ml EBV-DNA at the time of recurrent, and the survival outcome was dismal for them compared to the other 6 pts of $\leq1\times10^3$copies/ml(5- year OS: 0% vs 80%, P=0.001). **Conclusions:** Circulating EBV-DNA level can predict the efficacy of treatment as a dynamic marker of ENKL. Pts with early positive detection of EBV-DNA after 2 cycles of chemotherapy maybe received more aggressive treatments.

**8563 General Poster Session (Board #250), Mon, 1:15 PM-5:00 PM**

**Responses to romidepsin by line of therapy in patients with relapsed/refractory (R/R) peripheral T-cell lymphoma (PTCL).** *Presenting Author: Francine M. Foss, Yale Cancer Center, New Haven, CT*

**Background:** Most patients with PTCL, an aggressive form of non-Hodgkin lymphoma, experience R/R disease with few effective salvage treatments. Romidepsin is a histone deacetylase inhibitor approved by the US FDA for treatment of patients with PTCL who have received $\geq$ 1 prior therapy. Durable clinical responses (objective response rate [ORR] of 25% and median duration of response [DOR] of 28 mo; median follow up 22.3 mo) and tolerability with extended dosing have been reported. As heavily pretreated patients are especially challenging, responses to romidepsin by line of therapy were examined herein. **Methods:** Patients with PTCL (N = 130) who were R/R to $\geq$ 1 prior therapy received romidepsin 14 mg/m$^2$on days 1, 8, and 15 every 28 days. The primary endpoint was confirmed/unconfirmed complete response (CR/CRu), and secondary endpoints included ORR (CR/CRu + partial responses) and DOR; progression-free and overall survival (PFS, OS) were also assessed. In this analysis, baseline characteristics, responses to therapy, and safety are examined for patients who received 1, 2, or $\geq$ 3 prior therapies. **Results:** Nearly all patients received chemotherapy in the first line, and patients with more lines of prior therapy were more likely to have prior radiation, monoclonal antibody or other immunotherapy or stem cell transplant. Response rates, DOR, and survival with romidepsin were not significantly different for patients with R/R PTCL who received 1, 2, or $\geq$ 3 prior therapies, though heavily pretreated patients discontinued due to adverse events (AEs) more frequently (Table). **Conclusions:** Romidepsin resulted in durable responses in patients with 1, 2, or $\geq$ 3 prior treatments for PTCL. These data support the use of romidepsin in the second line, particularly as patients with PTCL may receive a limited number of regimens due to age or comorbidities. Clinical trial information: NCT00426764.

| | Prior therapies | | |
|---|---|---|---|
| | 1 (n = 38) | 2 (n = 44) | ≥ 3 (n = 48) |
| ORR, n (%) | 9 (24) | 10 (23) | 15 (31) |
| CR/CRu | 5 (13) | 7 (16) | 8 (17) |
| DOR, median (range), mo | NE (1.9-33.9) | NE (< 0.1-56.3) | 16.4 (< 0.1-37.3) |
| PFS, median (range), mo | 5.4 (0.4-35.5) | 3.1 (0.3-57.9) | 3.8 (0.3-38.9) |
| OS, median (range), mo | 18.2 (0.4-36.6) | 9.4 (0.3-58.1) | 9.2 (1.3-53.8) |
| Discontinuation due to AEs, n (%) | 6 (16) | 6 (14) | 12 (25) |

Abbreviation: NE, not estimable.

**8564 General Poster Session (Board #251), Mon, 1:15 PM-5:00 PM**

**Treatment outcomes and prognostic factors for primary mediastinal B-cell lymphoma: The MD Anderson experience.** *Presenting Author: Mohamed Amin Ahmed, Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Primary mediastinal B-cell lymphoma (PMBL) has been treated with different chemotherapy regimens. We reviewed medical records and histopathology to determine predictive factors and outcomes for patients (pts) with PMBL seen at the MD Anderson Cancer Center (MDACC) between 1995 and 2013. **Methods:** Baseline characteristics complete (CR) and partial (PR) response to initial therapy, and status of disease and survival over time were collected. Event-free survival (EFS) was based on dates of relapse, progression, or death. Radiotherapy data will be presented separately. **Results:** 274 pts with PMBL were identified, making this the largest single-center retrospective report of PMBL. Median age was 40 years (range, 17-86), and 149 pts (54%) were female. For patients treated with R, the CR rates were higher, and EFS and overall survival (OS) were improved for all pts at the median follow-up (MFU) of 38 months (mo), and for CHOP-treated pts at MFU of 37 mo (Table). As R is now standard with initial therapy, we analyzed results for the 3 main R-containing therapies (Table). By univariate log-rank analysis, therapy choice affected the CR rate, and EFS at MFU of 39 mo. R-HCVAD had superior EFS vs. R-CHOP (p=0.015), even though low-stage pts were more common for R-CHOP. For pts given the 3 main R-containing therapies, higher stage (III/IV vs. I/II) was an adverse univariate predictor for EFS (p=0.036) and OS (p=0.04), and B symptoms were adverse for OS (p = 0.026). Multivariate Cox analysis including stage, B symptoms, and therapy (CHOP vs. EPOCH/HCVAD) found only B symptoms to be predictive of shorter OS (p = 0.032), and only treatment to be predictive of shorter EFS (p=0.029). **Conclusions:** Response rates and survival outcomes are improved for pts with PMBL by R and its use with intensified therapy (R-HCVAD or R-EPOCH). Longer follow-up is needed to compare R-HCVAD and R-EPOCH.

| Rituximab (R) | No (n=74) | | | Yes (n=200) | | | | |
|---|---|---|---|---|---|---|---|---|
| Front line | CHOP | Triple therapy | Other | Other | R-CHOP | R-HCVAD | R-EPOCH | P value |
| Patients, # | 42 | 25 | 7 | 6 | 123 | 41 | 30 | |
| CR, % | | 58 | | | | 81 | | <0.001 |
| EFS, % | | 37 | | | | 72 | | <0.001 |
| OS, % | | 58 | | | | 87 | | <0.001 |
| EFS, % | 35 | | | | 65 | | | <0.001 |
| OS, % | 51 | | | | 86 | | | <0.001 |
| CR, % | | | | | 76 | 93 | 83 | 0.046 |
| CR+PR, % | | | | | 90 | 98 | 97 | NS |
| EFS, % | | | | | 65 | 88 | 79 | 0.013 |
| OS, % | | | | | 85 | 92 | 100 | NS |
| Stage I/II, % | | | | | 83 | 61 | 77 | 0.014 |

Abbreviation: NS, not significant.

**8565 General Poster Session (Board #252), Mon, 1:15 PM-5:00 PM**

**The utility of HTS TCR analyses in the management of patients with T-cell malignancies.** *Presenting Author: Ilan Lanny Kirsch, Adaptive Biotechnologies, Seattle, WA*

**Background:** We have pioneered a method to sequence the diversity of the TCR CDR3 rearrangements that exploits the capacity of high-throughput sequencing (HTS) to document the diverse repertoire of *TCR* CDR3 chains. **Methods:** These assays can describe both the breadth of T-cell repertoire diversity and quantify individual clones. This technology thus provides an opportunity to identify and then track the presence and frequency of clones in lymphoid malignancies. **Results:** HTS improves the detection and monitoring of minimal residual disease in precursor acute T lymphoblastic leukemias over other available methods. We have also sequenced the *TCRB* repertoire in a morphologic mix of T-cell lymphoma specimens. HTS of *TCRB* was concordant with flow cytometry or PCR-based evaluation of *TCRG* rearrangement in 46 of 59 samples with recognition of residual disease based on the previously identified diagnostic index clones. However, 5 samples were only positive for recurrent disease based on HTS. We have also demonstrated the ability of HTS to detect malignant cells beneath the level of detection of flow cytometry in a cohort of patients with Sezary Syndrome and have also demonstrated the utility of this assay for early detection of relapse and for providing potential useful information that distinguishes among drug toxicity, GVHD, or clinical relapse in skin lesions from this same patient population following allogeneic transplant. In an analysis of skin biopsies from patients with CTCL in which data from flow cytometry, qPCR, and HTS were performed comparatively, HTS was able to identify a significantly greater number of trackable diagnostic clones in the suspect lesions and distinguish malignant from non-malignant lesions. **Conclusions:** HTS TCR repertoire profiling is the most sensitive and accurate method for clonal detection and monitoring in T-cell malignancies. The assay is now being incorporated into clinical management in CTCL.

**8566 General Poster Session (Board #253), Mon, 1:15 PM-5:00 PM**

**A phase 1/2 study of lenalidomide and bendamustine (LEBEN) in chemorefractory Hodgkin lymphoma.** *Presenting Author: Gaetano Corazzelli, Hematology-Oncology and Stem Cell Transplantation Unit, Istituto Nazionale Tumori, Fondazione G. Pascale, Naples, Italy*

**Background:** Implementing strategies for Hodgkin lymphoma (HL) patients failing stem cell transplantation (SCT) remains a crucial need. We investigated for the first time safety and efficacy of a combination of lenalidomide and bendamustine (LEBEN), two agents synergistically framing different targets on both neoplastic and microenvironment tumor-supporting cells of HL. **Methods:** A weekly schedule of bendamustine (60 $mg/m^2$; d 1, 8, 15) plus continuous daily lenalidomide (10, 15, 20 or 25 mg), in a 28-day cycle, was tested in a Bayesian phase 1/2 study (Thall & Cook, Biometrics 2004) defining the optimal lenalidomide dosage through the best efficacy/toxicity trade-off. Response (CR or PR at PET/CT) and toxicity (CTCv3.0 grade >3 lasting >2 weeks) endpoints were assessed at 2 cycles (day +56). Non-progressing patients received additional 4 courses. **Results:** Seventeen chemorefractory patients [SCT failures n=12 (single auto SCT, n=4; tandem n=3; tandem auto/allo, n=5 ); unresponsive to pre-SCT salvage, n=5] were enrolled in 6 cohorts of 3. Patients [males, 80%; median age 29 years (r,19-56)] had a median of 4 prior therapies (r, 2-9), including brentuximab (n= 5). A median of 5 cycles was delivered to 15 evaluable patients. The primary endpoint analysis at 2 cycles showed response without toxicity in 9 patients (60%), response with toxicity in 2 (13%), neither efficacy and toxicity in 4 (27%), toxicity without response in none. The overall response rate (ORR; CR+PR) was 73% with 6 CRs (40%). After 4 cycles, ORR increased to 12/15 (80%) and CRs to 8/15 (53%). The median PFS was 8.7 months. Response was associated to change in circulating myeloid-derived suppressor and dendritic cells. Most common AEs (71 cycles) were (any grade%/≥G3%) diarrhea (27/3), rash (14/3), neutropenia (72/44), thrombocytopenia (65/24), lymphopenia (88/34). Due to the highly favorable efficacy/toxicity trade-off achieved, the Monitoring Committee proposed 10 mg as the optimal lenalidomide dose for subsequent patients. **Conclusions:** Continuous lenalidomide with low-dose protracted bendamustine was very active and well tolerated in highly refractory HL patients. Enrollment continues, and updated results with correlative data will be presented. Clinical trial information: NTC01412307.

**8567 General Poster Session (Board #254), Mon, 1:15 PM-5:00 PM**

**Temsirolimus (TEM) and lenalidomide (LEN) in relapsed/refractory Hodgkin lymphoma including in patients with prior exposure to brentuximab vedotin (BV).** *Presenting Author: Jagoda Jasielec, The University of Chicago, Chicago, IL*

**Background:** Hodgkin lymphoma (HL) patients (pts) ineligible for or relapsed after transplant pose a considerable treatment (tx) challenge. While BV is an active agent in this setting, HL remains incurable and new therapies are needed. The PI3K/Akt/mTOR axis and the microenvironment are rational targets in HL. We previously reported phase I results of a phase I/II study of TEM and LEN across lymphoma subtypes demonstrating good tolerability (J Clin Oncol 30, 2012 abstr 8075). Here we report the results of an interim analysis of HL patients. **Methods:** NCI8309 is a multi-institutional phase II trial with 3 cohorts. Cohort C includes R/R HL.Key inclusion criteria are: ANC > 1,000/uL, platelets > 75,000/uL, normal renal and hepatic function, ECOG performance status of ≤2. Pts receive TEM 25 mg IV weekly and LEN 20 mg orally on D1-D21, q28 days until progression/intolerability up to 1 year. Responses are evaluated using the Cheson 2007 criteria at 2 months (mos), then every 3 mos thereafter. **Results:** Thirteen pts (8 male, 5 female) with a median age of 32 years (range, 23-53) were enrolled and evaluable. Pts received a median of 4 prior therapies (range, 2-11); 5 had prior radiation, 8 had prior autologous stem cell transplant (ASCT), and two received both ASCT and an allogeneic transplant. Importantly, 11/13 pts relapsed after BV. With a median follow-up of 9 mos, pts received a median of 4 cycles (range, 2-11) of therapy. The best overall response rate was 85%: 5 (38%) complete responses, 6 (46%) partial responses, 1 (8%) stable disease; median time to best response was 2 cycles. One pt progressed prior to planned evaluation and subsequently died of disease. Of the remaining 12 pts, 5 eventually progressed and 4 went on to transplant including 1 pt with progressive disease. The most common grade 1/2 toxicities included hyperglycemia (77%), fatigue (70%), and LFT abnormalities (77%). The most common grade 3/4 toxicities were neutropenia (46%), thrombocytopenia (38%), and lymphopenia (38%). **Conclusions:** The combination of TEM plus LEN shows promising activity in R/R HL, including prior BV exposure or failure and warrants further evaluation. Clinical trial information: NCT01076543.

**8568 General Poster Session (Board #255), Mon, 1:15 PM-5:00 PM**

**Allogeneic hematopoietic stem cell transplantation in a cohort of 314 advanced lymphoma patients.** *Presenting Author: Sylvain Garciaz, Institut Paoli Calmettes, Marseille, France*

**Background:** Patients with refractory/relapsed Hodgkin Lymphoma and Non Hodgkin Lymphoma (R/R HL-NHL) have poor prognosis. Allogeneic stem cell transplantation (allo-HSCT) represents a potentially curative strategy. The increased use of Reduced Intensity conditioning (RIC) regimens has decreased the non-relapse mortality (NRM) previously reported with myeloablative conditioning. However, Chronic Graft versus Host disease (cGVHD) is still matter of concern. The aim of this study is to evaluate the long-term survival of a cohort of R/R HL-NHL. **Methods:** From 9/1999 to 10/2013, 314 patients from 2 associated institutions received allo-HSCT. Diagnoses were aggressive-NHL in 157 patients, indolent-NHL in 59 and HL in 98. 148 patients relapsed after autologous transplant (auto-HSCT). Out of the 166 remaining patients, 109 received a tandem auto-allo-HSCT and 57 benefit of allo-HSCT without prior auto-HSCT. At transplant, 172 were on complete remission, 86 were on partial remission and 56 were not in response. Donors were HLA identical sibling in 54%, unrelated in 21% and haploidentical in 21%. Conditioning regimen consisted in RIC in 68% of cases. **Results:** With a median follow-up of 29 months [2-160] the 5-year overall survival (OS), the 5-years progression free survival (PFS) and the five years incidence of relapse were 53.9% [47-61], 47.2% [41-54] and 26%[21-32]. The 1-years NRM was 18% [14-23]. Incidence of acute and chronic GVHD was 28% (9% grade 3-4) and 35% (severe NIH cGVHD: 14%). The median duration of immunosuppressive therapy was 7 months [2-117] and it was interrupted in 72% at 1 year for patients who did not relapse. In multivariate analysis, disease status at transplant only influences OS. Age, comorbidities, prior auto-ASCT, donor and conditioning regimen do not have any significant prognostic impact. **Conclusions:** Allo-ASCT is an option for patients with R/RHL-NHL with a 5-years OS of 54% and PFS of 47%. Taking into account population characteristics and period of treatment, toxicity is acceptable with only 14% of severe NIH cGVHD. Most of patient (72%) could stop immunosuppressive therapy demonstrating the absence of GVHD affecting their quality of life.

**8569 General Poster Session (Board #256), Mon, 1:15 PM-5:00 PM**

**PET/CT in lymphoma surveillance: A large single-center experience.** *Presenting Author: Lourdes M. Mendez, Beth Israel Deaconess Medical Center, Boston, MA*

**Background**: The role of FDG PET-CT in the modern management of lymphoma continues to evolve. Current guidelines are largely based on studies with limited numbers of patients. The aim of this study was to define the utility of PET-CTs in identifying asymptomatic relapsed disease during post-treatment follow-up. **Methods**: We performed a large, retrospective cohort study of all PET-CTs performed for patients with pathologically proven lymphoma at our institution from 2003-2005. 1,085 consecutive PET-CTs from 370 patients with lymphoma and accompanying clinical data were reviewed. 81 patients had Hodgkin lymphoma (HL), 154 aggressive Non-Hodgkin lymphoma (a-NHL) and 135 indolent Non-Hodgkin lymphoma (i-NHL). Most scans were obtained in the post-treatment setting (861: either at completion of therapy or during follow-up); 110 and 114 were performed as part of initial staging and during therapy respectively and were excluded from the following analysis. **Results**: 44% of all scans were positive of which 75.7% were associated with progressive disease and 24.3% with disease remission. PET-CT had a sensitivity of 97.5%, specificity of 90.3%, PPV of 75.7% and NPV of 99.2% for relapsed disease in our cohort (Table 1 shows sub-group statistics). The false positive rate for PET-CT was 24.3% most often leading to further imaging. In comparison, the presence of symptoms had a sensitivity of 43.6%, specificity of 88.5%, PPV of 53.8% and NPV of 83.7% without significant variation among HL, a-NHL and i-NHL. Notably, 52% of a-NHL patients with relapsed disease documented by PET-CTs were asymptomatic. **Conclusions**: Our results indicate that PET-CT is highly sensitive for detecting progressive lymphoma in the context of post-treatment follow-up offset by a high rate of false-positives. This highlights the need for algorithms incorporating additional parameters for risk stratification. In this series, a significant portion of a-NHL recurrences detected by PET-CTs were clinically silent. Analysis of how detection of asymptomatic relapse affects patient outcomes is underway.

**Measures of performance of PET-CT by lymphoma subgroup.**

| Lymphoma | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|
| **HL** | 100 | 94 | 80.5 | 100 |
| **a-NHL** | 97.8 | 76.1 | 50.9 | 99.3 |
| **i-NHL** | 96.3 | 90.2 | 82.3 | 98.1 |

**8570 General Poster Session (Board #257), Mon, 1:15 PM-5:00 PM**

**CNS involvement in patients with AIDS-related lymphomas.** *Presenting Author: Jitesh Joshi, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY*

**Background:** CNS involvement (CNSi) at baseline and CNS relapse (CNSr) appears increased in pts with AIDS-related lymphomas (ARL) although this has not been systematically examined. The aim of our study was to better describe factors and outcomes associated with CNSi at baseline and relapse in patients with ARL. **Methods:** We used an existing database of patients with newly diagnosed ARL (Barta et al, Blood 2013) and identified 886 pts with complete information on CNSi at baseline and relapse. We used descriptive statistics to define the prevalence of baseline CNSi and incidence of CNSr. We used Cox-proportional hazard models to assess associations of baseline characteristics (age, sex, time of enrollment, CD4 count, viral load, hx of prior AIDS, concurrent cART, lymphoma subtype, IPI, type of initial chemotherapy, rituximab use) with CNSr, and the Kaplan-Meier method to assess overall survival (OS) for patients with baseline CNSi or CNSr. **Results:** 69% of the pts (n=607) were treated in the post-cART era; 31% (n=276) received rituximab-containing induction chemoimmunotherapy. All included 880 pts received either intrathecal (IT) therapy for CNSi or IT prophylaxis (ppx) with 1- or 3-agent regimens. CNSi at diagnosis was found in 13 % (BL/BLL 27%; DLBCL 6%; $p < 0.001$). There was no difference in the prevalence of baseline CNSi between pre- and post-cART era (13% each). 5.3% of pts experienced CNSr at a median of 4.2 mo (0.3-19.3) after diagnosis (12% if CNSi at baseline; 4% if not). Median OS after CNSr was 1.6 mo (0-86.4). On multivariate analysis, only baseline CNSi was significantly associated with frequency of CNSr (HR 2.9, p=0.01), but no other baseline characteristic. When restricted to pts with no CNSi at diagnosis, IT CNS ppx with 3 vs. 1 agent did not significantly impact the frequency of CNSr (HR 0.33, p= 0.38). CNSi vs. no CNSi at diagnosis was not associated with reduced OS (HR 0.85, p= 0.32). **Conclusions:** 5% of patients with ARL treated with IT CNS-directed therapy experience CNS relapse; it occurs early and has a poor outcome. We did not find a reduced frequency of CNSr with the use of cART, rituximab, or 1- vs. 3-agent IT CNS ppx. Although CNSi at diagnosis confers a 2.9-fold higher risk for CNSr, it does not appear to impact OS, likely because of the low overall frequency of CNSr.

**8571 General Poster Session (Board #258), Mon, 1:15 PM-5:00 PM**

**Association of *helicobacter pylori* CagA translocation with the expression of CagA-signaling transduction molecules in gastric mucosa-associated lymphoid tissue lymphoma.** *Presenting Author: Sung Hsin Kuo, National Taiwan University Hospital, Taipei, Taiwan*

**Background:** We previously reported that a direct contact of *Helicobacter pylori* (HP) with B cells results in CagA translocation into the latter, and the translocated CagA regulates intracellular signaling pathways. Toward this end, we recently found that CagA do exist in the malignant B cells of gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and its presence is closely associated with HP-dependence. In this study, we further evaluate whether CagA expression regulates signaling transduction molecules in tumor cells of HP-positive gastric MALT lymphoma. **Methods:** Forty-seven patients of stage IE HP-positive gastric MALT lymphoma, who received *HP* eradication as their frontline therapy, were included. The expression of CagA, and its signaling pathway-related proteins, such as phosphorylated-SHP-2 (p-SHP-2), p-ERK, p-p38MAPK, Bcl-2, and Bcl-xL in tumor cells were evaluated by immunohistochemistry. **Results:** There were 25 HP-dependent and 22 HP-independent cases. Expression of CagA was closely associated with p-SHP-2 ($P = .012$), p-ERK ($P = .002$), p-p38MAPK ($P = .006$), Bcl-2 ($P = .020$, and Bcl-xL ($P = .006$) expression. Spearman's correlation coefficient analysis showed the strong correlation between CagA-signaling transduction molecules. Combined CagA expression, p-SHP-2 expression and p-ERK expression showed an increased positive predictive value (93.3% [14/15] versus 81.8% [18/22]) and an increased specificity (95.5% [21/22] versus 81.8% [18/22]) for HP-dependence than CagA expression alone. **Conclusions:** Our results indicate that the expression of CagA protein is biologically active and is associated with activation of its downstream signals of HP-dependent gastric MALT lymphoma.

**8572 General Poster Session (Board #259), Mon, 1:15 PM-5:00 PM**

**Hodgkin lymphoma-like post-transplant lymphoproliferative disorder (HL-PTLD): Characteristics, survival, and prognostication in a large U.S. cohort.** *Presenting Author: Aaron Seth Rosenberg, Tufts Medical Center, Boston, MA*

**Background**: Post-transplant lymphoproliferative disorder is a well described complication of solid organ transplant (SOT), however relatively little is known about HL-PTLD. **Methods**: We examined a large cohort of HL-PTLD (1999-2011) in the Scientific Registry of Transplant Recipients (SRTR), focusing on detailed characteristics, overall survival (OS), and prognostic factors. Cox-proportional hazards models were utilized to estimate hazard ratios (HR) and 95% confidence intervals (CI); and we compared characteristics and OS with HL pts from SEER 18. **Results**: We identified 204 HL-PTLD pts. Median age at diagnosis was 52 years (0-80); 74% were male, 82% Caucasian and the most common SOT was renal (52%). Median time from SOT to HL-PTLD was 6.9 years (<0.1-20 years), while tumor was EBV+ in 73%. Older pts were more likely to have EBV- disease (OR 1.42/decade, (95% CI 1.14-1.81), $P<0.01$), however early vs late HL-PTLD was not associated with EBV status. Compared with SEER HL, HL-PTLD pts were older (median 52 vs 38 years, $P=0.006$), more often male (74% vs 55%, $P<0.001$) and with more extranodal (43% vs 3%, $P<0.001$). Median OS for HL-PTLD was 6.3 years with 3- and 5-year OS rates of 65% and 55%, respectively. These rates were significantly inferior compared with SEER HL pts (83% and 79%, respectively, $P<0.001$). For HL-PTLD pts, age (HR 1.29/decade (95% CI 1.15-1.44) $P<0.001$), EBV- (2.03 (95% CI 1.03-4.01) $P=0.04$), increased creatinine (Cr) (HR 1.87 (95% CI 1.43-2.44) $P<0.01$), and performance status <80 (HR 2.10 (95% CI 1.06-4.17) $P=0.03$) were associated with increased risk of death. When controlling for age, only Cr remained significant. Finally, on multivariable analysis controlling for diagnosis date, age, sex and extranodal status, HL-PTLD pts had twice the risk of death (HR 2.05 (95% CI 1.65-2.55) $P<0.001$) vs SEER HL pts. **Conclusions**: These data represent the largest report of HL-PTLD to date. HL-PTLD pts are commonly older, male, and have EBV+ disease, the latter despite typically having "late" PTLD. The dominant factors predicting OS were age and Cr. In addition, OS for HL-PTLD was modest and significantly inferior to a SEER HL population. Continued study of HL-PTLD is needed.

**8573 General Poster Session (Board #260), Mon, 1:15 PM-5:00 PM**

**Polymorphism *BCL2* c(-717)a and prognosis in diffuse large B-cell lymphoma patients.** *Presenting Author: Angelo Borsarelli Carvalho Brito, Department of Internal Medicine, Faculty of Medical Sciences, University of Campinas, Campinas, Brazil*

**Background:** High expression of the anti-apoptotic BCL-2 protein was previously described as a predictor of poor prognosis in diffuse large B cell lymphoma (DLBCL). The *BCL2* gene is polymorphic in humans and the single *BCL2* C(-717)A nucleotide polymorphism (SNP) has its variant AA genotype associated with increased Bcl2 expression. The aim of this study was to evaluate whether the *BCL2* C(-717)A SNP influence the outcome of DLBCL patients. **Methods:** Our prospective analysis included 122 consecutive DLBCL patients at diagnosis seen at the Hematology and Hemotherapy Center, between December 2007 and October 2013. Median age of patients was 57 years old (range: 17-89), 63 patients (51.6%) were females, 89 patients (72.9%) had B symptoms, 21 patients (17.2%) had bone marrow involvement (BMI), and 73 (59.8%) patients had advanced tumors (Ann Arbor stage III or IV). Genomic DNA from peripheral blood of all individuals was analysed by polymerase chain reaction followed by enzymatic digestion for discrimination of distinct *BCL-2* C (-717)A genotypes. Patients received 6 cycles of R-CHOP as treatment. Overall survival (OS) time was calculated using the Kaplan-Meier estimate probabilities, and differences between survival curves were analysed by the log-rank test. OS was calculated from date of diagnosis until the date of death or last follow-up. **Results:** The median of observation of patients enrolled in the study was 23 months (range: 1-68). On univariate analysis, B symptoms (68% *versu*s 86%, P=0.04), BMI (52% versus 77%, P=0.01), stage IV (59% versus 82% P=0.01), and BCL2 -717 CA+AA genotype (68% versus 88%, P=0.04) were predictive of worse outcome of DLBCL patients at 24 months of follow up. **Conclusions:** The data present, for the first time, preliminary evidence that inherited abnormality in intrinsic pathway of apoptosis, related to the SNP *BCL2* C(-717)A, influence the outcome of DLBCL patients treated with conventional chemotherapy regimen.

**8574 General Poster Session (Board #261), Mon, 1:15 PM-5:00 PM**

**Reverse phase protein microarray for identification of IL6 receptor ligation-induced insulin receptor, PI3K/AKT, and JAK/STAT signaling pathways in the CARD11 mutated lymphoma cell line OCI-Ly3.** *Presenting Author: Greg Coffey, Portola Pharmaceuticals, Inc., South San Francisco, CA*

**Background:** A subset of diffuse large B cell lymphoma of the activated B cell subtype bear mutations that drive B cell antigen receptor (BCR) independent chronic activation of NFkB. The consequence appears to be loss of dependency for survival on BCR proximal kinases (BTK, SYK) and the initiation of a cytokine autocrine stimulation loop conferring an alternate survival mechanism. In the OCILy3 cell line, for example, IL6 is produced de novo as a consequence of NFkB gene transcription, and both neutralizing anti-IL6 antibody and small molecule JAK inhibition affects cell survival. The exact nature of this survival mechanism, however, is unclear. The goal of our studies was to more clearly define the molecular events induced by IL6 stimulation that promote survival inOCILy3 DLBCL. **Methods:** Reverse phase protein microarray is a high throughput methodology to evaluate multiple intracellular phosphoryaltion events in whole cell lysates. Using a panel of 180 phospho-specific antibodies, we assessed phosphorylation events in OCILy3 cells following IL6 receptor stimulation with and without treatment with the dual SYK/JAK inhibitor PRT062070 (Cerdulatinib). **Results:** 28 of the 180 phosphorylation events tested were induced by approximately 20% or greater upon IL6 receptor stimulation. The most heavily represented categories were within the PI3K/AKT/mTOR, insulin receptor, and JAK/STAT signaling pathways. This was evidenced most notably by robust IL6-mediated induction of Akt, Foxo3a, insulin growth factor receptor and insulin substrate, as well as STAT3 and STAT5 phosphorylation. Treatment with PRT062070 completely inhibited these phosphorylation events. Moreover, PRT062070 dramatically reduced basal phosphorylation of STAT3 Y705, Foxo3a S253, S6Rb S235/236, NFkB p65 S536, BIM S69, and BCL2 T56, and inhibited OCILy3 survival. **Conclusions:** We conclude from these data that in a subset of B cell lymphomas, IL6 receptor signaling likely contributes to survival via induction of multiple signaling arms, not limited to JAK/STAT pathway activation.

**8575 General Poster Session (Board #262), Mon, 1:15 PM-5:00 PM**

**Responses to romidepsin in patients with cutaneous T-cell lymphoma (CTCL) with tumors and/or folliculotropic involvement.** *Presenting Author: Francine M. Foss, Yale Cancer Center, New Haven, CT*

**Background:** CTCL is a heterogeneous group of non-Hodgkin lymphomas that arises in the skin (patches, plaques, tumors, and/or erythroderma) but can involve the lymph, blood, and/or viscera. Additionally, patients with cutaneous tumors or folliculotropic involvement typically have poor prognoses. Romidepsin is a histone deacetylase inhibitor approved by the US FDA for the treatment of patients with CTCL who have received ≥ 1 prior systemic therapy. Durable responses (objective response rate [ORR; complete [CR] + partial responses] of 34% and median duration of response of 15 mo) and tolerability with extended dosing have been reported. To examine responses to romidepsin in these less favorable prognostic subsets, patients with tumors or folliculotropic involvement in the pivotal study of romidepsin for the treatment of CTCL were analyzed. **Methods:** Patients with CTCL (N = 96) who had ≥ 1 prior systemic therapy received romidepsin 14 mg/m$^2$on days 1, 8, and 15 every 28 days. Responses were determined by a rigorous composite endpoint that included changes in the skin, blood, and lymph. Patients with cutaneous tumors or folliculotropic involvement were identified by reviewing diagnosis and histology reports. **Results:** Of 96 patients with CTCL, 20 had tumors, and 10 had folliculotropic involvement (2 had both). All but 2 patients with tumors and 1 with folliculotropic involvement achieved ≥ stable disease (SD) with romidepsin (Table). Time to response and DOR ranged from 0.9-4.7 mo and 1.4-18.7+ mo, respectively, for patients with tumors and 1.0-8.3 mo and 2.1-5.0+ mo for patients with folliculotropic involvement. Discontinuation due to an adverse event occurred in 1 patient with tumors (fatigue) and 0 with folliculotropic involvement. **Conclusions:** In the pivotal study of romidepsin for the treatment of CTCL, patients with cutaneous tumors or folliculotropic involvement commonly responded to therapy. Additionally, despite rapid onset of response, patients with tumors rarely discontinued romidepsin due to adverse events, with the longest duration of response ongoing at 18.7 mo. Clinical trial information: NCT00106431.

| Best response, n (%) | Tumors (n = 20) | Folliculotropic involvement (n = 10) |
|---|---|---|
| ORR | 9 (45) | 6 (60) |
| CR | 2 (10) | 1 (10) |
| SD | 9 (45) | 3 (30) |

**8576 General Poster Session (Board #263), Mon, 1:15 PM-5:00 PM**

**Effect of siltuximab on lean body mass (LBM) in multicentric Castleman's disease (MCD) patients (pts).** *Presenting Author: Michael B. Sawyer, Cross Cancer Institute, Edmonton, AB, Canada*

**Background**: MCD is a rare lymphoproliferative disease with wasting, fever, night sweats, and fatigue. Interleukin-6 (IL-6) plays a pivotal role in MCD and has a major role in cachexia. Siltuximab is a chimeric anti−IL-6 monoclonal antibody being studied for MCD treatment. A randomized, double-blind, placebo-controlled study in MCD showed significant improvement in durable tumor and symptomatic response (34 vs 0% placebo; $P$ = 0.0012), with consistent improvements in major secondary endpoints and no increase in AEs compared with placebo. **Methods**: Pts with confirmed symptomatic MCD were randomized 2:1 to siltuximab 11 mg/kg (n = 53) or placebo (n = 26) IV q3wk. Mean baseline wt was 77 kg for placebo and 69 kg for siltuximab. Pts received best supportive care, and were treated to treatment failure. Abdominal CT scans suitable for body composition analysis were available for 57 (37 on siltuximab, 20 on placebo)/79 subjects. CT scans for each pt time point were landmarked at the 3rd lumbar vertebra (L3). L3 images were analyzed using Slice-O-Matic with Hounsfield units (HU) set at different levels for each tissue: skeletal muscle range of -29 HU to 150 HU, visceral adipose tissue: within -150 HU to -50 HU, intramuscular adipose tissue: within -190 HU to -30 HU, and subcutaneous adipose tissue: within -190 HU to -30 HU. **Results**: The median age of 79 treated pts was 48 years and 53M/26F. 58% had previous therapy and 30% were on steroids. 30 % of pts reported weight loss and 38% of pts reported anorexia at baseline. Mean maximal gain in lean body mass (LBM) in siltuximab pts was 2.4 vs. 1.1 kg in placebo ($P$ = 0.04). Mean maximal gain in fat mass (FM) in siltuximab pts was 6.4 vs. 1.4 kg in placebo pts ($P$ = 0.003). At the first CT scan at 9 wks 50% of siltuximab pts had gained 1 kg of LBM, at no point did 50% of placebo pts gain 1 kg. Gain in fat mass preceded gain in LBM. **Conclusions**: This study has shown that siltuximab caused statistically and clinically meaningful LBM gains compared to placebo pts with MCD. Further study of siltuximab for treating decreases in LBM in IL-6 associated malignancies is warranted. Clinical trial information: NCT01024036.

| | Siltuximab | Placebo |
|---|---|---|
| LBM gain >1 kg | 73% | 35% |
| Stable LBM (gain/loss <1 kg) | 22% | 40% |
| LBM loss >1 kg | 5% | 25% |
| *P* (Fisher's Exact test) | $P$ = 0.01 | |

**8577 General Poster Session (Board #264), Mon, 1:15 PM-5:00 PM**

**Feasibility and efficacy of high doses of antimetabolites followed by high-dose sequential chemoimmunotherapy (R-HDS) and autologous stem cell transplant (ASCT) in patients (pts) with systemic B-cell lymphoma (BCL) and central nervous system (CNS) involvement: A multicenter phase II trial.** *Presenting Author: Andres J.M. Ferreri, Università Vita e Salute; San Raffaele Scientific Institute, Milano, Italy*

**Background:** This is a phase II trial addressing a new treatment in pts with BCL and CNS disease (NCT00801216). Treatment is based on the encouraging experiences with high doses of antimetabolites in pts with primary CNS lymphoma (Ferreri et al. Lancet 2009) and with R-HDS/ASCT in pts with relapsed BCL (Tarella et al.JCO 2008). **Methods:** HIV- pts (18-70 ys; ECOG PS ≤3) with BCL and CNS disease at diagnosis or relapse were treated with 2 c. of methotrexate 3.5 g/m$^2$ d1 + cytarabine 2 g/m$^2$ x2/d d2-3, followed by R-HDS (cyclophosphamide 7 g/m$^2$ d1, cytarabine 2 g/m$^2$ x2/d d22-25, VP16 2 g/m$^2$ d43) and BCNU-thiotepa conditioning + ASCT. Treatment included 8 doses of rituximab and 4 of intrathecal liposomal cytarabine. Primary endpoint: 2-yr PFS; planned accrual: 38 pts. **Results:** 40 pts were registered (age 32-70 ys, median 59; M/F ratio 1.5): 34 had DLBCL, 3 MCL blastoid variant, 3 FL. CNS disease (brain 23, meninges 6, spinal cord 2, multiple 9) was detected at diagnosis in 17 pts (all with extra-CNS disease) and at relapse in 23 (8 with extra-CNS disease). Response: CR in 23 pts and PR in 1 (ORR= 60%; 95%CI=45-75%), 1 pt had SD, 11 PD (CNS in all pts; plus extra-CNS in 4), 4 died of toxicity (sepsis 2, stroke). G4 neutropenia, thrombocytopenia and anemia were recorded in 90%, 76% and 8% of courses, febrile neutropenia in 26%; opportunistic infections (CMV 6 pts, aspergillosis 1) were successfully managed. Transient transaminases increase (2) and intestinal perforation (1) were the only G4 non-hematol toxicities. ASCs were collected in 23/25 (92%) pts (median 9.5 x 10$^6$/kg; range 6-19); 20 pts underwent ASCT. At a median f-up of 3 ys, 16 pts remain relapse-free, with a 2-yr PFS of 40±8%; 17 pts are alive, with a 2-yr OS of 41±8%; 2-yr OS of transplanted pts was 64±11%. Extra-CNS and/or meningeal disease did not affect survival. **Conclusions:** This feasible and effective treatment is recommended in pts ≤70 ys with secondary CNS lymphoma. Toxicity is usually haematological and manageable. Survival benefit is attainable also in pts with extra-CNS and/or meningeal disease. Clinical trial information: NCT00801216.

**8578 General Poster Session (Board #265), Mon, 1:15 PM-5:00 PM**

**Hepatitis C co-infection in HIV-positive patients treated for lymphoma.** *Presenting Author: Ashwin Sridharan, Montefiore Medical Center, Bronx, NY*

**Background:** While reactivation of Hepatitis B virus (HBV) infection is well described in patients treated for hematological malignancies, less is known about outcomes in patients co-infected with the Hepatitis C virus (HCV). Co-infection with HCV is frequent in HIV+ patients. We aimed to describe characteristics and outcomes of HIV+ patients co-infected with HCV and treated for lymphoma. **Methods:** HIV+ patients diagnosed with lymphoma between 01/01/1997 - 12/31/2013 at the Albert Einstein Cancer Center were identified. HBV+ alone and PCNSL patients were excluded. Characteristics of HCV+ and HCV- patients were compared using Fisher's exact, Chi-Square, or Mann-Whitney U tests. HCV reactivation was defined as a 3-fold increase in ALT from baseline or 1-log increase in HCV viral load within 1 year of diagnosis. The association of HCV co-infection with OS was assessed by multivariate analysis adjusting for age, sex, race, CD4 count, presence of cirrhosis, type of lymphoma, stage, LDH, and Charlson comorbidity score (CCS). We compared overall survival (OS) of HCV+ and HCV- patients using the Kaplan-Meier method and log-rank test. **Results:** 190 HIV+ lymphoma patients were identified. 28% (n=53) were co-infected with HCV, and 8.4% were co-infected with HBV (n=16); 1 patient was co-infected with both HCV and HBV. 50 HCV+HBV-, 107 HCV-HBV- and 1 HCV+HBV+ patients were included in the final analysis. HCV+ patients were older (52 vs. 44, $p < 0.001$), had higher CCS (13 vs. 11, $p < 0.01$), and more often cirrhosis (24% vs. 0%, $p < 0.001$) than HCV- patients. In HCV+ patients, HCV reactivation occurred 33% (n=17) and persisted in 7.4% (n=4) until 1 year after lymphoma diagnosis; none died from liver failure. Median OS in HCV co-infected patients was 59.7 mo vs. 88.6 mo in HCV-HBV- patients (p=0.76). In multivariate analysis, HCV co-infection was not associated with worse survival (HR 0.98, 95% CI 0.54-1.8; p=0.96), while low CD4 count (<100 cell/mm3), NHL subtype, advanced stage, high LDH (>190 U/L), and cirrhosis were independently associated with worse OS. **Conclusions:** While HCV reactivation is common in co-infected HIV+ patients treated for lymphoma, HCV co-infection did not portend worse OS in our cohort. Our analysis is limited by the small size of the cohort.

**8579 General Poster Session (Board #266), Mon, 1:15 PM-5:00 PM**

**Longitudinal diffusion MRI in PCNSL treated with methotrexate, rituximab, and temozolomide (MRT).** *Presenting Author: Vyshak Chandra, Massachusetts General Hospital, Boston, MA*

**Background:** High-dose methotrexate (HD-MTX) is the backbone of therapy for PCNSL but induction chemotherapy can also include temozolomide and rituximab (MRT). We evaluated baseline tumor ADC values and change in ADC values as markers of response. **Methods:** After receiving IRB consent, we retrospectively evaluated PCNSL patients treated at our hospital with MRT. Patients were treated in 28-day induction cycles: HD-MTX (8g/m$^2$-dose adjusted based on creatinine clearance) on days 1 and 15; rituximab (375 mg/m$^2$) weekly for 6 doses; and temozolomide (150-200 mg/m$^2$) on days 7-11 of each cycle for a goal of 12 cycles. HD-MTX was continued every 2 weeks until complete response (CR). Brain MRI was done after every other MTX treatment to assess response. Volume of contrast enhancing tumor and median tumor ADC values at baseline, 1 month, and 2 months after treatment began was measured. **Results:** From August 2003 to September 2013, 42 patients received MRT as first-line therapy at the time of initial diagnosis and 10 received MRT as salvage therapy at first or second recurrence. The median age of all patients was 63 (range 49-84). With first-line MRT therapy, there were 34 CRs (median cycles to CR = 4), 5 PRs, 2 PD's, and 1 nonevaluable for response. With salvage MRT therapy, there were 6 CRs (median cycles to CR = 4), and 4 PR's. After a median follow-up of 23.5 months in the first-line group and 51.6 months in the relapse group, 14 patients have progressed and 6 died (1 from an unrelated heart attack). After analysis of 22 imaging datasets, 18/22 patients saw a reduction of >70% in enhancing volume from baseline to month 2 of treatment. Shorter time to CR was associated with lower baseline median tumor ADC (p=0.035). There was no statistically significant association in baseline or change in ADC and PFS or OS. **Conclusions:** MRT resulted in a promising early response rate. Lower baseline tumor ADC was associated with shorter time to CR so may be a helpful biomarker. Lower ADC may reflect hypercellular, rapidly proliferating tumor that is more sensitive to chemotherapy. The lack of association with tumor ADC and survival was likely because of the few progression/death events in our dataset and longer term follow-up is needed with more imaging time points.

**8580 General Poster Session (Board #267), Mon, 1:15 PM-5:00 PM**

**Antitumor activity of inhibiting SYK kinase with TAK-659, an investigational agent, in DLBCL models.** *Presenting Author: Jessica Huck, Takeda Pharmaceuticals International Co., Cambridge, MA*

**Background:** Spleen Tyrosine Kinase (SYK) is a non-receptor cytoplasmic tyrosine kinase that is a common member of various signal transduction cascades in cells of the hematopoietic lineage including those involved in B-cell receptor (BCR) activation, B cell migration, and B cell polarization. Abnormal SYK activation has been implicated in several hematopoietic malignancies including chronic lymphocytic leukemia (CLL), peripheral T-cell lymphoma (PTCL) and diffuse large B-cell lymphoma (DLBCL). **Methods:** TAK-659 is an investigational inhibitor of SYK that is currently being evaluated in a Phase I clinical trial (NCT02000934). **Results:** TAK-659 inhibits SYK with an IC50 of 3.2nM and has the ability to inhibit cellular proliferation in relevant models with an EC50 between 25 to 400nM. Daily oral administration of 60 mg/kg TAK-659 showed anti-tumor activity in DLBCL cell-line xenograft models representing ABC (OCI-LY-10 (TGI 50%), HBL-1 (TGI 40%) and a primary human tumor xenograft model, PHTX-95L (TGI 70%), GCB (OCI-LY-19 (TGI 37%) and non-ABC/GCB (WSU (TGI 50%)) subtypes. Interestingly, in the OCI-LY-19 GCB-type DLBCL model, 60 mg/kg TAK-659 (TGI 37%) showed increased activity over a BTK inhibitor (TGI 15%) suggesting the hypothesis that inhibition of BCR signaling upstream of BTK could be beneficial in treating a broader range of sub-types of B-cell malignancies. The time course of pSYK (pSYK$^{525}$) and pBLNK (pBLNK$^{65}$) expression were assessed following single doses of TAK-659. Time dependent inhibition of these phosphoproteins and also increase in expression of cleaved caspase 3, an apoptosis marker was observed in the DLBCL models studied here. Phenotypic assessment of 15 primary DLBCL samples for pSYK and other relevant pathway markers revealed that SYK activation occurs in a considerable number of molecularly heterogeneous DLBCL samples and is consistently associated with activation of the BCR pathway. **Conclusions:** These results together suggest that SYK activation occurs in various subsets of DLBCL samples and TAK-659 showed activity in pre-clinical models of the various subtypes of DLBCL supporting its clinical investigation in DLBCL patients.

**8581 General Poster Session (Board #268), Mon, 1:15 PM-5:00 PM**

**Efficacy, safety, and cost efficiency of rituximab, gemcitabine, dexamethasone, and oxaliplatin (RGDOx) in B-cell NHL: Report of the prospective multicentric trial NCT01019863.** *Presenting Author: Marco Lefebvre, CHUS, Sherbrooke, QC, Canada*

**Background:** Cisplatinum-based 2nd line therapy is poorly tolerated. We evaluated the activity and toxicity of an outpatient RGDOx regimen **Methods:** Patients (pts) with CD20+ NHL, without limitation of age, general condition or prior treatments, were eligible for up to 8 biweekly cycles of rituximab 375 mg/m², gemcitabine 1000 mg/m², oxaliplatin 100 mg/m² on day 1 and dexamethasone 40mg/day orally on day 1- 3. Toxicity was reported according to NCI criteria. Response was assessed at mid and end of treatment. Pts were followed up to 24 months. Costs were collected on per diem canadian interprovincial rates and hospital pharmacy medication costs as of Oct. 2011. **Results:** The planned 50 pts were included from 2009 to Jan. 2013. Two died before starting therapy and were not included in this analysis; 17 females, 31 males, median age 70 (47 - 86) yrs with relapsed (37) or refractory (11) B-NHL (DLBCL 25, FL 8, MCL 11, Richter 2 and CLL 2). 83% had stage III/IV disease, aaIPI / FLIPI ≥2 (85%), median Charlson co-morbidity score of 4, average 2 (1-8) previous treatment lines, 47 previously treated with rituximab and 9 with cisplatin. A total of 250 cycles were given. This was well tolerated. Common grade I-II AE: Sensory neuropathy 66%, diarrhea 36% asthenia 35%, and bone pain 18%. Grade III/IV: Lymphopenia 12%, neutropenia 3% and thrombocytopenia 4%. Two died after 1 and 3 cycles, before documenting response. The overall response was 57% (n=46, CR 40%, PR 17%, PD: 43%). DLCBL (40%, 8%, 52%), FL (38%, 25%, 38%), MCL (50%, 20%, 30%). The median survival was 18.4 months (n=48) and disease-free median survival among responders was 15.7 months (n=27). Refractoriness to previous treatment or response lasting less than 12 months was associated with poorer outcome. Previous cisplatin therapy tended to predict lower response. Average 6-cycle course was associated with 4.8 days of hospitalization, 0.7 medical visits for iatrogenic side effects and 7.3 visits for additional laboratory tests. Mean cost for 6 cycles of RGDOX was $Can 54,991 with a median cost per life year of $Can 35,863. **Conclusions:** RGDOx is safe, effective and cost-effective for relapsing/refractory B-Cell NHL. Clinical trial information: NCT01019863.

**8582 General Poster Session (Board #269), Mon, 1:15 PM-5:00 PM**

**A phase I/II trial of the combination of romidepsin and lenalidomide in patients with relapsed/refractory lymphoma and myeloma: Phase I results.** *Presenting Author: Matthew Alexander Lunning, University of Nebraska Medical Center, Omaha, NE*

**Background:** Epigenetic manipulation and immunomodulation are therapeutic strategies in hematologic malignancies. Romidepsin (Romi), a histone deacetylase inhibitor, and lenalidomide (Len), an immunomodulatory agent, both have efficacy and lack cumulative toxicity in relapsed/refractory (rel/ref) lymphoma and myeloma. We report the phase I results from an ongoing phase I/II study. **Methods:** The phase I portion evaluated toxicity (tox), maximum tolerated dose (MTD) and clinical activity of Romi-Len. Romi was given IV on days 1, 8, and 15 and Len was given orally on days 1-21 of a 28-day cycle. A standard 3+3 dose escalation schema was followed and 4 cohorts were planned: 1) Romi 8 mg/m²-Len 15 mg, 2) Romi 8 mg/m²-Len 25 mg, 3) Romi 10 mg/m²-Len 25 mg, 4) Romi 14 mg/m²-Len 25 mg. Dose-limiting tox (DLT) was defined as any of the following in cycle 1: ≥ grade 3 non-heme tox, ≥ grade 4 heme tox or grade 3 heme tox resulting in a significant delay of treatment. Tumor response was based on disease-specific criteria. Patients (pts) could be treated to progression or intolerance. **Results:** Nineteen pts with rel/ref lymphoma have been enrolled with 15 pts evaluable for DLT (13 pts for response). Three pts progressed prior to study drug and 1 pt progressed in cycle 1; all were replaced for DLT assessment. Two DLTs have occurred to date: cohort 2, 1/7 pts had grade 4 pneumonia; cohort 4, 1/3 pts had grade 3 thrombocytopenia delaying therapy. One grade 3 neutropenic fever has been seen post cycle 1. Of the 13 pts evaluable for response, the overall response rate is 54% (7/13) with complete response in 15% (2/13) and partial response in 39% (5/13). Four responses are ongoing at 4-13 cycles. Responses by subtype include B-cell 50% (2/4), T-cell 67% (4/6), and Hodgkin 33% (1/3). No cumulative tox has been seen. **Conclusions:** The combination of Romi-Len appears to be well tolerated without unexpected tox up to standard single agent doses of each drug. Responses have been seen across multiple lymphoma subtypes. Disease specific phase II cohorts will include B-cell lymphomas, T-cell lymphomas, and multiple myeloma. Final phase 1 safety and efficacy data will be presented. Clinical trial information: NCT#01755975.

**8583 General Poster Session (Board #270), Mon, 1:15 PM-5:00 PM**

**Treatment of HIV-associated plasmablastic lymphoma: A single-center experience with 25 patients.** *Presenting Author: Ibrahim Fuad Ibrahim, The University of Texas Southwestern Medical Center, Dallas, TX*

**Background:** Plasmablastic lymphoma (PBL) is a rare and aggressive subtype of B-cell lymphoma with a predominant occurrence in patients with HIV and other immune compromised states. It commonly affects the jaw and oral cavity but has also been described involving the gastrointestinal tract, bone, bone marrow, and lymph nodes. The historical treatment regimens have typically included CHOP, but more recently dose-adjusted EPOCH has become the standard for HIV-associated lymphomas. It is unclear if regimens other than CHOP can significantly improve the outcome in patients with PBL. **Methods:** We identified 25 patients with PBL at Parkland Hospital treated between 2000 to 2012. Data regarding patient age, gender, HIV status, initiation of antiretroviral therapy, immunophenotype, EBV status, administration of radiotherapy and primary site of presentation were recorded. Log-rank test was used to assess differences in survival by treatment regimen. **Results:** The median age at presentation was 44 years with a 4:1 male predominance. Most (92%) were infected with HIV and had a median CD4+ count of 87 cells/mm3. A minority of patients (32%) were on antiretroviral therapy at the time of diagnosis. The most common primary sites of disease were oral/maxillofacial sites and the gastrointestinal tract with most patients presenting with stage III or IV disease (64%). EBV was detected in the majority of cases (91%) and HHV-8 was detected in none of the cases. CD20 positivity was rare (12%). MYC rearrangements were described in 32% of the cases. Chemotherapy was used to treat most patients (76%) with EPOCH being the most common treatment choice (56%). Radiotherapy was administered in 28% of patients. Primary refractory disease was observed in 16% of the patients. The median overall survival observed in all patients who received chemotherapy was 11.6 months (range 2-63 months). Those who were treated with EPOCH demonstrated a better median overall survival (17 months) compared to those treated with CHOP and CHOP-like regimens (7 months, p=0.04). **Conclusions:** This retrospective single center study suggests that EPOCH may improve survival in PBL.

**8584 General Poster Session (Board #271), Mon, 1:15 PM-5:00 PM**

**Older patients and risk of developing and dying from bleomycin-induced lung toxicity.** *Presenting Author: Preethi Reddy Marri, Mayo Clinic, Pediatric Hematology-Oncology, Rochester, MN*

**Background:** Bleomycin-induced pneumonitis (BIP) has been well described in classical Hodgkin lymphoma (cHL) patients treated with bleomycin-containing chemotherapy regimens. The incidence of acute and subacute pulmonary toxicity varies widely and multiple factors contribute to mortality in patients with BIP. We therefore reviewed the outcome of cHL patients treated at a single institution to further define the incidence of BIP and to identify major contributors to BIP-associated morbidity and mortality. **Methods:** One hundred sixty-one pediatric and adult patients who were treated with bleomycin-containing chemotherapy for newly diagnosed cHL between January 2000 and December 2012 were eligible for this retrospective review. BIP was defined by fever, pulmonary symptoms, pulmonary infiltrates, or a decline in DLCO, with no evidence of an infectious etiology. **Results:** BIP was observed in 43.5 % (n=70) of patients. Age >/=45 years was associated with both an increased incidence (p= <0.0001) and increased severity (p=0.0005) of lung toxicity. ABVD regimen as initial therapy (p= <0.001), obesity (p=0.0331) and the presence of at least one cardiac or respiratory comorbidity (p=0.0088) was also associated with the development of BIP. Higher BMI was associated with earlier onset of lung toxicity. No significant increase in pulmonary toxicity was noted with co-administration of G-CSF (p=0.7249). Bleomycin related mortality rate was 4.97 % (n=8) when all patients were considered and 11.43 % (8/70) in patients who developed pulmonary symptoms. Seventy five percent (6/8) of those who died were older than 60 years. **Conclusions:** The risk of BIP is significant in cHL with the use of bleomycin-containing regimens. Age >/= 45 years appears to increase the risk of BIP and is associated with increased mortality. These findings highlight the need for testing novel treatment combinations in cHL patients that omit bleomycin.

**8585 General Poster Session (Board #272), Mon, 1:15 PM-5:00 PM**

**Mantle cell lymphoma: Toll-like receptors (TLRs) and B-cell receptor (BCR) gene expression analysis for identification of a distinct BCR-activated subset, with germinal center signature and indolent biology.** *Presenting Author: Ariz Akhter, University of Calgary, Calgary, AB, Canada*

**Background:** Mantle cell lymphoma (MCL) is an aggressive disease with complex biology. Enhanced understanding of pathogenesis can result in better utilization of novel therapies. MCL is believed to arise from naïve B-lymphocytes; however, there are indications that at least a subset of MCL arises from antigen-experienced B cells; where Toll-like Receptors (TLRs) and B-cell receptor (BCR) play an intricate role. **Methods:** Here, we report Gene Expression Profile (GEP) data on TLRs/BCR related genes and associated down stream pathways (154 gene-set) in a cohort (n=81) of MCL patients (pts.). GEP was assessed by Nano string technology utilizing mRNA from diagnostic biopsy tissue. **Results:** Hierarchical clustering based on TLR/BCR genes (n= 18), revealed four distinct clusters (A, n=12; B, n=30; C, n=19 and D, n=20) with differential expression of *CD79b, SYK, LYN; BTK* ($p<0.002$) and *TLRs* (2,3,6,7,8,9,) ($p<0.01$). On further analysis, Cluster C revealed higher expression of Germinal Centre (GC) associated genes (GCET, LMO2 and HGAL) ($p<0.001$). This cluster (C) showed lower expression of PI3K/Akt pathway ($p<0.005$) and MAP/ERK pathway associated genes ($p<0.009$) as compared to cluster B. Patients in cluster C, had a trend toward better overall survival (OS), in comparison with cluster B &D ($p=0.07$)(Log Rank (Mantel-Cox). **Conclusions:** Our data suggest that MCL pts. can be stratified based on BCR activity and these pts. can benefit from array of BCR inhibitors as second line therapy. A subset of MCL shows exposure to GC microenvironment, low PI3K/Akt and MAP/ERK pathway activity and a trend towards a better overall survival.

**8586 General Poster Session (Board #273), Mon, 1:15 PM-5:00 PM**

**Cyclophosphamide, bortezomib, and dexamethasone (CYBORD) treatment for relapsed/refractory multiple myeloma.** *Presenting Author: Jorge Monge, Mayo Clinic, Scottsdale, AZ*

**Background:** Patients with multiple myeloma have experienced an increase in survival due to rescue options provided by novel agents used alone and in combination. There is a paucity of data for combinatorial regimens in this population. CYBORD has been validated as an upfront strategy with excellent long-term outcomes, but its use in relapsed disease has not been fully reported. We report a series of 55 pts with relapsed/refractory MM and their response to CYBORD. **Methods:** 55 pts with relapsed/refractory MM were treated with CYBORD on a 28 day cycle. Dosing was cyclophosphamide 300 mg/m$^2$ PO q.wk; bortezomib 1 (2%), 1.3 (22%) or 1.5 mg/m$^2$ (76%), IV (89%) or SQ (11%), once (87%) or twice weekly (13%); and dexamethasone 40 mg PO q.wk. We report response using the IMWG criteria, and new onset neuropathy based on NCI CTCAE. **Results:** Mean age was 65.6 years and 56% were male. Of the 55 pts, 64% had progressed while on therapy and 56% had a previous ASCT. Mean number of previous treatment lines was 3.3, and 36% and 82% were proteasome inhibitor (PI) and CYBORD naïve. Median follow up time was 24.1 mos and mean number of cycles was 5 ($\pm$4.4). ORR was 71%, 26% had $\geq$VGPR, and 13% CR. PI naïve pts had an ORR of 95% while pts who had previously received a PI had an ORR of 57%. Median PFS and OS were 9.2 and 29 mos. After a mean of 6 cycles, 22% of pts underwent subsequent ASCT. New onset grade 1 neuropathy was present in 16% of pts, while only 2% had grade 2 and none had grade 3 neuropathy. We found an increase in PFS in PI naïve pts (14.8 v 5.2 mos, HR 0.4, 95%CI 0.2-0.7), pts that underwent subsequent ASCT (19.7 v 6.3 mos, HR 0.3, 95%CI 0.2-0.7) and pts that had $\leq$3 prior treatment lines (12.1 v 6.1 mos, HR 0.5, 95%CI 0.2-0.8); no difference was found by mSMART risk or prior ASCT. An increase in OS was found only in PI naïve pts (35.4 v 21.2 mos, HR 0.5, 95%CI: 0.3-0.98) and pts that underwent subsequent ASCT (53.1 v 26.7 mos, HR 0.3, 95%CI 0.2-0.8); no difference was found by number of previous treatment lines, mSMART risk or prior ASCT. **Conclusions:** CYBORD is an effective treatment regimen without significant increase in side effect profile for pts with relapsed/refractory MM, achieving better outcomes in PI naïve pts and those who undergo subsequent ASCT, regardless of mSMART risk.

**8587 General Poster Session (Board #274), Mon, 1:15 PM-5:00 PM**

**Focal bone marrow processes and early bone lesions in patients with multiple myeloma (MM) precursor diseases: A prospective study using molecular imaging.** *Presenting Author: Manisha Bhutani, Lymphoid Malignancies Branch, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, MD*

**Background:** The incidence and impact ofbone marrow processes and/or early bone lesions in patients with MM precursor diseases is largely unknown. We prospectively compared the sensitivity of several imaging modalities among patients with monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM) and MM. **Methods:** Ninety-one patients were evaluated: Thirty (10 each with MGUS, SMM and MM) had skeletal survey, [$^{18}$F]-FDG PET/CT, [$^{18}$F]-NaF PET/CT, and lumbosacral dynamic contrast enhanced (DCE)-MRI. Sixty-one newly diagnosed patients (16 high risk SMM and 45 MM) had skeletal surveys and FDG PET/CT. **Results:** Among ten patients with MGUS, MRI found only one unifocal marrow process; all other evaluations were negative. Among 26 SMM patients who by definition had negative skeletal surveys, 11(42%) had abnormalities on FDG PET/CT including four with lytic bone lesions on CT, one with a biopsy-confirmed intramedullary lesion that was negative on both CT and NaF PET/CT and six with unifocal or diffuse marrow process; DCE-MRI was negative in those assessed. Among 55 MM patients, 35 (70%) and 47 (85%) had lytic lesions on skeletal survey and CT, respectively, with 15 and five having >7 sites on CT and skeletal survey, respectively. Marrow involvement was observed on FDG PET/CT in seven (31%), and on DCE-MRI in 6/9 (67%). NaF uptake was observed only in patients with lytic lesions on CT, and provided no additional information. The normal vertebral FDG or NaF $SUV_{mean}$ was not correlated with marrow plasmacytosis and did not increase from MGUS>SMM>MM. **Conclusions:** Using sensitive molecular imaging tools we detected bone and marrow changes not present on skeletal surveys in SMM patients, consistent with the concept of a disease continuum leading to MM. These results provide a framework to include molecular imaging in trials with SMM and MM patients with the hope of improving risk/prognosis categorization. Molecular image-guided biopsies will also allow longitudinal evaluation of bone marrow processes. By integrating modern imaging and molecular profiling, we may be able to develop more precise treatment strategies for precursors to myeloma. Clinical trial information: NCT01237054; NCT01402284; NCT01572480.

**8588 General Poster Session (Board #275), Mon, 1:15 PM-5:00 PM**

**Effect of combination of proteasome inhibitor marizomib and immunomodulatory agent pomalidomide on synergistic cytotoxicity in multiple myeloma.** *Presenting Author: Dharminder Chauhan, Dana-Farber Cancer Institute, Boston, MA*

**Background**: Our prior studies showed that the proteasome inhibitor marizomib, distinct from bortezomib, triggers apoptosis in multiple myeloma (MM) cells resistant to bortezomib, and induces synergistic anti-MM activity in combination with immunomodulatory agent lenalidomide. Like lenalidomide, pomalidomide is an analogue of thalidomide, has immunomodulatory properties, and has been approved by FDA for treatment of MM. The approved indication for pomalidomide is for MM patients who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified. Here, we examined the combined anti-MM activity of marizomib and pomalidomide using in vitro models of MM. **Methods**: MM cell lines, patient MM cells, and PBMCs from normal healthy donors were utilized to assess the synergistic anti-MM activity of marizomib and pomalidomide. **Results**: MM cells were pretreated with DMSO control or with pomalidomide for 24h; marizomib was then added for an additional 24h, followed by analysis of cell viability. A significant decrease in viability of all cell lines was observed in response to treatment with combined low doses of marizomib and pomalidomide, compared with either agent alone. Isobologram analysis confirmed the synergistic anti-MM activity of these agents. The cytotoxicity of combination therapy was observed in MM cells resistant to bortezomib therapies. Marizomib plus pomalidomide-induced apoptosis was associated with: 1) activation of caspase-8, caspase-9, caspase-3, and PARP; 2) downregulation of IRF4, c-myc, and Mcl-1; 3) inhibition of migration of MM cells and angiogenesis; and 4) suppression of proteasome activity. Finally, low doses of marizomib and pomalidomide overcomes the cytoprotective effects of MM-host bone marrow microenvironment. **Conclusions**: Our study provides the preclinical rationale for a clinical protocol evaluating pomalidomide together with marizomib to potentially improve patient outcome in MM.

**8589 General Poster Session (Board #276), Mon, 1:15 PM-5:00 PM**

**MM-005: Phase 1 trial of pomalidomide (POM), bortezomib (BORT), and low-dose dexamethasone (LoDEX [PVD]) in lenalidomide (LEN)-refractory and proteasome inhibitor (PI)-exposed myeloma.** *Presenting Author: Paul G. Richardson, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Combination treatment (Tx) with IMiDs immunomodulatory agents and PIs demonstrated substantial efficacy in myeloma patients (pts) (Richardson, *Blood,* 2010). MM-005 was designed to identify the optimal PVD dose for a phase 3 trial (MM-007) comparing PVD vs. BORT + LoDEX in RRMM pts. A secondary objective examined subcutaneous (SC) BORT as part of PVD Tx. **Methods:** Eligible pts had 1-4 prior Tx lines, including ≥2 consecutive cycles (C) of LEN and a PI. Pts must have been LEN-refractory and PI-exposed but not BORT refractory. MTD was determined using a 3+3 design; an SC BORT cohort was added at the MTD. Tx continued until PD or unacceptable AE. MTD was the primary endpoint; additional endpoints included safety, overall response rate (ORR; ≥ partial response [PR]), time to response (TTR), duration of response (DoR), and pharmacokinetics. **Results:** The trial is fully enrolled (N=28): 22 pts in intravenous (IV) BORT and 6 pts in SC BORT cohorts. Median prior Tx was 2 (1-4). No dose-limiting toxicities (DLTs) were observed. Recommended PVD dose (21-day C) is POM 4 mg D1-14, BORT 1.3 mg/m$^2$ on D1, 4, 8, 11 for C1-8; D1, 8 for C9+, and LoDEX 20 mg (10 mg for pts > 75 y) on D1-2, 4-5, 8-9, 11-12 for C1-8; D1-2, 8-9 for C9+. Most common grade (Gr) 3-4 AEs included (IV cohorts): neutropenia (36%) and thrombocytopenia (27%); (SC cohort): 7 Gr 3 AEs occurred in one pt each; no Gr 4 AEs were observed. Peripheral neuropathy (PN) in IV cohorts was 0% (Gr 3-4), 14% (Gr 2), and 32% (Gr 1); 1 pt reported Gr 2 PN (SC cohort). No pt discontinued due to Tx-related AEs. ORR (IV cohorts) was 71% (38% ≥ very good PR [VGPR]), median TTR was 1 C, and median DoR was 11 C. Preliminary (median 5 C) ORR for SC pts was 67% (1 PR, 2 VGPRs, 1 complete response). 4 of 6 pts receiving BORT SC still remain on Tx; 1 of 4 pts has not yet responded. BORT administration route (IV/SC) did not impact POM exposure, which was within the range previously observed. Long-term follow-up will be presented. **Conclusions:** PVD was effective and well tolerated across all cohorts in LEN-refractory/BORT-exposed pts with no DLTs or discontinuations due to Tx-related AEs to date. PVD is now under evaluation in the MM-007 phase 3 trial. Clinical trial information: NCT01497093.

**8591 General Poster Session (Board #278), Mon, 1:15 PM-5:00 PM**

**A randomized phase 3 trial of thalidomide and prednisone (TP) as maintenance therapy following autologous stem cell transplantation (ASCT) in patients with multiple myeloma (MM): An updated analysis of the NCIC Clinical Trials Group MY10 trial.** *Presenting Author: Annette E. Hay, NCIC Clinical Trials Group, Kingston, ON, Canada*

**Background:** Primary analysis of the MY.10 trial (Stewart, Blood 2013) demonstrated, with a median f/u of 4.1 yrs, MM patients completing ASCT and randomized to receive 4 yrs of TP experienced superior progression free survival (PFS) and poorer quality of life scores as compared with those randomized to observation. No differences in overall survival (OS) were detected (HR=0.77). We now report long term survival. **Methods:** From 2002-09, 332 patients were enrolled. Primary endpoint was OS; secondary endpoints were myeloma-specific PFS (MS-PFS) defined as time from randomization to progressive myeloma, and PFS which also includes death without myeloma progression as an event. Trial arms were compared with a stratified (by age and response to transplant) log-rank test; all analyses were by intent-to-treat. This report is based on the final 2013 December 20 locked database. **Results:** Median age at study entry was 58 years. Among 166 TP patients, 8 (5%) completed 4 years of at least one drug. With a median follow-up of 6.1 years (range 0 – 10.4), TP continued to be associated with superior MS-PFS and PFS. No differences in OS were detected. There were 17 second cancers in 13 TP patients (6 skin, 2 acute myeloid leukemia (AML), 9 solid tumors) compared with 9 in 8 observation patients (3 skin, 2 AML / myelodysplasia, 4 solid tumors). A higher incidence of thromboembolic events was observed in the TP arm (12 vs. 1, p = 0.003). **Conclusions:** A PFS advantage of TP maintenance therapy continues to be seen at 6 years without improvement in OS. As the HR for OS has increased from 0.77 with median f/u of 4.1 yrs to 0.88 with median f/u of 6.1 yrs, we expect that longer f/u will not permit detection of a difference in OS. Our data are consistent with other data showing that PFS is an unreliable surrogate for OS when evaluating maintenance therapies for MM patients. Clinical trial information: NCT00049673.

| | 6 yr estimate | | | HR (95% CIs) Median FU | |
|---|---|---|---|---|---|
| | Maintenance N = 166 | Observation N = 166 | p-value | 6.1 yr | 4.1 yr |
| MS-PFS | 28% | 10% | <0.0001 | 0.58 (0.46, 0.75) | 0.56 (0.42, 0.73) |
| PFS | 26% | 9% | <0.0001 | 0.58 (0.45, 0.73) | 0.56 (0.43, 0.73) |
| OS | 56% | 49% | 0.41 | 0.88 (0.65, 1.19) | 0.77 (0.53, 1.14) |

**8592 General Poster Session (Board #279), Mon, 1:15 PM-5:00 PM**

**Age-related trends in utilization and outcome of autologous haematopoietic cell transplantation for multiple myeloma.** *Presenting Author: Holger W Auner, Imperial College London, London, United Kingdom*

**Background:** Autologous haematopoietic cell transplantation (AHCT) is considered a standard of care in eligible patients with multiple myeloma (MM) aged <65 years but is not generally recommended in patients ≥65 years of age. We analysed all first AHCTs that were reported to the EBMT 1991-2010 to study trends in utilisation and outcome of AHCT for the treatment of MM in relation to age. **Methods:** A total of 53675 patients from 31 European countries and 497 centres were included in the analysis. Patients were grouped into six age groups (<40, 40-49, 50-59, 60-64, 65-69, ≥70 years) and four calendar periods (1991-1995, 1996-2000, 2001-2005, and 2006-2010) by age at, and year of, first AHCT. **Results:** Median age at AHCT increased from 52.8 years in 1991-1995 to 59 years in 2006-2010 (p<.001). The number of patients undergoing AHCT increased throughout all four calendar periods for all age groups. The highest proportional increase was observed for patients aged 65-69 and ≥70 years. While the number of tandem AHCTs decreased in 2006-2010 in all age groups, patients aged ≥70 years showed the smallest decrease and had the highest rate of tandem transplants in this calendar period (19%). Two-year survival rates increased for all age groups since 1991-1995. The greatest improvement was observed in patients aged 65-69 years (from 55.3% in 1991-1995 to 82.9% in 2006-2010). The smallest improvement in 2-year survival was seen in patients aged <40 years (from 82.2% in 1991-1995 to 85.9% in 2006-2010). Consequently, the maximum difference in 2-year survival between age groups decreased from 27.9% in 1991-1995 to 5.7% in 2006-2010. Five-year survival was higher in 2006-2010 compared to 1991-1995 in all age groups. However, we observed an emerging trend of decreasing 5-year survival for patients aged <40 and 40-49 years in the most recent calendar period. **Conclusions:** The data demonstrate that utilisation of AHCT for MM continued to increase in recent calendar periods, particularly in patients aged ≥65 years. The data also show that post-transplant survival improved considerably more in older than in younger patients. Thus, AHCT is a commonly used treatment strategy with good outcome in MM patients aged ≥ 65 years.

**8593 General Poster Session (Board #280), Mon, 1:15 PM-5:00 PM**

**Pomalidomide plus low-dose dexamethasone (POM plus LoDEX) versus high-dose dexamethasone (HiDEX) for relapsed or refractory multiple myeloma (RRMM): Overall survival (OS) results of MM-003 after adjustment for crossover.** *Presenting Author: Gareth J Morgan, Centre for Myeloma Research, Institute of Cancer Research, London, United Kingdom*

**Background:** The pivotal, randomized phase 3 MM-003 trial in patients (pts) with RRMM demonstrated significantly longer median progression-free survival (PFS) with POM + LoDEX (n = 302, 4 months) than with HiDEX (n = 153; 1.9 months; $P < 0.0001$). Unadjusted median OS was also significantly longer with POM + LoDEX than with HiDEX (HR 0.74; $P = 0.0285$) despite the crossover of approximately 50% of pts from the HiDEX arm to POM + LoDEX or POM monotherapy. In the presence of extensive crossover, conventional survival analysis methods are biased. Here, we used the 2-stage Weibull method for crossover adjustment to estimate the OS difference between POM + LoDEX and HiDEX. **Methods:** A 2-stage model was used to estimate counterfactual, adjusted survival data for the HiDEX arm, using a secondary baseline defined by the time of disease progression. To extrapolate the counterfactual data as required by health technology assessment bodies, standard model selection methods were used to identify the best fitting parametric model. **Results:** Unadjusted median OS in MM-003 was 12.7 and 8.1 months in the POM + LoDEX and HiDEX groups, respectively. After adjusting for crossover, the difference in median OS in the 2 groups was 7.0 months (12.7 vs 5.7 months). Median OS in the POM + LoDEX arm was therefore more than double that in the HiDEX arm. Extrapolation using a log-normal model fitted to the adjusted OS data produced an estimated difference in mean survival times of 14.6 months (28.0 vs. 13.4 months). Predicted survival at 3 years was 21% for pts on POM + LoDEX compared with 8% for pts on HiDEX. **Conclusions:** The MM-003 intent-to-treat analysis showed a significant increase in median PFS and OS for POM + LoDEX vs HiDEX. The present analysis suggests that OS with POM + LoDEX is double that with HiDEX after accounting for crossover. Extrapolation over a lifetime horizon predicts a mean survival difference between POM + LoDEX and HiDEX of more than 14 months. These data provide important evidence for understanding the clinical efficacy and evaluating the overall economic value of POM in the treatment of RRMM. Clinical trial information: NCT01311687.

**8594^ General Poster Session (Board #281), Mon, 1:15 PM-5:00 PM**

**Results of the dose-escalation portion of a phase 1/2 study (CHAMPION-1) investigating weekly carfilzomib in combination with dexamethasone for patients with relapsed or refractory multiple myeloma.** *Presenting Author: James R. Berenson, Institute for Myeloma and Bone Cancer Research, West Hollywood, CA*

**Background:** Carfilzomib (CFZ) is a selective proteasome inhibitor approved in the US for the treatment of relapsed and refractory multiple myeloma (MM). This multicenter, single-arm phase 1/2 study (NCT01677858) is evaluating the safety and efficacy of once-weekly CFZ with dexamethasone (DEX). **Methods:** Patients (pts) with relapsed or refractory MM who received 1−3 prior regimens were eligible. Pts received CFZ as a 30-minute IV infusion on days (D) 1, 8, and 15 of a 28-day cycle in a standard 3+3 dose-escalation scheme. All pts received CFZ at 20 mg/m$^2$ on D1 of cycle 1; subsequent doses started at 45 mg/m$^2$ and were escalated to 56, 70, or 88 mg/m$^2$in successive cohorts until the maximum tolerated dose (MTD) was reached. Pts received 40 mg DEX (IV or oral) on D1, 8, 15, and 22 of cycles 1–8; DEX was omitted on D22 in cycles ≥9. Response was assessed by IMWG criteria; minimal response (MR) was assessed by EBMT criteria. The primary objective of the phase 1 portion of the study was to determine the MTD. **Results:** As of 11/5/2013, 27 pts were enrolled (median age, 64 years [range, 43–84]; median prior regimens, 1 [range, 1–3]). At 88 mg/m$^2$, 2 dose-limiting toxicities (DLTs) were observed: grade [Gr] 3 dyspnea and Gr 3 vomiting. At the MTD (70 mg/m$^2$), 1 patient of 15 experienced a DLT (Gr 3 dyspnea). Gr ≥3 AEs reported in >1 pt were thrombocytopenia, increased blood creatinine, dyspnea, and hyperglycemia (n=2 each; all Gr 3). No Gr ≥3 peripheral neuropathy was reported. All 27 pts were included in the preliminary efficacy evaluation. The overall response rate (ORR; ≥partial response) was 63% and the clinical benefit rate (CBR; ≥MR) was 74%. At the MTD, the ORR was 60% and the CBR was 67%. Pharmacokinetic analysis (n=21) showed a dose-dependent increase in mean $C_{max}$ and AUC for 20−88 mg/m$^2$CFZ. The mean terminal half-life was ~0.8 hours. **Conclusions:** At the MTD, weekly CFZ with DEX had an acceptable safety and tolerability profile with promising efficacy after a short follow-up period in pts with relapsed or refractory MM. The phase 2 portion of the study is currently enrolling pts at 70 mg/m$^2$ CFZ. Updated results from the phase 1/2 study will be presented. Clinical trial information: NCT01677858.

**8595 General Poster Session (Board #282), Mon, 1:15 PM-5:00 PM**

**Free light chain assay and cytogenetic abnormalities for identification of high-risk smoldering myeloma.** *Presenting Author: Jeremy Todd Larsen, Mayo Clinic, Rochester, MN*

**Background:** Translocation (4;14) and deletion 17p in smoldering multiple myeloma (SMM) have been identified as high risk cytogenetic abnormalities (CAs). Risk stratification incorporating CAs and biomarkers are needed to identify high risk SMM patients. The aim of this study was to determine the predictive value of the free light chain (FLC) assay in combination with high-risk CAs. **Methods:** The study included SMM patients seen at Mayo Clinic from 1991-2010 screened for available FISH and serum FLCs at diagnosis. Receiver operating characteristics analysis determined the optimal involved FLC (iFLC) cut-point to predict progression to MM within 24 months. Univariate analysis and multivariate analysis were performed. Time to progression (TTP) was calculated using Kaplan-Meier analysis. **Results:** The FLC was measured in 249 patients; t(4;14) was found in 33 (13.3%) and deletion 17p in 6 (2.4%). Median age at SMM diagnosis was 62 years (range, 30-90). The optimal iFLC cut-point was 41 mg/dL. The iFLC was >40 in 23% of the 39 high-risk CA (n=9) and 22% of non-high risk CA patients (n=46). In the high-risk CAs group, median TTP if iFLC >40 was 20 months (95% CI 5-24) versus 30 months (19-60) in the iFLC <40 group. In the low-risk CAs, median TTP if iFLC >40 was 34 months (26-51) versus 62 months (48-86) in the iFLC <40 group (p <0.0001). One and two-year progression rates for iFLC >40 in high-risk CAs were 23% and 89%. In comparison, progression rates were 7% and 14% at one and two years in low-risk CAs with iFLC <40. Table 1 shows the univariate and multivariate analysis. **Conclusions:** Integration of the FLC assay and CAs may facilitate recognition of SMM patients at highest risk for rapid progression as increasing hazard with each risk factor was demonstrated . Elevation of the iFLC >40 in the presence of adverse CAs identified a high-risk subset with 90% progression at 24 months for whom early intervention strategies may be considered.

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| **Variable** | **HR** | **95% CI** | **P** | **HR** | **95% CI** | **P** |
| **iFLC >40** | 1.9 | 1.3-2.8 | 0.0007* | 1.8 | 1.2-2.5 | 0.004* |
| **Age >65** | 1.8 | 1.3-2.4 | 0.001* | 1.6 | 1.1-2.2 | 0.007* |
| **BMPC % >20** | 2.0 | 1.4-2.7 | 0.0001* | 1.7 | 1.3-2.4 | 0.0007* |
| **M-spike >3** | 1.3 | 0.89-1.8 | 0.19 | | | |
| **$\beta$-2 microglobulin >3.5** | 1.7 | 0.72-3.8 | 0.21 | | | |
| **Albumin <3.5** | 1.1 | 0.44-2.5 | 0.80 | | | |

**8596 General Poster Session (Board #283), Mon, 1:15 PM-5:00 PM**

**Treatment of dendritic cell sarcoma: 18-year experience at the MD Anderson Cancer Center.** *Presenting Author: Preetesh Jain, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Dendritic cell sarcomas (DCS) are rare tumors including follicular dendritic cell sarcoma (FDCS) and interdigitating cell sarcoma (IDCS). Typically DCS are difficult to diagnose and are associated with poor outcomes with standard therapy. **Methods:** This is a comprehensive retrospective analysis of 35 pts with confirmed diagnosis of DCS (FDCS n=31; IDCS n=4) treated at MDACC between 1995 and 2013. Pts were identified from an institution database and data was collected on the diagnosis, management and clinical outcomes of pts. **Results:** Median age at diagnosis was 50 yrs (range 17-74 yrs) and 58% were female. 60% pts presented with localized disease and 40% with systemic involvement. Abdomen was involved in 17/35 pts and the spleen (7/35) was the most common extranodal site. Bulky disease (> 5 cm) was noted in 21 pts. Nine pts had pre-existing or subsequent autoimmune disease. Common markers for FDCS were clusterin; EGFR, CD21, CD35 and CD23 in 94%, 87%, 89%, 77% and 63% samples. For IDCS, common markers included S-100 and CD68 in 100% and 75% pts. Molecular studies were performed in 2 pts who were negative for *BRAF* mutations. One pt had *TP53* exon 8 and another *PTEN* mutation. Surgery followed by adjuvant chemotherapy was initial treatment in (23/35) and chemotherapy alone in (12/35) pts. Gemcitabine with taxanes and CHOP based regimens were most commonly used, and were associated with response rates of 86% and 60% respectively. Complete responses were rare. Median progression free and overall survival following systemic therapy was 41 and 59 months respectively. Pts with systemic presentation had inferior outcomes compared to those with localized disease. **Conclusions:** We present the largest single center report of pts with DCS. While detailed histopathological studies are necessary to define DCS, we identified several makers common to both FDC and IDCS. We observed higher responses with gemcitabine/docetaxel combinations compared to CHOP based therapy, but limited numbers make comparisons difficult and prospective studies are needed to define optimal treatment in this rare disease. Studies are currently underway at our institution to define the genomic profile in DCS and identify potential targets for therapy.

**8597 General Poster Session (Board #284), Mon, 1:15 PM-5:00 PM**

**Large granular lymphocyte (LGL) subsets in smoldering multiple myeloma (SMM): Immunophenotypic profiles that predict progression to multiple myeloma (MM).** *Presenting Author: Talib Dosani, Lymphoid Malignancies Branch, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, MD*

**Background:** SMM is an asymptomatic precursor condition to MM. The immune system is known to play an important role in progression of SMM to MM. However, current risk-stratification schemes are often discordant, and there are presently no reliable biomarkers to predict progression to MM. In this study, we quantified various LGL subsets of SMM patients and identified potential LGL markers that may predict progression. **Methods:** Flow cytometric analysis was used to quantify LGL subsets in the peripheral blood (PB) of SMM patients (N=80) enrolled in the NCI Natural History of SMM/MGUS prospective clinical trial. PB samples were collected at enrollment and at every 12 months, in addition to regular 3-6 month clinical follow-ups. We conducted an analysis of LGL subsets using samples collected at diagnosis or follow-up on patients who progressed to MM at a subsequent 6-month or 12-month follow-up (N=8, median age 64) versus patients who had not progressed at 12 months of follow-up (N=72, median age 60). Two-tailed Mann-Whitney U test was used for all statistical analyses. **Results:** SMM patients who progressed to MM demonstrated a distinct LGL profile 6-12 months before progression. These patients had decreased levels of both relative and absolute numbers of CD3(-) CD16(+) CD57(-) NK cells (p=.03 and .09, respectively) and decreased levels of both relative and absolute numbers of CD56(+) CD57(-) lymphocytes (p=.003 and .02, respectively). Furthermore, there was an increase in relative numbers of total CD57(+) lymphocytes and CD57(+) CD8(-) NK cells (p=.23 and .13, respectively). There were no statistically significant differences in total WBCs, absolute lymphocyte counts, CD3(-) CD16(+) CD56(+) NK cells or CD3(+) CD16(+) CD56(+) NKT-like cells between the cohorts. **Conclusions:** SMM patients who progressed to MM possessed a distinct LGL immunophenotypic profile that was characterized by a decrease in CD57(-) lymphocyte subsets and a mild increase in CD57(+) lymphocyte subsets. These results suggest an LGL immunophenotypic profile that may be used as a marker of progressive disease in SMM patients.

**8598 General Poster Session (Board #285), Mon, 1:15 PM-5:00 PM**

**Outcomes after relapse from first autologous stem cell transplantation in multiple myeloma.** *Presenting Author: Wilson I. Gonsalves, Mayo Clinic, Rochester, MN*

**Background:** Autologous stem cell transplant (ASCT) is an integral treatment for eligible patients (pts) with multiple myeloma (MM). However, disease relapse post-ASCT remains inevitable for many pts. We describe the natural course of the disease and its outcomes in MM pts relapsing post-ASCT. **Methods:** Pts were included if they met the following criteria: 1) ASCT at the Mayo Clinic within 12 months of diagnosis; AND relapse post-ASCT between 2000 to 2012. Pts were excluded if they received a tandem or an allogeneic transplant post first ASCT. Multivariate analysis was performed using a Cox proportional hazards model. **Results:** Median (range) age at ASCT was 59 yrs (29-74). The median time to ASCT was 6 mos (2-12). Pts were transplanted in the years of 1994-2012. The median time to relapse was 16 mos (2-184). The median follow-up (95% CI) from relapse was 79 mos (72-89). The median (range) number of regimens prior to ASCT and post relapse were 1 (0-3) and 2 (1-11), respectively. Of the 254 pts who had FISH testing, 28% were categorized as high risk. Seventy-nine pts (17%) had a prior diagnosis of MGUS or SMM. All pts received novel agent therapy during their disease course with 57% receiving them during induction. At Day 100 post-ASCT, a PR or better was seen in 416 (92%) pts, including a stringent CR in 10%, CR in 12% and VGPR in 36%. Only 9% of pts received maintenance therapy with immunomodulators or proteasome inhibitors. The median (95% CI) post-ASCT relapse survival (PRS) and overall survival from diagnosis was 40 (34-45) and 67 (62-75) mos, respectively. In a multivariate analysis, only shorter time to relapse, presence of CRAB symptoms or extramedullary disease at relapse, shorter time to initiating salvage therapy, higher pre-ASCT plasma cell labeling index and beta-2 microglobulin predicted for a shorter PRS. Prior history of MGUS/SMM, high-risk FISH, choice of salvage therapy and use of maintenance therapy did not affect PRS. **Conclusions:** In a population of mostly unmaintained pts who relapse post-ASCT, PRS is longer than PFS. Predictors for increased PRS include a longer duration of response to ASCT, biochemical progression (rather than CRAB symptoms or extramedullary disease at relapse) and a longer time to salvage therapy initiation.

**8599 General Poster Session (Board #286), Mon, 1:15 PM-5:00 PM**

**Effect of a novel agent, SL-401, targeting interleukin-3 receptor (IL-3R) on plasmacytoid dendritic cell (pDC)-induced myeloma cell growth and osteolytic bone disease.** *Presenting Author: Dharminder Chauhan, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Multiple myeloma (MM) remains incurable despite novel therapies, highlighting the need for further identification of factors mediating disease progression and resistance. We showed that plasmacytoid dendritic cells (pDCs) in the MM bone marrow promote MM cell growth *(Chauhan et al., Cancer Cell 2009, 16:309-323)*. pDC-MM interactions trigger secretion of interleukin-3 (IL-3), which in turn, induces MM cell growth, and pDCs survival. Additionally, IL-3 contributes to the progression of osteolytic bone disease in MM. Here, we examined the effect of SL-401, a novel targeted therapy directed to IL-3R, on pDC-induced MM cell growth and osteoclast (OCL) formation. **Methods:** Patient MM cells, pDCs, and MNCs were obtained from normal donors or MM patients. Cell growth/viability was analyzed using MTT assays. OCL function and bone resorption was measured using the OsteoAssays and TRAP staining. **Results:** SL-401 decreased the viability of pDCs even at low concentrations ($IC_{50}$: 0.83 ng/ml; 14.6 pM). SL-401 decreased the viability of MM cells at clinically achievable doses without significantly affecting the viability of normal PBMCs. Co-culture of MM patient-derived pDCs triggered proliferation of MM cell lines and primary MM cells; and importantly, SL-401 inhibited pDC-triggered MM cell growth ($P < 0.005$). Moreover, 3 of 5 samples were obtained from patients whose disease was progressing while on bortezomib, dexamethasone, and lenalidomide therapies. SL-401 blocked pDC-induced growth of dexamethasone-, doxorubicin- or melphalan-resistant MM cells.Combination of SL-401 with bortezomib, melphalan, lenalidomide, or pomalidomide showed synergistic anti-MM activity. Finally, SL-401 inhibited monocyte-derived osteoclast formation in a dose-dependent manner as well as stabilized MM patient BM-derived osteoblast formation. **Conclusions:** Our study provides the basis for directly targeting pDCs and inhibiting the pDC-MM interaction, as well as targeting osteolytic bone disease, in novel therapeutic strategies with SL-401 to enhance MM cytotoxicity, overcome drug-resistance, and improve patient outcome.

**8600 General Poster Session (Board #287), Mon, 1:15 PM-5:00 PM**

**ECOG multiple myeloma (MM) clinical trial (CT) accrual performance evaluation utilizing the NCI–Trial Complexity and Elements Scoring (NCI-TCES) and the NCI Myeloma Steering Committee Accrual Working Group (NCI MYSC AWG) scoring models.** *Presenting Author: Matthias Weiss, Marshfield Clinic, Marshfield, WI*

**Background:** Accrual to NCI CTs is often slower than planned and at times mandating premature closure resulting in loss of valuable resources and delay of scientific progress. The NCI MYSC AWG identified 10 barriers to accrual (BtA) to MM CTs (reimbursement, competing treatment options, treatment at NCI designated sites only, etc.). The NCI-TCES was created to objectively assess CT complexity (study arms, registration/randomization steps, treatment and follow-up complexity and duration, etc.). We evaluated the accrual performance of all previously conducted and currently ongoing (as of 12-31-2013) therapeutic ECOG MM CTs (excluding transplant) utilizing these tools. **Methods:** The planned and actual accrual, duration of open enrollment and accrual per month of each selected CT was determined. The NCI-TCES model was applied to each CT and a total score calculated (range 0-18). The 10 NCI MYSC AWG BtA were reviewed as it concerns their relevance for each selected CT and described as unlikely (0), possibly (1) or definitely (2) impacting accrual adversely. A total score was calculated (range 0-20). **Results:** 11 ECOG MM CTs were evaluated. 6 of 11 achieved planned accrual goals and 5 of 11 did not due to premature closure due to lack of accrual, less than half of planned accrual per month or more than twice the planned enrollment period. CTs achieving planned accrual performance had a NCI MYSC AWG score average of 4.83 versus 8.0 for those CTs failing accrual goals. The NCI-TCES score was 4.83 versus 4.2, respectively. None of the 6 CTs, which successfully enrolled were identified to have BtA, which definitely impacted accrual adversely versus 3 out of 5 of the CTs which failed planned accrual performance. **Conclusions:** In this retrospective analysis of ECOG MM CT accrual performance, the NCI MYSC AWG scoring model correlated well with actual accrual performance. Given its general applicability to therapeutic CTs evaluating any malignant disease, this tool may be useful for prospective accrual performance assessment of planned therapeutic clinical trials.

**8601 General Poster Session (Board #288), Mon, 1:15 PM-5:00 PM**

**Autologous stem cell transplantation in dialysis-dependent myeloma patients.** *Presenting Author: Riad Omar El Fakih, Baylor College of Medicine, Houston, TX*

**Background:** The incidence of renal insufficiency at presentation is approximately 30% in patients with multiple myeloma (MM). 5% of these patients are dialysis dependent. Presence of renal dysfunction is associated with increased treatment related toxicity and poor survival. **Methods:** We retrospectively analyzed our transplant database from July 2000 to June 2012 to identify myeloma patients who received autologous hematopoietic stem cell transplantation (autoHCT) while they were dialysis dependent. Univariate Cox proportional hazards regression was performed to assess the association between survival and covariates of interest. Kaplan Meier curve was used to estimate progression free survival (PFS) and overall survival (OS). **Results:** 2,091 patients underwent autoHCT during this interval. 24 (1.1%) were dialysis dependent (21 on hemodialysis and 3 on peritoneal dialysis). Median age was 53 (29-70) years. 63% were male. ISS stage at diagnosis was I & II in 4%, III in 54%, and unknown in 38%. Median duration of dialysis prior to auto-HCT was 235 (1-1481) days. Four patients had high risk cytogenetics. Melphalan dose was 200 $mg/m^2$ in 58% and $<$ 200 $mg/m^2$ in 42%. The median collected CD34+ cells count was 4.35 x $10^6$/Kg. All patients engrafted. 100 day and 6 month treatment related mortality (TRM) was 0%. The incidence of grade II-IV non hematological toxicity was similar across different melphalan doses. Overall response rate was 92% (CR = 25%, VGPR = 29.2%, PR = 37.5%). Two patients had SD. The median follow up is 6.7 years. At the time of last follow up, 13 patients had died and 11 (45.8%) were still alive. The median PFS and OS were 1.9 years and 3.8 years, respectively. In univariate analysis, high-risk cytogenetics was a significant predictor of poor PFS (p0.04) and OS ($p<0.009$). A multivariate analysis was not performed due to the small sample size. Only 3 patients (12.5%) became dialysis independent after transplant. No variable was predictive of becoming dialysis independent. **Conclusions:** AutoHCT can be safely performed in dialysis dependent myeloma patients. While majority of patients continue to require dialysis after transplant, long term disease control can be expected. Dialysis dependent renal failure should not be an exclusion for autoHCT.

**8603 General Poster Session (Board #290), Mon, 1:15 PM-5:00 PM**

**Further exploring the mutational landscape of multiple myeloma via a targeted gene panel assay.** *Presenting Author: Donald Joseph Johann, Myeloma Institute for Research and Therapy, Little Rock, AR*

**Background:** Multiple myeloma (MM) is a cancer of the bone marrow characterized by a malignant transformation of plasma cells. The pathogenesis of MM is only partially understood. Identifying the acquired somatic mutations in MM is a practical approach to reveal and clarify the mechanisms of a particular patient's cancer. By identifying the mutational status of key and relevant genes, pathways and targets in these pathways may be examined, and a rationally-based therapy plan devised for each individual patient. Since patients eventually become refractory to available therapies, the identification of additional therapeutic targets has important clinical utility. **Methods:** DNA sequencing was performed utilizing a targeted approach of ~300 genes relevant to heme malignancies on 115 heavily pretreated patients as of 4/2013 - 12/2013. gDNA was obtained from CD-138 selected cells from bone marrow aspirates. All libraries were sequenced on an Illumina HiSeq at a depth of ≥ 500X. **Results:** Clinically actionable mutations (n = 197) were found in 105 of the 115 patients, ranging from 1-14 mutations per patient with an avg of 2. Mutations important in hematologic malignancies but still classified as variants of unknown significance (VUS, n=861) were found in 97 of the 115 patients, ranging from 3 to 39 VUS per patient with an average of 9. The top 10 genes showing actionable mutations were: KRAS (41%), TP53 (37%), NRAS (23%), BRAF (11%), RB1(10%), TRAF3(7%), CDKN2C(7%), ATM, LRP1B and MYC (all 6%). The MAPK pathway displayed a high frequency of mutations including concomitant mutations of KRAS and NRAS in five patients, and BRAF V600E mutation in six patients. RAS hotspot analysis showed KRAS Q61H and G13D combining to a frequency of 45%, and for NRAS, Q61-mutations occurring at a 67% frequency. Top genes in the VUS category showing mutations included the methyltransferase MLL2 (24%), PCLO (20%), LRP1B (16%), the MEK kinase MAP3K1 (12%), and NOTCH1 (11%). **Conclusions:** Next generation sequencing of CD-138 selected bone marrow aspirate cells allows for the identification of actionable mutations and targets, and helps facilitate consideration of individualized clinical strategies for MM patients refractory to standard of care therapies.

**8604 General Poster Session (Board #291), Mon, 1:15 PM-5:00 PM**

**Differentiating asymptomatic monoclonal gammopathy (AMG including MGUS and AMM) from clinical multiple myeloma (CMM) by gene expression profiling of purified plasma cells (PC-GEP).** *Presenting Author: Rashid Khan, MIRT/UAMS, Little Rock, AR*

**Background:** Previous research indicated that PC from AMG and CMM could not be distinguished at the GEP level. We reported that a GEP70 risk score could identify a subset of AMG patients at high risk for progression to CMM requiring therapy. We now re-address this issue in a larger population of patients (pts) in order to contribute to a better understanding of the genetics of this progression event from clinically benign to malignant disease. **Methods:** We identified baseline GEPs of 89 pts with AMG and 38 pts with MGUS in our observational study and compared them to 785 GEPs of previously untreated pts with MM who were enrolled in Total Therapy 2 and 3. GEPs were separated into training and test sets of 60 and 29 pts for AMM, 26 and 12 pts for MGUS and 524 and 261 pts for CMM respectively. We performed t-tests to identify differentially expressed probesets between AMM and CMM, MGUS and CMM and AMM and MGUS. Results adjusted for multiple testing and probesets were ranked by q-value for each comparison. **Results:** In the comparison between AMM and CMM we identified 74 probesets significantly differentially expressed with a q-value $<1 \times 10^{-6}$. Using a class predictor approach the log2 transformed expression values for each gene were summed. An optimal cutpoint was identified in the training set and validated in the test set, performance was satisfactory with a sensitivity of 79.3%, a specificity of 92.0% and a positive predictive (PPV) value of 90.7%. AMM samples classified as CMM had a significantly shorter time to progression to CMM than those classified as AMM. Conversely pts with CMM who were classified as AMM had a better PFS and OS than those classified as CMM. 206 genes were differentially expressed between MGUS and CMM and a predictive model based on these genes showed a sensitivity of 83%, specificity of 92.3% and PPV of 91.9%. 11 probesets were common between the AMM/CMM and MGUS CMM gene lists. **Conclusions:** Gene expression profiling can readily differentiate between MGUS or AMM and CMM. More importantly pts with AMM who have a CMM-like GEP signature have a significantly shorter time to progression to CMM while AMM-like signature in CMM predicts better outcome.

**8605 General Poster Session (Board #292), Mon, 1:15 PM-5:00 PM**

**Clarifying immunoglobulin gene usage in immunoglobulin light chain amyloidosis by mass spectrometry of amyloid in clinical tissue specimens.** *Presenting Author: Taxiarchis Kourelis, Department of Medical Oncology, Mayo Clinic, Rochester, MN*

**Background:** The goal of this study was to investigate the relative use of light chain variable region genes (LCVG) among patients with systemic (SAL) and localized (LAL) amyloidosis and assess for associations between LCVG and organ tropism. **Methods:** We evaluated charts from 361 AL patients seen at Mayo who had tissue samples typed using laser dissection mass spectrometry (MS). **Results:** We identified 240 patients with SAL and 105 with LAL. When compared to LAL, lambda light chain (LC) overall and LV6 in particular were more common in SAL. KV3 and LV2 were overrepresented in LAL. KV1 accounted for 71% of kappa genes in SAL and for 37% in LAL. LV4, KV2 and KV4 were distinctly uncommon, each identified in ≤ 5% of patients in both SAL and LAL. Among patients SAL who had clinical cardiac involvement, only KV3 was underrepresented as compared to patients without clinical cardiac involvement (1% vs 9%, p=0.008). In patients with clinical renal involvement, LV6 was more common (26% vs 9%, p=0.002) and KV3 less common (1% vs 7%, p=0.03).LV6 was also more commonly identified in SAL patients with clinically isolated renal involvement (35% vs.13%, p=0.02). **Conclusions:** LCVG usage in SAL is different from that of LAL. It is also restricted, with KV1, LV1, LV3 and LV6 accounting for 70% of cases.

| | All patients (N=345) | | | Systemic patients (n-240) | | | |
|---|---|---|---|---|---|---|---|
| | Localized (N=105) | Systemic (N=240) | p | Cardiac (n=152) | p | Renal (n=108) | p |
| Kappa | 49 (47%) | 78 (33%) | 0.02 | 48 (32%) | NS | 25 (23%) | 0.01 |
| Kappa NOS | 4 (4%) | 1 (0.4%) | 0.03 | | | | |
| KV1 | 18 (17%) | 55 (23%) | NS | 38 (25%) | NS | 19 (18%) | NS |
| KV2 | 1 (1%) | 2 (1%) | NS | 0 | NS | 1 (1%) | NS |
| KV3 | 21 (20%) | 9 (4%) | <0.001 | 2 (1%) | 0.008 | 1 (1%) | 0.03 |
| KV4 | 5 (5%) | 11 (5%) | NS | 8 (5%) | NS | 3 (3%) | NS |
| Lambda | 56 (53%) | 162 (67%) | 0.02 | 104 (68%) | NS | 83 (77%) | 0.01 |
| Lambda NOS | 8 (8%) | 31 (13%) | 0.09 | | - | - | - |
| LV1 | 13 (12%) | 30 (13%) | NS | 18 (12%) | NS | 13 (12%) | NS |
| LV2 | 15 (14%) | 17 (7%) | 0.04 | 9 (6%) | NS | 7 (7%) | NS |
| LV3 | 13 (12%) | 44 (18%) | NS | 31 (20%) | NS | 20 (19%) | NS |
| LV4 | 1 (1%) | 1 (0.4%) | NS | 1 (0.6%) | NS | 0 | NS |
| LV6 | 6 (6%) | 39 (16%) | 0.008 | 23 (15%) | NS | 28 (26%) | 0.002 |

**8606 General Poster Session (Board #293), Mon, 1:15 PM-5:00 PM**

**Plerixafor plus G-CSF (P+G) compared with G-CSF alone (G) for hematopoietic progenitor cell (HPC) mobilization in AL amyloidosis (AL).** *Presenting Author: Binod Dhakal, Medical College of Wisconsin, Milwaukee, WI*

**Background:** Cytokine-based HPC mobilization in AL is frequently complicated by fluid overload, weight (wt.) gain, arrhythmia, collection failure and peri-mobilization mortality. **Methods:** We analyzed HPC mobilization outcomes of 49 consecutive AL pts. at our institution between 2004-2013 with G alone (10$\mu$g/kg/d) (n=25) vs. an institutional protocol to limit G exposure using plerixafor (P+G) (P at 0.24mg/kg SC starting 3 day of G 10$\mu$g/kg) (n=24). CD34+ HPC yield on day 1 of collection, total CD34+ yield, apheresis days and perimobilization morbidity were analyzed. Mobilization failure was defined as failure to collect $\geq 2\times10^6$cells/kg body weight. **Results:** Baseline characteristics of two groups are shown in Table. P+G strategy yielded higher total CD34+ cells/kg ($12.8 \times10^6$ vs. $6.3 \times10^6$; p<0.001), CD34+ cells/kg collected on day 1($10.8 \times10^6$ vs. $4.9 \times10^6$, p=0.004) compared with G alone cohort. More P+G pts. collected $\geq 5 \times10^6$ CD34+HPCs/kg (22 vs.16, p=0.02) and $\geq 10 \times10^6$ CD34+ HPCs/kg (13 vs. 5,p=0.01). Four pts. (16%) had mobilization failure with G alone, none with P+G. G exposure was less and peri-mobilization weight gain lower with P+G strategy (median weight gain 1 lbs. vs. 7 lbs., p=0.009). Numbers of apheresis sessions (median 1 vs. 1,p=0.52), the hospital days during mobilization (1.1 vs. 1.6,p=0.52), transfusion, antibiotic needs and arrythmia were similar between groups. **Conclusions:** This first report of upfront P+G mobilization in AL provides key feasibility data. Robust HPC mobilization in AL pts. with no unexpected adverse events was achieved with P+G.Superior HPC numbers, no mobilization failure and less weight gain are advantages compared to G alone.

| Variables | G | G+P | P value |
|---|---|---|---|
| Age yr. (median, range) | 56.6(30.1-75) | 56.9(44.1-71.1) | 0.34 |
| Male sex, N (%) | 11(44%) | 12(50%) | 0.67 |
| Prior lines of therapy (median, range) | 0(0-4) | 1(0-3) | <0.001 |
| KPS (median, range) | 90(60-100) | 90(60-100) | 0.05 |
| BM plasma cell (%) Dx | 0.1(0-0.4) | 0.1(0-0.8) | 0.19 |
| ≥PR with therapy | 3(12%) | 10(42%) | <0.001 |
| 3+ organs involved, N (%) | 14(56) | 7(29.2) | 0.20 |

**8607 General Poster Session (Board #294), Mon, 1:15 PM-5:00 PM**

**Modeling the risk of progression in smoldering multiple myeloma.** *Presenting Author: Adam J Waxman, Department of Medicine, University of Pennsylvania, Philadelphia, PA*

**Background:** Smoldering multiple myeloma (SMM) is a precursor state to multiple myeloma (MM) with a highly variable risk of progression to active MM. Identifying patients at risk of imminent progression to MM is critical for redefining MM requiring therapy and for designing clinical trials of early intervention. Existing biomarkers and risk models have not been validated. We sought to validate the Mayo Clinic risk models and biomarkers and to derive a novel risk model for an ethnically diverse SMM population seen at an urban academic medical center. **Methods:** We performed a retrospective study of all SMM patients seen within the University of Pennsylvania Health System (2008-2012). Patients were identified by ICD9 codes for MGUS and MM and classified as SMM per IMWG criteria after review of electronic medical records. Using classification and regression tree and Cox regression analyses, we developed a model for risk of progression to active MM. **Results:** We identified 126 SMM patients, median age 62 years, 55% male, 78% Caucasian, 19% African-American, and 3% other races. Median follow-up was 4 years. We validated the Mayo models and biomarkers (table). The Penn model included 3 factors: bone marrow plasma cells (BMPC) ≥40% (HR 2.72, CI 1.28-5.77, p<0.009), serum free light chain ratio (sFLCR) ≥50 (HR 4.57, CI 1.99-10.5, p <0.001) and albumin ≤ 3.5 gm/dL (HR 3.38, CI 1.57-7.27, p<0.001) [Low-risk = 0 factors, Intermediate risk = 1 factor, high risk ≥ 2 factors]. Adjusting for race did not impact risk of progression in any of the models. All patients with BMPC ≥60% progressed to MM within 2 years. **Conclusions:** We validated the Mayo risk models and biomarkers. In our population, albumin was a useful biomarker for risk of progression in SMM.

| | | N | Median TTP (yrs) | 2-yr Progression Free Survival + SE | HR | 95% CI | *P* value |
|---|---|---|---|---|---|---|---|
| **Mayo 2003** | BMPC ≥ 10 and M-s < 3 | 98 | 8.4 | 80 + 6 | 1.00 | | <0.001 |
| | BMPC ≥ 10 and M-s ≥ 3 | 23 | 1.7 | 42 + 11 | 3.05 | 1.66 – 5.59 | |
| **Mayo 2008** | Low risk | 47 | NR | 83 + 6 | 1.00 | | 0.003 |
| | Intermediate risk | 54 | 5.6 | 71 + 7 | 1.98 | 0.99 – 4.00 | |
| | High risk | 13 | 0.7 | 31 + 13 | 4.59 | 1.92 – 11.01 | |
| **Penn** | Low risk | 73 | NR | 84 + 4 | 1.00 | | <0.001 |
| | Intermediate risk | 24 | 3.07 | 56 + 12 | 3.24 | 1.55 – 6.75 | |
| | High risk | 14 | 0.35 | 19 + 11 | 11.16 | 5.03 – 24.78 | |
| **BMPC** | < 60 | 115 | 6.8 | 76 + 4 | 1.00 | | <0.001 |
| | ≥ 60 | 6 | 0.1 | 0 | 15.42 | 6.19 – 38.41 | |
| **sFLCR** | < 100 | 107 | 8.4 | 73 + 5 | 1.00 | | 0.009 |
| | ≥ 100 | 11 | 1.7 | 47 + 17 | 2.99 | 1.32 – 6.78 | |

Abbreviations: NR, not reached.

**8608 General Poster Session (Board #295), Mon, 1:15 PM-5:00 PM**

**Trends in survival of patients with primary plasma cell leukemia: A population-based analysis from 1973 to 2010.** *Presenting Author: Wilson I. Gonsalves, Mayo Clinic, Rochester, MN*

**Background:** Primary plasma cell leukemia (pPCL) is a rare plasma cell malignancy with a very aggressive course and poor outcome compared to multiple myeloma (MM). There has been significant improvement in the survival of MM patients over the past decade as a result of the incorporation of novel agents that are now also used in pPCL. The time period after 1995 represented adoption of autologous stem cell transplantation as a standard treatment modality and 2003 marked the wide availability of the novel agents in the relapsed and refractory setting due to accelerated FDA approval. However, it was not until 2006 that these novel agents were approved to be utilized in the first-line treatment of MM. The question remains whether the survival of pPCL has improved since the advent of these novel agents. **Methods:** We analysed the Surveillance, Epidemiology, and End Results (SEER) database for trends in survival of patients with pPCL (ICD-O: 9733) over the time period of 1973-2010 using the *SEER Stat 8.1.2*software. Kaplan-Meier analysis was used to analyze the overall survival (OS) and the Cox proportional hazards model was used to assess the influence of various prognostic factors on OS. **Results:** A total of 318 pPCL patients were identified in the SEER database. The median age at diagnosis was 62 years (range, 19-91) and 52% were females. The median follow up was 56 months (range, 39-102) and 83% of patients had died at the time of this analysis. The median 1, 2 and 5-year OS rates were 57%, 32% and 6% respectively. The median OS based on time periods of diagnosis of 1973-1995, 1996-2002, 2003-2005 and 2006-2010 were 9, 9, 8, and 19 months, respectively (P = 0.002). OS was similar regardless of subgroups based on age, gender, and marital status at diagnosis. Among patients <70 years age, the median OS was 11 months compared to 10 months in patients >70 years age (P = 0.378). Only diagnosis in the 2006-2010 era predicted for a better OS (HR: 0.65; 95% CI: 0.45-0.94; P = 0.0018, with reference to 1973-1995 era). **Conclusions:** Our study identifies a recent major improvement in survival amongst patients diagnosed with pPCL within a large US population. This suggests a positive impact of incorporating novel agents in the treatment of pPCL since 2006.

**8609 General Poster Session (Board #296), Mon, 1:15 PM-5:00 PM**

**Outcomes of young patients with Waldenstrom macroglobulinemia (WM).** *Presenting Author: Nishanth Vallumsetla, Mayo Clinic, Rochester, MN*

**Background:** WMis infrequentin young population, and data in patients (pts) ≤50 years of age are sparse. We present outcomes of a large cohort of young WM pts seen at Mayo Clinic, Rochester between 01/2000-12/2013. **Methods:** Sixty-nine (10.7%) of 640 consecutive pts were ≤50 years at diagnosis. Overall survival (OS) was calculated with Kaplan-Meier method and years of life lost were computed based on expected mortality for the age group. **Results:** Males constituted 65% of pts. Nine (14%) pts had familial WM. Patient characteristics and therapy related information are tabulated. Median follow up (FU) was 8years from diagnosis and 7.8 years from initial therapy. Eight-year OS was 84%from frontline therapy (median 14.8 years). Of all deaths (n=18), only 1 was non WM related. Over 30 years of FU, the average years of life lost were 10.8 years. Stem cells were successfully harvested from 10 of the 12 attempted. Only 5 (8%) pts underwent autologous stem cell transplantation (ASCT), one of whom had ASCT post transformation. In the non-transformed pts, ASCT was used as salvage therapy after a median of 6.5 regimens. Among these pts, median FU was 4.6 years from ASCT and median OS was not reached. Of 67 pts treated, 65 (97%) received rituximab (R) during their disease course. Overall, 6/25 (24%) who received nucleoside analogs (NA) developed therapy related myelodysplastic syndrome (t-MDS) or transformed lymphoma compared to 1/42 (2%) who received non NA based therapy (p=0.009). These events occurred at a median of 7.6 years from NA therapy. Median number of regimens utilized was 3.75. **Conclusions:** Despite its indolent course, WM remains a major cause of morbidity and mortality in young pts with this cancer. NA-based therapy is best avoided in this population due to high risk of developing t-MDS or transformation. Although effective, ASCT appears to be an underutilized approach.

| Parameters | Median (Range) | Symptoms/signs | % | Initial therapy | % |
|---|---|---|---|---|---|
| **Age (years)** | 45 (31-50) | Constitutional | 43 | R Monotherapy | 24 |
| **Hemoglobin (g/dL)** | 10 ( 5.4-14.6) | Paresthesias | 17 | DRC | 15 |
| **Platelet count ($10^9$/L)** | 220 (80-501) | Hyperviscosity | 23 | NA-based | 22 |
| **β2 Microglobulin (mcg/ml)** | 2.7 (1.3-7.8) | Lymphadenopathy | 29 | Chlorambucil-based | 10 |
| **IgM (mg/dl)** | 4501 (68-14400) | Splenomegaly | 14 | Other therapies | 28 |

**8610 General Poster Session (Board #297), Mon, 1:15 PM-5:00 PM**

**Clinical and cost benefit of aprepitant in patients receiving high-dose chemotherapy prior to autologous peripheral blood stem cell transplantation.** *Presenting Author: Ayumi Nakamura, Department of Pharmacy, National Hospital Organization Nagoya Medical Center, Aichi, Japan*

**Background:** The clinical benefit of aprepitant has not been elucidated in the patients (pts) receiving high-dose chemotherapy (HD-CT) prior to autologous peripheral blood stem cell transplantation (APBSCT). We retrospectively surveyed the efficacy of aprepitant and the total cost during hospitalization of APBSCT. **Methods:** All pts received HD-CT at our institute between 2009 and 2013 were registered. We identified a total 38 pts (27 non-Hodgkin lymphomas and 11 multiple myelomas). Thirteen pts received aprepitant and granisetron (aprepitant group) for the prophylaxis of the emesis, whereas, 25 pts received granisetron only (non-aprepitant group). Nausea, vomiting, and appetite loss during were evaluated according to NCI-CTCAE version 4.0. Total costs including hospitalization, and supportive care were calculated from medical records. **Results:** The incidence of severe nausea (>=grade 3) was 15.4% in aprepitant group and 52.0% in non-aprepitant group (p=0.028). Percentages of pts with appetite loss (>=grade 3) in the aprepitant group were 23.1% in aprepitant group and 72.0% non-aprepitant group (p=0.028). In addition, the median length of total hospitalization from day of HD-CT in aprepitant group and non-aprepitant group were 22 and 29 days (p=0.005), respectively. The time of engraftment of the hematopoietic stem cells from auto-PBSCT and the incidences of infectious events were not significantly different between these groups. Furthermore, in aprepitant group, the mean total costs decreased from $20,204 to $17,256 per patient, respectively. The common causes for reduction of total costs in the aprepitant group were reduction in costs of hospitalization, transfusion, and treatment for infections. **Conclusions:** Our data indicated that the addition of aprepitant for the prophylaxisis of the emesis decreased the incidence of severe nausea and appetite loss, and might introduce some economic benefits in the total management of HD-CT followed by APBSCT.

**TPS8611^ General Poster Session (Board #298A), Mon, 1:15 PM-5:00 PM**

**A phase 3 study of ibrutinib in combination with either bendamustine and rituximab (BR) or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in patients with previously treated follicular lymphoma or marginal zone lymphoma.** *Presenting Author: Nathan Hale Fowler, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Follicular lymphoma (FL) and marginal zone lymphoma (MZL) are indolent non-Hodgkin lymphomas (iNHL) and account for approximately 22% and 10%, respectively, of all NHLs. Although patients often respond to initial therapy, most will relapse and suffer substantial morbidity and mortality related to persistence/recurrence of disease. For patients with relapsed iNHL, the most common chemoimmunotherapy regimens are BR and R-CHOP; however, outcomes in the relapsed setting remain suboptimal. Ibrutinib is an oral Bruton's tyrosine kinase (BTK) inhibitor that has demonstrated activity in a phase 1 study in patients with various B-cell malignancies, including iNHL. A phase 2 monotherapy study in chemoimmunotherapy-resistant FL is ongoing. Other completed and ongoing studies have demonstrated that ibrutinib can be safely combined with BR or R-CHOP. Based on these observations, this phase 3 trial has been designed to investigate the combination of ibrutinib with BR or R-CHOP in patients with iNHL. **Methods:** The SELENE study, PCI32765FLR3001, is a randomized, double-blind, placebo-controlled, multicenter, phase 3 study of ibrutinib combined with either BR or R-CHOP for previously treated FL or MZL. The study aims to enroll approximately 400 patients with disease that has relapsed after, or was refractory to, prior chemoimmunotherapy. All patients will receive 6 cycles of BR or R-CHOP (based on prior treatment) and either a daily oral dose of 560 mg ibrutinib or placebo continued up to progression. The primary objective is to evaluate whether the addition of ibrutinib to BR or R-CHOP will prolong progression-free survival, with secondary objectives of evaluation of overall survival, CR rate, ORR, patient-reported lymphoma symptoms, and safety. Exploratory objectives include the minimal residual disease negative rate in FL patients, patient-reported outcomes related to general health status, and the pharmacokinetics of ibrutinib. Approximately 145 sites in Europe, Asia, Australia, USA and South America will participate. Enrollment began in Q1 2014. Clinical trial information: NCT01974440.

**TPS8612 General Poster Session (Board #298B), Mon, 1:15 PM-5:00 PM**

**Phase 3 trial of brentuximab vedotin and CHP versus CHOP in the frontline treatment of patients (pts) with CD30+ mature T-cell lymphomas (MTCL).** *Presenting Author: Owen A. O'Connor, Columbia University Medical Center/ New York Presbyterian Hospital, New York, NY*

**Background:** MTCL including systemic anaplastic large cell lymphoma (sALCL) are aggressive neoplasms. Anthracycline-based multiagent chemotherapy regimens have demonstrated response rates ranging from 76 to 88%. Five-year overall survival rates range from 12 to 49% depending on the histologic subtype. Brentuximab vedotin is an antibody drug conjugate that has shown efficacy in a pivotal phase 2 study as a single agent in relapsed sALCL (Pro et al., J Clin Oncol, 2012) and evidence of clinical activity in combination with CHP in the frontline treatment of MTCL including sALCL in a phase 1 study (Fanale et al., ASH 2012). **Methods:** This randomized, double-blind, placebo-controlled, multicenter, phase 3 study (NCT01777152) is evaluating the safety and efficacy of 1.8 mg/kg brentuximab vedotin with CHP (A+CHP) vs CHOP for frontline treatment of CD30+ MTCL. Pts must have FDG-avid disease by PET and measureable disease of at least 1.5 cm by CT. Approximately 300 pts will be randomized 1:1 to receive A+CHP or CHOP for 6–8 cycles (q3wk). Randomization will be stratified by ALK+ sALCL vs other histologic subtypes and IPI score (0–1, 2–3, or 4–5). The target proportion of pts with a diagnosis of sALCL will be 75%. The primary objective is to compare progression-free survival (PFS) between the 2 treatment arms as determined by an independent review facility (IRF). Secondary objectives include comparisons of PFS per IRF in sALCL patients, safety, overall survival, and complete remission rate between the 2 arms. After completion of treatment, pts will be followed for disease progression, medical resource utilization, quality of life, and survival. Post-treatment stem cell transplant is permitted. Efficacy assessments will use the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). CT and PET scans will be performed at baseline, after Cycle 4, and after the completion of treatment. CT scans will also be performed at regular intervals during follow-up until disease progression, death, or analysis of the primary endpoint. Safety assessments will occur throughout the study until 30 days after last dose of study treatment. Enrollment for this global trial began in early 2013. Clinical trial information: NCT01777152.

**TPS8613 General Poster Session (Board #299A), Mon, 1:15 PM-5:00 PM**

**Phase 3 study of brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (A+AVD) versus doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) as front-line treatment for advanced classical Hodgkin lymphoma (HL): Echelon-1 study.** *Presenting Author: Stephen Maxted Ansell, Mayo Clinic, Rochester, MN*

**Background:** Brentuximab vedotin (ADCETRIS), a CD30-targeted antibody-drug conjugate, has been approved for adults with relapsed or refractory CD30+ HL in 39 countries including the US and Europe. Front-line ABVD achieves complete response (CR) rates of 70–80% in patients (pts) with advanced HL. However, 10–20% of pts are refractory to front-line treatment and an additional ≤25% relapse. Further, bleomycin-induced pulmonary toxicity occurs in 10–25% of pts (Horning, J Clin Oncol 1994). In pts with relapsed HL post-autologous stem cell transplantation, objective response rate to single-agent brentuximab vedotin is 75% (CR, 33%; Chen, ASH 2012). In a ph 1 dose-escalation study (NCT01060904), 51 pts with treatment-naïve HL stage IIA bulky or stage IIB–IV disease were enrolled to evaluate safety, maximum tolerated dose and antitumor activity of brentuximab vedotin combined with ABVD (A+ABVD) or AVD (A+AVD) (Younes, Lancet Oncol 2013). 80% pts had stage III–IV, 25% had International Prognostic Score ≥4. Brentuximab vedotin was given on days 1 and 15 of 28-day cycles (≤6 cycles), 25 pts received ABVD plus brentuximab vedotin at 0.6, 0.9, or 1.2 mg/kg; 26 received AVD plus brentuximab vedotin 1.2 mg/kg. A+AVD was associated with a PET2 negative rate of 92%, CR rate of 96% and manageable toxicity. Although A+ABVD induced an unacceptably high rate of pulmonary toxicity compared to known rates with ABVD alone, pulmonary toxicity was not observed in the A+AVD cohort. We hypothesized that substituting bleomycin with brentuximab vedotin may improve progression-free survival (PFS) compared to ABVD and, eliminate bleomycin-related pulmonary toxicity. **Methods:** ECHELON-1 (NCT01712490), an ongoing, open-label, randomized, ph 3 study, will compare A+AVD vs ABVD in 1,040 pts with untreated stage III/IV classical HL. Pts will receive A+AVD (brentuximab vedotin 1.2 mg/kg with each dose of AVD) or ABVD on Days 1 and 15 of 28-day cycles (≤6 cycles). Primary endpoint: modified PFS (death, progression, receipt of chemotherapy or radiotherapy by pts not in CR after completing front-line therapy). Clinical trial information: NCT01712490.

**TPS8614 General Poster Session (Board #299B), Mon, 1:15 PM-5:00 PM**

**AUGMENT: A phase 3, randomized trial to compare efficacy and safety of lenalidomide plus rituximab versus placebo plus rituximab in patients with relapsed/refractory indolent non-Hodgkin lymphoma (NHL).** *Presenting Author: John Leonard, Weill Cornell Medical College, New York, NY*

**Background:** Lenalidomide (L) is an immunomodulatory drug with both anti-inflammatory and antiangiogenic properties. Preclinical studies demonstrate that the immunological function of tumor-infiltrating lymphocytes is impaired in patients with follicular lymphoma (FL) and that treatment with L can repair this dysfunction (Ramsay, *Blood*, 2009). In phase 2 investigations of frontline L + rituximab (R), in patients with indolent NHL, overall response rate (ORR) reached 90% and complete response/complete response unconfirmed (CR/CRu) was 64% (Fowler, ASH, 2012); a second study in patients with FL achieved 93% ORR and 72% CR (Martin, ICML, 2013). In patients with recurrent FL, treatment with L+R yielded higher response rates (73% ORR, 36% CR) compared with L alone (51% ORR, 13% CR; Leonard, ASCO 2012 oral presentation). Together, these preclinical and phase 2 data provide a rationale for further investigation of L+R in indolent NHL. **Methods:** This phase 3, multicenter, double-blind, randomized study (AUGMENT) is designed to evaluate the efficacy and safety of L+R versus placebo (P)+R in patients with relapsed/refractory indolent lymphoma. Eligible patients must have grade 1, 2, or 3a FL or marginal zone lymphoma; have received previous systemic therapy; be refractory to or have relapsed after their last treatment; be R-sensitive if prior R therapy was administered; have ≥1 measurable lesion; and have adequate bone marrow, liver, and renal function (moderate renal impairment acceptable). Approximately 350 patients will be randomized 1:1 to one of two study arms (experimental or control). During each 28-day cycle, patients enrolled in the experimental group will receive L (20 mg/day; days 1 to 21 up to 12 cycles) + R (375 mg/m$^2$; days 1, 8, 15, 22 of cycle 1 and day 1 of cycles 2 to 5). Patients in the control group will receive P+R (375 mg/m$^2$) in the same schedule. The primary endpoint is progression-free survival. Key secondary endpoints include rate of durable CR, overall survival, ORR, safety, and time to next anti-lymphoma treatment. This trial is currently enrolling patients. Clinical trial information: NCT01938001.

**TPS8615^ General Poster Session (Board #300A), Mon, 1:15 PM-5:00 PM**

**A randomized, double-blind, placebo-controlled phase 3 study of ibrutinib in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in subjects with newly diagnosed nongerminal center B-cell subtype of diffuse large B-cell lymphoma (DLBCL).** *Presenting Author: Anas Younes, Memorial Sloan-Kettering Cancer Center, New York, NY*

**Background:** The standard regimen for frontline treatment of DLBCL is R-CHOP, which results in a complete response (CR) in 76% of patients and a 10-year overall survival (OS) rate of 44%. DLBCL can be classified by immunohistochemistry (IHC) into 2 subgroups: germinal center B-cell-like (GCB) or non-GCB (including the activated B-cell-like and some intermediate molecular subtypes). Prognosis is suggested to be least favorable for non-GCB DLBCL, the subgroup associated with NF-κB pathway activation and chronic active B-cell receptor (BCR) signaling. Ibrutinib inhibits BCR signaling by covalently binding to Bruton's tyrosine kinase. A phase 2 monotherapy study in relapsed/refractory DLBCL showed a 41% overall response rate (ORR) in the non-GCB subgroup (ASH 2012). A phase 1 study combining ibrutinib with R-CHOP showed an ORR of 100% in DLBCL and a favorable safety profile (ASH 2013), suggesting that ibrutinib can be safely combined with R-CHOP. **Methods:** The PHOENIX study, PCI32765DBL3001, is a phase 3 randomized, placebo-controlled, double-blind study of ibrutinib in combination with R-CHOP versus R-CHOP for the treatment of newly diagnosed non-GCB DLBCL. The study aims to enroll 800 patients (≈400 per arm). All patients will receive standard doses of R-CHOP therapy for 6 or 8 cycles (according to local practice), with ibrutinib 560 mg daily or placebo. The primary objective is to evaluate if the addition of ibrutinib to R-CHOP will result in prolongation of event-free survival. Secondary objectives include progression-free survival, OS, ORR (CR + PR), CR rate, and safety. The study will enroll previously untreated adult patients with the non-GCB subgroup of DLBCL determined by central IHC (Hans algorithm). Key exclusion criteria include central nervous system involvement or primary mediastinal lymphoma, diagnosis or treatment for malignancy other than DLBCL, or history of indolent lymphoma. Approximately 280 sites globally will enroll patients. Enrollment began in Q4 of 2013. Clinical trial information: NCT01855750.

**TPS8616 General Poster Session (Board #300B), Mon, 1:15 PM-5:00 PM**

**Phase 1-2 open-label, multiple-dose, dose-escalation study to evaluate the safety and tolerability of intravenous infusion of SNS01-T, a first-in-class modulator of eukaryotic translation initiation factor 5A (eIF5A) in patients (pts) with relapsed or refractory B-cell malignancies.** *Presenting Author: Michael Craig, West Virginia University, Morgantown, WV*

**Background:** eIF5A has been implicated in the regulation of cell proliferation, apoptosis, and inflammation. It is the only known protein to be modified by hypusination, and is highly conserved across species and is active in plants and animals. Hypusinated eIF5A, the predominant form in normal and cancer cells, is involved in cell survival and inflammatory pathway activation. siRNAs targeting eIF5A inhibit NF-kB activation and reduce pro-inflammatory cytokine production. Accumulation of the unhypusinated lysine form of eIF5A is associated with apoptosis. Mutants of eIF5A that cannot be hypusinated (e.g. $eIF5A_{K50R}$) are pro-apoptotic in vitro and have anti-tumoral activity in vivo in multiple cancer types including melanoma and lung cancer. SNS01-T is a novel therapeutic with a dual mechanism of eIF5A modulation: inducing cell death via siRNA-mediated inhibition of hypusinated eIF5A while simultaneously causing over-expression of pro-apoptotic $eIF5A_{K50R}$ via a DNA plasmid with a B-cell promoter to induce tumor cell death. SNS01-T significantly inhibited tumor growth and increased survival in mouse models of myeloma (MM), mantle cell and diffuse large B-cell lymphoma. **Methods:** This is an open label, phase 1-2 dose escalation study in pts with refractory B-cell cancers. The study has 4 dose cohorts: 0.0125, 0.05, 0.2 and 0.375 mg/kg twice weekly IV for 6 weeks. Main inclusion criteria are: MM per IMWG criteria or lymphomas or plasma cell leukemia with histologic confirmation; measurable disease; relapsed or refractory disease after ≥2 prior regimens; life expectancy ≥3 months; not eligible for any other standard therapy known to extend life expectancy. Primary endpoints are safety and tolerability of SNS01-T. Secondary endpoints include pharmacokinetics, tumor response (M protein, % plasma cells, radiologic response) and time to relapse or progression. To date, 15 patients have been included in the study. Enrolment (n=6) at the highest dose cohort has commenced (1 pt enrolled). Cohort 4 is expected to be completed in 1H2014. Clinical trial information: NCT01435720.

**TPS8617 General Poster Session (Board #301A), Mon, 1:15 PM-5:00 PM**

**MAGNIFY: A phase 3B, randomized trial of lenalidomide plus rituximab induction and maintenance therapy followed by lenalidomide single-agent versus rituximab maintenance in patients with relapsed/refractory indolent non-Hodgkin lymphoma (NHL).** *Presenting Author: David J Andorsky, Rocky Mountain Cancer Centers, Boulder, CO*

**Background:** Immunomodulation with lenalidomide (L) + rituximab (R) is a promising treatment approach for patients (pts) with indolent NHL. In indolent NHL, frontline L+R provided a 90% overall response rate (ORR) and 64% complete response/complete response unconfirmed (CR/CRu) (Fowler, ASH, 2012). In phase 2 trials of L+R in relapsed/refractory (R/R) disease, pts with mantle-cell lymphoma (MCL) achieved 57% ORR and 36% CR (Wang, *Lancet Oncol*, 2012); pts with follicular lymphoma (FL) treated with L+R had a higher response rate (73% ORR, 36% CR) compared with those receiving L alone (51% ORR, 13% CR; Leonard, ASCO, oral presentation, 2012). **Methods:** The phase 3b MAGNIFY study will compare the efficacy and safety of 12 cycles of combination L+R for induction with randomization to L+R (Arm A) vs R (Arm B) maintenance in pts with R/R FL, MCL, or marginal zone lymphoma (MZL). Target enrollment is ~500. Pts will be randomized 1:1 to 28-day (d) treatment cycles. In both arms, pts will receive induction L (20 mg/d on d 1-21; 12 cycles) + R (375 mg/m$^2$ on d 1, 8, 15, 22 in cycle 1; d1 of cycles 3, 5, 7, 9, 11). In Arm A, pts will receive maintenance L (10 mg/d on d 1-21; cycles 13-30) + R (375 mg/m$^2$ on d1 of every other cycle from 13-29), followed by L (10 mg/d on d 1-21) until progression. Following 12 cycles of induction with L+R, pts in Arm B will receive maintenance R (375 mg/m$^2$ on d1 of every other cycle from 13- 29). Eligible pts must have R/R grade 1, 2, or 3a FL, MZL, or MCL; have completed previous systemic therapy; have ≥1 measurable lesion; and have adequate bone marrow, liver, and renal function (moderate renal impairment acceptable). The primary endpoint is progression-free survival. Key secondary endpoints include rate of CR/CRu, overall survival, ORR, duration of response, duration of CR/CRu, and safety. Health-related quality of life, as measured by the FACT-Lym questionnaire, will be assessed as an exploratory endpoint. This trial is currently enrolling pts. Clinical trial information: NCT01996865.

**TPS8618 General Poster Session (Board #301B), Mon, 1:15 PM-5:00 PM**

**LEGEND: A randomised phase II study comparing lenalidomide plus rituximab, gemcitabine, and methylprednisolone (R-GEM-L) to rituximab, gemcitabine, methylprednisolone, and cisplatin (R-GEM-P) in second-line treatment of diffuse large B-cell lymphoma (DLBCL).** *Presenting Author: Mary Gleeson, The Royal Marsden NHS Foundation Trust, London and Surrey, United Kingdom*

**Background:** Diffuse Large B-cell lymphoma (DLBCL) exhibits high sensitivity to first-line chemo-immunotherapy, however approximately one-third of patients (pts) will relapse. A number of salvage regimens including R-GEM-P (rituximab, gemcitabine, cisplatin and methylprednisolone), are used in the relapsed/refractory (RR) setting, with overall (OR) and complete (CR) response rates of 50-70% and 20-50% respectively. Pts eligible for post-salvage consolidation with autologous stem cell transplantation (ASCT) have an overall survival (OS) of 40% at 3 years, while ASCT-ineligible pts have a very poor prognosis. More efficacious salvage regimens are urgently needed for this patient group. Lenalidomide has shown activity in RR DLBCL (both as monotherapy and in combination with rituximab), and has been safely combined with gemcitabine in pancreatic cancer. In the LEGEND trial R-GEM-L (rituximab 375mg/m$^2$ D1 and 15, gemcitabine 1000mg/m$^2$ D1, 8 and 15, methylprednisolone 1000mg D1-5 and lenalidomide 25mg od D1-21) and R-GEM-P are compared as second-line regimens in RR DLBCL. **Methods:** This is a randomised phase II open-label multicenter study. 92 eligible pts with RR DLBCL after 1 previous line of therapy, PS 0-2 and FDG-avid disease will be randomised on a 1:1 basis to 3 cycles of R-GEM-P (Arm A) or R-GEM-L (Arm B), following which pts in CR may undergo ASCT if eligible. Response will be assessed according to the Modified IWG 2007 Revised Response Criteria incorporating PET/CT. Following R-GEM-L (+/-ASCT) pts on Arm B and in CR will receive an additional 12 months of single-agent lenalidomide maintenance (25mg od D1-21 every 28 days). The primary endpoint is CR rate following induction chemotherapy. Secondary endpoints include ORR, event free survival (EFS), OS, rates of successful stem cell harvest and toxicity. Sample size was estimated using an optimal Simon 2-stage design (based on a true response probability of ≥60% and closing either arm if <40%, one-sided $\alpha$: 0.05, 80% power). A total of 46 patients will be recruited to each arm. Clinical trial information: 2012-002620-32.

**TPS8619 General Poster Session (Board #302A), Mon, 1:15 PM-5:00 PM**

**DYNAMO: A phase 2 trial of the PI3K-δ,γ inhibitor IPI-145 in patients with refractory indolent non-Hodgkin lymphoma.** *Presenting Author: Nina Wagner-Johnston, Washington University in St. Louis, St. Louis, MO*

**Background:** Phosphoinositide 3-kinase (PI3K)-δ,γ isoforms are preferentially expressed in leukocytes, have significant roles in normal B and T cell function, and are central to the growth and survival of certain B and T cell malignancies. Inhibition of these isoforms by IPI-145, an oral PI3K-δ,γ inhibitor, has unique therapeutic potential in hematologic malignancies. IPI-145 has shown clinical activity and a favorable safety profile across a broad range of hematologic malignancies in an ongoing phase 1 trial (IPI-145-02). Based on these results, the DYNAMO phase 2 trial (IPI-145-06) was initiated in May 2013 to evaluate the efficacy and safety of IPI-145 in patients with indolent non-Hodgkin lymphoma (iNHL) refractory to rituximab and chemotherapy or radioimmunotherapy (RIT). **Methods:** This open-label, single-arm trial includes adult patients diagnosed with iNHL (defined as follicular lymphoma [FL], marginal zone lymphoma, or small lymphocytic lymphoma) whose disease has progressed within 6 months of their last dose of a chemotherapy regimen or RIT. Eligible patients must have been previously treated with rituximab, and had either no objective response or documented progression within 6 months of completing therapy. Approximately 120 patients will be enrolled, including at least 100 patients with FL, at sites in and outside the US. All patients will receive 25 mg IPI-145 orally, twice daily during 28-day treatment cycles, for up to 12 cycles. After 12 cycles, patients may receive additional cycles of IPI-145 if they have documented evidence of response according to the International Working Group (IWG) criteria. The primary efficacy endpoint is the objective response rate and secondary endpoints include safety and tolerability of IPI-145, duration of response, progression-free survival, overall survival, and pharmacokinetic parameters. Assessment of response, best overall response, and progression status will be evaluated according to the IWG response criteria for NHL. This trial is currently enrolling patients. Clinical trial information: NCT01882803.

**TPS8620 General Poster Session (Board #302B), Mon, 1:15 PM-5:00 PM**

**A phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib in combination with rituximab for previously treated indolent non-Hodgkin lymphomas (iNHL).** *Presenting Author: Gilles A. Salles, Lyon Sud University Hospital, Pierre-Bénite, France*

**Background:** PI3Kδ is critical for activation, proliferation and survival of B cells and plays a role in homing and retention in lymphoid tissues. PI3Kδ signaling is hyperactive in many B-cell malignancies. Idelalisib (GS-1101) is a first-in-class, targeted, highly selective, oral inhibitor of PI3Kδ that reduces proliferation, enhances apoptosis, and inhibits homing and retention of malignant B cells in lymphoid tissues (Lannutti et al, 2011). A phase 2 trial demonstrated that idelalisib is highly active in pts with heavily pretreated iNHL: response rate was 57% (6% CR) and median PFS was 11 mos with an acceptable safety profile (Gopal et al, 2014). **Methods:** A planned 375 pts with previously treated recurrent iNHL, who have measurable lymphadenopathy, have received prior anti-CD20-antibody-containing therapy, and who have iNHL that is not refractory to rituximab (R) will be randomized in a 2:1 ratio into Arm A or Arm B of the study. In Arm A, subjects will receive idelalisib at 150 mg BID continuously + R at 375 mg/m$^2$ (weekly x 4 then every 8 weeks x 4). In Arm B, subjects will receive placebo BID instead of idelalisib. Stratification factors include tumor type (follicular lymphoma vs others), tumor burden (high vs low), and time since completion of last prior therapy for iNHL ($<$18 months vs $\geq$18 months). The primary endpoint is PFS and secondary endpoints include ORR, lymph node response rate, CR rate, and OS. This is an event-driven trial and primary endpoint evaluation will be based on independent central review. For the primary efficacy analysis, the difference in PFS between the treatment arms will be assessed in the ITT analysis set using Kaplan-Meier methods and the stratified log-rank test. The study opened for enrollment in Dec 2012. Clinical trial information: NCT01732913.

**TPS8621 General Poster Session (Board #303A), Mon, 1:15 PM-5:00 PM**

**A phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with bendamustine and rituximab for previously treated indolent non-Hodgkin lymphomas (iNHL).** *Presenting Author: Myron Stefan Czuczman, Roswell Park Cancer Institute, Buffalo, NY*

**Background:** PI3Kδ is critical for activation, proliferation and survival of B cells and plays a role in homing and retention in lymphoid tissues. PI3Kδ signaling is hyperactive in many B-cell malignancies. Idelalisib is a first-in-class, targeted, highly selective, oral inhibitor of PI3Kδ that reduces proliferation, enhances apoptosis, and inhibits homing and retention of malignant B cells in lymphoid tissues (Lannutti et al, 2011). A phase 2 trial demonstrated that idelalisib is highly active in pts with heavily pretreated iNHL: response rate was 57% (6% CR) and median PFS was 11 mos with an acceptable safety profile (Gopal et al, 2014). **Methods:** A planned 450 pts with recurrent iNHL, who require therapy for iNHL, have received prior anti-CD20-antibody-containing therapy and chemotherapy, and who have iNHL that is not refractory to bendamustine (B) with measurable lymphadenopathy, will be randomized in a 2:1 ratio into Arm A or Arm B of the study. In Arm A, subjects will receive rituximab (R) at 375 mg/m$^2$ every 28 days + B at 90 mg/m$^2$ on days 1 and 2 of each 28-d cycle up to 6 cycles with idelalisib at 150 mg BID continuously until progression. In Arm B, subjects will receive placebo BID instead of idelalisib. Stratification factors include tumor type (follicular lymphoma vs others), tumor burden (high vs low), and time since completion of last prior therapy for iNHL ($<$18 months vs $\geq$18 months). The primary endpoint is PFS, and secondary endpoints include CR rate, ORR, lymph node response rate, and OS. This is an event-driven trial and primary endpoint evaluation will be based on independent central review. For the primary efficacy analysis, the difference in PFS between the treatment arms will be assessed in the ITT analysis set using Kaplan-Meier methods and the stratified log-rank test. The study opened for enrollment in Dec 2012. Clinical trial information: NCT01732926.

**TPS8622 General Poster Session (Board #303B), Mon, 1:15 PM-5:00 PM**

**Anti-CCR4 monoclonal antibody KW-0761 (mogamulizumab) or investigator's choice of chemotherapy in subjects with relapsed or refractory adult T-cell leukemia-lymphoma (ATL).** *Presenting Author: Adrienne Alise Phillips, Columbia University, New York, NY*

**Background:** The receptor for macrophage derived chemokine (MDC) and thymus- and activation-regulated chemokine (TARC) CC chemokine receptor 4 (CCR4) is over expressed in several T-cell malignancies including HTLV-1 related ATL where approximately 90% of malignant cells have been shown to overexpress this chemokine receptor. The HTLV-1 transactivator gene (Tax) does not directly induce CCR4 expression. Rather, expression of CCR4 is controlled by the constitutive activation of several transcription factors in HTLV-1 infected cells. Inhibiting the expression of these transcription factors with small-interfering RNAs has been shown to block CCR4 expression and also reduce proliferation of the affected cells.[2] Patients with CCR4 positive ATL are more likely to have skin involvement and shorter overall survival (OS; median 9.5 months) compared with CCR4-negative (20.6 months). Mogamulizumab is a defucosylated, humanized, monoclonal antibody with enhanced antibody-dependent cellular cytotoxicity (Potelligent) against primary ATL cells that bind to CCR4. **Methods:** This study includes patients with previously treated ATL, excluding smoldering type, who have relapsed or are refractory after at least 1 prior systemic therapy. CCR4 expression is not required for eligibility. Patients are randomized (2:1 ratio) to either mogamulizumab or Investigator's choice (pralatrexate; gemcitabine plus oxaliplatin; or dexamethasone, cisplatin and cytarabine) and stratified by disease type (ie, acute, chronic, and lymphomatous). Patients who progress on the Investigator's choice regimen may cross over to treatment with mogamulizumab. The primary endpoint is the overall response rate. Efficacy evaluation is based on the Tsukasaki criteria and includes assessment of lymph nodes, extranodal masses, the spleen, liver, skin, peripheral blood, and bone marrow. Safety analyses and an exploratory evaluation of mogamulizumab exposure-response relationship will be performed. The study is being conducted in the US, Europe, and Central/South America. As of 24 January 2014, 44% of 70 planned patients have been randomized. Clinical trial information: NCT01626664.

**TPS8623 General Poster Session (Board #304A), Mon, 1:15 PM-5:00 PM**

**Phase 3 study of anti-CCR4 monoclonal antibody mogamulizumab versus vorinostat in relapsed or refractory cutaneous T-cell lymphoma (CTCL).** *Presenting Author: Youn H. Kim, Stanford Cancer Institute, Stanford, CA*

**Background:** CC chemokine receptor 4 (CCR4) is selectively expressed on type 2 helper T cells and certain functional regulatory T cells. Its expression allows T-cell trafficking to skin and lymph nodes. CCR4 is also expressed on CTCL cells. Expression increases with advancing disease stage and is closely associated with an unfavorable disease outcome. Advanced CTCL is a clinically unmet need due to short survivals and absence of curative treatments. Mogamulizumab (KW-0761) is a humanized anti-CCR4 monoclonal antibody with a defucosylated Fc region that enhances antibody-dependent cell-mediated cytotoxicity (ADCC). In an in vitro ADCC assay and a humanized mouse in vivo model, mogamulizumab exhibited potent antitumor activity against T-cell lymphoma cell lines as well as against primary CTCL cells from patients. Preliminary clinical data suggest mogamulizumab may lead to responses in CTCL, even in CCR4 negative disease by immunohistochemistry. **Methods:** This is a first-in-kind Phase 3 trial that compares mogamulizumab to a standard of care in patients with relapsed/refractory CTCL afterat least 1 prior systemic therapy, regardless of CCR4 expression. Inclusion criteria include: ECOG performance score $<$ 1; adequate hematological, hepatic, and renal function. Patients are stratified by disease type (Sézary syndrome vs mycosis fungoides) and stage, and are randomized (1:1) to receive mogamulizumab or vorinostat. Patients who are unable to tolerate or progress on vorinostat may cross over to mogamulizumab. Response assessments are done by the modified skin weighted assessment tool and global composite response including skin, blood, lymph node and viscera assessments. The study's primary endpoint is progression free survival (PFS). The PFS of the experimental and comparator arms will be compared using a stratified log-rank test at the one-sided 2.5% significance level. The median PFS for mogamulizumab therapy is targeted for 254 days, a 50% improvement over the reference median PFS for vorinostat of 169 days. A total of 255 PFS events will give 90% power. Clinical trial information: NCT01728805.

**TPS8624 General Poster Session (Board #304B), Mon, 1:15 PM-5:00 PM**

**SWOG 1211: A randomized phase I/II study of optimal induction therapy for newly diagnosed high-risk multiple myeloma (HRMM).** *Presenting Author: Saad Zafar Usmani, Carolinas Healthcare System, Charlotte, NC*

**Background:** The introduction of immunomodulatory agents and proteasome inhibitors, and advances in high dose therapy administration have made an impact on progression free survival (PFS) and overall survival (OS) for multiple myeloma (MM) patients in general, but patients with HRMM still have a poor long-term prognosis. Therefore, it is imperative to develop novel therapeutic regimens that will extend PFS and OS in this group. The SWOG 1211 is the first national and inter-group study targeting the HRMM population. **Methods:** Eligibility and Trial Design: A randomized phase I/II trial was designed to evaluate the efficacy of incorporating novel agents into first line therapy for HRMM patients comparing lenalidomide, bortezomib and dexamethasone (RVD) with or without addition of elotuzumab (Elo). Eligible patients must have a documented history of HRMM defined by one or more of the following: Poor risk genomics defined by 70-gene model. Translocation (14;16), translocation (14;20) and/or deletion (17p) by florescent in-situ hybridization (FISH). Primary plasma cell leukemia. Serum LDH $>$ 2 times normal levels. Objectives: Phase I: To determine the maximum tolerated dose (MTD) of RVD-Elo. Phase II: To assess whether incorporation of the novel agent Elo into treatment algorithm of HRMM will improve PFS. Statistical Considerations: The phase I study enrolled 6 DLT evaluable patients; no DLTs were observed. The phase II study is now open and will accrue 100 eligible patients (50 per arm). An additional 10 patients (5 per arm) will be accrued to account for ineligibility/patients withdrawing consent. The median expected PFS in the control arm (RVD) is 2.2 years, based on the experience in Total Therapy 3a and 3b studies (high risk genomics defined by 70-gene model). Assuming uniform accrual of 25 patients per year, four years of accrual and an additional 2 years of follow-up yields a study with 82% power and a one-sided significance level alpha of 0.1 to detect a hazard ratio of 1.75 between two treatment arms, or an increase in median PFS from 2 years to 3.5 years in the RVD-Elo arm versus the RVD arm. Clinical trial information: NCT01668719.

**TPS8625 General Poster Session (Board #305A), Mon, 1:15 PM-5:00 PM**

**The STRATUS trial (MM-010): A single-arm phase 3b study of pomalidomide plus low-dose dexamethasone (POM + LoDEX) in refractory or relapsed and refractory multiple myeloma.** *Presenting Author: Meletios A. Dimopoulos, Alexandra Hospital, University of Athens School of Medicine, Athens, Greece*

**Background:** POM is a distinct oral IMiD immunomodulatory agent with direct anti-myeloma, stromal cell support-inhibitory, and immune-modulating activities. In the phase 3 MM-003 trial, POM + LoDEX significantly extended progression-free survival (PFS) and overall survival (OS) vs. high-dose dexamethasone in patients (pts) who failed bortezomib (BORT) and lenalidomide (LEN) treatment (Tx; Dimopoulos, ASH 2013). STRATUS is a multicenter, single-arm, open-label phase 3b trial with $>$ 85 sites across Europe to further evaluate safety and efficacy and explore cytogenetics, pharmacokinetics (PK), and biomarkers in a large pt population (target enrollment: 720 pts; NCT01712789). **Methods:** Eligible pts have refractory or relapsed and refractory disease, having failed BORT and LEN and received adequate prior alkylator therapy. Key exclusion criteria include absolute neutrophil count $<$ 800/$\mu$L, platelet count $<$ 75,000 or 30,000/$\mu$L (for pts with $<$ 50% or $>$ 50% of bone marrow nucleated cells as plasma cells, respectively), creatinine clearance $<$ 45 mL/min, hemoglobin $<$ 8 g/dL, and peripheral neuropathy $>$ grade 2. POM is administered 4 mg D1-21/28-day cycle and LoDEX 40 mg/day (20 mg for pts aged $>$ 75 yrs) on D1, 8, 15, and 22 until progressive disease or unacceptable toxicity. All pts receive low-dose ASA or equivalent thromboprophylaxis. Upon Tx discontinuation, follow-up will continue up to 5 yrs from enrollment of last pt for survival, second primary malignancies, and subsequent anti-MM Tx. The primary endpoint is safety. Secondary endpoints include POM exposure, PK, efficacy (overall response rate, time to response, duration of response, PFS, time to progression, OS, and cytogenetics). Cytogenetics are collected at initial diagnosis, study entry, and upon discontinuation to better understand the evolution of cytogenetics throughout the disease course and elucidate the role of POM in pts with different cytogenetic profiles. As exploratory endpoints, bone marrow and blood samples are collected for biomarker analysis to predict response or resistance to POM Tx. As of Jan 22, 2014, 400 pts have been enrolled and enrollment continues. Clinical trial information: NCT01712789.

**TPS8626 General Poster Session (Board #305B), Mon, 1:15 PM-5:00 PM**

**MM-013: An ongoing phase 2 trial of pomalidomide and low-dose dexamethasone (POM + LoDEX) in relapsed/refractory multiple myeloma (RRMM) with moderate or severe renal impairment (RI) including patients (pts) undergoing hemodialysis.** *Presenting Author: Pieter Sonneveld, Erasmus MC, Rotterdam, Netherlands*

**Background:** RI occurs in $>$ 40% of MM pts and can be associated with poor prognosis (Knudsen, *EJH* 2000). Data from 2 pivotal trials (MM-002, MM-003) suggested comparable efficacy and tolerability for POM + LoDEX in pts with or without moderate RI (Siegel, ASH 2012; Weisel, ASCO 2013). However, pts with severe RI were excluded from these trials. Because POM is extensively metabolized, with $<$ 5% of active substance eliminated in the urine, RI may not affect POM exposure in a clinically relevant manner. However, this has not been definitively tested in a clinical trial, and is under investigation in the US in MM-008. MM-013is a European, multicenter, open-label phase 2 study designed to assess the efficacy, safety, and pharmacokinetics (PK) of POM + LoDEX in RRMM pts with moderate or severe RI, including those undergoing dialysis (NCT02045017). **Methods:** The trial is enrolling RRMM pts (N = 80) across 3 cohorts: Cohort A (n = 33 with moderate RI, estimated glomerular filtration rate [eGFR] $\geq$ 30 and $<$ 45 mL/min/1.73 m$^2$), Cohort B (n = 33 with severe RI [eGFR $<$ 30 mL/min/1.73 m$^2$] and no dialysis), and Cohort C (n = 14 with severe RI requiring dialysis). Pts must have biopsy-confirmed MM-related RI and RRMM with $\geq$ 1 prior therapy (Tx; including lenalidomide). POM 4 mg is administered D1-21/28-day cycle and LoDEX 40 mg/day (20 mg for pts $>$ 75 y) on D1, 8, 15, and 22 until progressive disease or unacceptable toxicity. Thromboprophylaxis is required for all pts not on dialysis; pts on dialysis should receive anticoagulants as appropriate. After Tx discontinuation, pts will be followed for survival, subsequent anti-MM Tx, and second primary malignancies for 5 y after enrollment of last pt. The primary endpoint is overall response rate; secondary endpoints include assessment of renal response ($\geq$ 2 mos improvement in eGFR from $<$ 15 to 30-59 mL/min/1.73 m$^2$ [partial] + improvement from $<$ 50 to $\geq$ 60 mL/min/1.73m$^2$ [complete]), time to renal response, PFS, TTP, OS, safety, and PK. Additional analyses will examine biomarkers predictive of response or resistance to POM. MM-013 is open for enrollment across Europe. Clinical trial information: NCT02045017.

**TPS8627 General Poster Session (Board #306A), Mon, 1:15 PM-5:00 PM**

**MM-014: A phase 2 trial evaluating efficacy, safety, and biomarkers of pomalidomide plus low-dose dexamethasone (POM + LoDEX) in relapsed/refractory multiple myeloma (RRMM) following second-line lenalidomide plus dexamethasone (LEN + DEX).** *Presenting Author: David Samuel DiCapua Siegel, John Theurer Cancer Center, Hackensack, NJ*

**Background:** Challenging relapsed disease with drugs of the same class remains an area of investigation. Subanalyses of MM-002 and MM-003 in advanced RRMM demonstrated comparable efficacy for POM + LoDEX in patients (pts) refractory to LEN as last prior treatment (Tx) vs. all pts (Richardson, 2014; San Miguel, 2013). To confirm this, MM-014, a multicenter, single-arm, open-label phase 2 trial in the US and Canada evaluating POM + LoDEX immediately following second-line LEN + DEX, was designed (NCT01946477). **Methods:** Pts (N = 85 planned) must have received 2 prior lines of myeloma Tx, with LEN + DEX as second line. Pts must have relapsed from or become refractory to LEN + DEX as last prior Tx ($\geq$ 2 cycles). Prior Tx may include all predetermined components of induction followed by ASCT and maintenance. Key exclusion criteria are creatinine clearance $<$ 30 mL/min requiring dialysis, ECOG PS $>$ 2, neutrophils $<$ 1000/$\mu$L, platelets $<$ 75,000 or $<$ 30,000/$\mu$L (for pts with $<$ 50% or $\geq$ 50% of bone marrow [BM] nucleated cells as plasma cells, respectively), Hb $<$ 8 g/dL, and prior ($<$ 5 y) non-MM malignancies. Pts must provide a BM sample at screening to establish presence or absence of myelodysplastic changes. Tx is POM 4 mg D1-21 of a 28-day cycle and LoDEX 40 mg/day (20 mg for pts aged $>$ 75 y) on D1, 8, 15, and 22 until progression or unacceptable toxicity. Thromboprophylaxis with low-dose aspirin or equivalent is mandated. Upon discontinuation, follow-up will continue for OS, second primary malignancies, and subsequent anti-MM Tx for up to 5 y from enrollment. The primary endpoint is ORR by modified IMWG criteria (with minimal response). Secondary endpoints include PFS, OS, duration of response, TTP, and safety. To elucidate POM mechanism of action in LEN-exposed disease, MM-014 includes exploratory endpoints to identify molecular, immune, and cellular biomarkers and evaluate clonality. Specifically, markers that may predict POM response or resistance, underlie POM + LoDEX synergy, indicate dysregulated pathways or key MM targets, and chromosomal aberrations will be evaluated. Sites are open for enrollment. Clinical trial information: NCT01946477.

**TPS8628 General Poster Session (Board #306B), Mon, 1:15 PM-5:00 PM**

**A randomized, double-blind, multinational trial comparing denosumab with zoledronic acid for treatment of bone disease in adults with newly diagnosed multiple myeloma.** *Presenting Author: Noopur S. Raje, Center for Multiple Myeloma, Massachusetts General Hospital Cancer Center, Boston, MA*

**Background:** A characteristic feature of multiple myeloma (MM) is bone destruction mediated by osteoclasts. This breakdown of bone releases factors that mediate myeloma cell growth, creating a cycle of skeletal damage and tumor cell growth. Patients with MM and bone lesions can experience debilitating pain and skeletal complications including pathologic fractures, need for radiotherapy or surgery to bone, and spinal cord compression, collectively termed skeletal-related events (SREs). RANKL is the key mediator of osteoclast activity. Denosumab, a fully human monoclonal antibody specific to RANKL, inhibits the formation, function, and survival of osteoclasts, thus decreasing cancer-mediated bone destruction. The primary endpoint of this trial is to determine whether denosumab is noninferior to zoledronic acid (ZA) in delaying the time to 1$^{st}$ on-study SRE in patients with MM. Secondary endpoints include superiority of denosumab vs ZA in delaying the time to 1$^{st}$ on-study SRE and time to 1$^{st}$-and-subsequent SRE and overall survival. Safety endpoints will be assessed. This trial is registered (ClinicalTrials.gov NCT01345019) and sponsored by Amgen Inc. **Methods:** We are targeting enrollment of ~1520 adults with newly diagnosed MM and $\geq$1 bone lesion. Patients with $\leq$30 days of anti-myeloma therapy, $\leq$1 prior dose of IV bisphosphonate, an ECOG status $\leq$2, and adequate organ function are eligible. Use of any approved treatment regimen is permitted as anti-myeloma treatment in this trial. Enrolled patients are stratified by whether they intend to undergo autologous stem cell transplant; use of novel vs non-novel anti-myeloma agents as 1$^{st}$-line therapy; stage at diagnosis per the International Staging System; SRE at time of presentation; and geographic region. Randomized (1:1) patients receive either SC denosumab 120 mg + IV placebo *or* IV ZA 4 mg (adjusted for CrCl) + SC placebo once every 4 weeks. Daily calcium ($\geq$500 mg) and vitamin D ($\geq$400 IU) supplements are strongly recommended. The primary analysis is planned when ~800 patients experience an on-study SRE. Enrollment is currently ongoing and enrollment rates are as planned. Clinical trial information: NCT01345019.

**TPS8629 General Poster Session (Board #307A), Mon, 1:15 PM-5:00 PM**

**Efficacy of lenalidomide maintenance (LEN) therapy versus placebo, after melphalan, prednisone, bortezomib (MPV) induction therapy in patients (pts) with newly diagnosed multiple myeloma (NDMM): The ARUMM (MM-026) trial.** *Presenting Author: Cyrille Hulin, Hematology Department, University Hospital, Nantes, France*

**Background:** Improved progression-free survival (PFS) benefits have been reported in several large phase 3 trials with LEN therapy (Attal NEJM 2012, Facon ASH 2013, McCathy NEJM 2012, Palumbo NEJM 2012, Palumbo ASCO 2013), overall survival (OS) advantage has also been observed in some of them. Treatment with LEN therapy has also been well tolerated. Effective continuous maintenance therapy is of great importance to prolong response duration and consequently improved disease outcomes (PFS, OS). **Methods:** ARUMM is a phase 3b, double-blind, 2-arm study which will compare efficacy and safety of continuous maintenance therapy with LEN vs. placebo until progressive disease (PD) in NDMM pts. Inclusion criteria are: pts $\geq$ 65 yrs or $<$ 65 yrs not candidates for stem cell transplantation, and who achieved $\geq$ partial response (PR) as best overall response after 6 to 9 cycles of MPV induction therapy. Exclusion criteria include: prior treatment (Tx) with other anti-myeloma therapies than MPV, and pts who did not reach $\geq$ PR after MPV induction Tx. Eligible pts will be randomized either to LEN (10 mg/day days 1–21/28-day cycle) or placebo (days 1–21/28-day cycle) until PD. Pts will be stratified according to disease stage (ISS) and prognostic factors at initial diagnosis, and response to MPV induction therapy. PFS is the primary study endpoint and defined as the time from randomization to PD based on IMWG criteria and reviewed by an independent physician or death from any cause, whichever occurs first; secondary endpoints will include overall response rate, OS, quality of life, cytogenetics and tolerability. Safety will include adverse events (AEs), laboratory abnormalities, serious AEs, and second primary malignancies. Exploratory endpoints will include the assessment of minimal residual disease. Approximately 351 pts will be enrolled. The trial has been powered at 80% with a hazard ratio of 0.66 (LEN vs. placebo) for PFS between the 2 arms (29 vs. 19 months) at the 2-sided significance level of 0.05. EudraCT Number: 2013-001729-26 Clinical trial information: 2013-001729-26.

**TPS8630 General Poster Session (Board #307B), Mon, 1:15 PM-5:00 PM**

**Continuous lenalidomide (LEN) therapy versus observation following nonimmunomodulatory compound-based induction therapy in newly diagnosed multiple myeloma (NDMM): MM-027 trial.** *Presenting Author: Saad Zafar Usmani, Levine Cancer Institute/Carolinas Healthcare System, Charlotte, NC*

**Background:** Several recent trials have shown improvements in progression-free survival (PFS) with continuous LEN treatment (Tx) in NDMM patients (pts). PFS was 45%-59% higher using LEN therapy vs. control arm and rates of overall survival (OS) were consistently improved (Attal, NEJM 2012; Facon, ASH 2013, McCarthy, NEJM 2012; Palumbo, NEJM 2012, Palumbo ASCO 2013). Therefore an effective strategy of continuous Tx is of great importance to outcomes. **Methods:** This phase 3b, multicenter, randomized, open-label study will compare PFS of LEN single-agent vs. observation after non-immunomodulatory compound based induction therapy in NDMM pts ($\geq$ 65 yrs) or $<$ 65 yrs non eligible for/decline SCT. Main inclusion criteria are: induction Tx with 6–12 cycles of non-immunomodulatory compound, achievement of $\geq$ stable disease (SD) according to the International Myeloma Working Group (IMWG) criteria. Exclusion criteria include: previous antimyeloma Tx and pts who did not achieve $\geq$ SD after $>$ 6 cycles of non-immunomodulatory Tx. Eligible pts will be screened and randomized 1:1 in either the LEN arm (10 mg/day on day 1–21/28-day cycle) or observation arm until progressive disease (PD). Dose adjustments will be made in case of adverse events (AEs). All pts who progress will enter long-term follow-up and will be monitored for OS and second primary malignancy every 3 months (mos) for at least 5 yrs. Primary endpoint is PFS from time of randomization to PD or death from any cause; secondary endpoints will include overall response rate and safety. AEs will be evaluated and graded according to the NCI CTCAE Version 4.0. Group sizes were calculated for a median PFS of 20 mos in the LEN arm and 10 mos in the observation arm, 90% power and a two-sided 0.05 level test. Counting for a non-evaluable rate of 15%, a total of 172 pts will be needed (86 per arm). Exploratory objectives will include assessment of minimal residue disease (MRD), clonal heterogeneity measurements and their correlation to clinical outcomes, molecular, immunological and mechanistic biomarkers will be assessed.

**LBA9000^** **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Efficacy and safety of the anti-PD-1 monoclonal antibody MK-3475 in 411 patients (pts) with melanoma (MEL).** *Presenting Author: Antoni Ribas, David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA*

**The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Monday, June 2, 2014, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2014, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.**

**9001** **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Phase 2, multicenter, safety and efficacy study of pidilizumab in patients with metastatic melanoma.** *Presenting Author: Michael B. Atkins, Georgetown University Lombardi Comprehensive Cancer Center, Washington, DC*

**Background:** Pidilizumab (CT-011), a humanized anti PD-1 IgG1k, was studied in two Phase 2 studies in aggressive and indolent lymphomas showing clinical activity correlated with PD-1/PD-L1+ lymphocytes. Thus, we initiated a Phase 2 multicenter, randomized, open-label, study to evaluate the safety and efficacy of pidilizumab in patients (pts) with metastatic melanoma (MM). **Methods:** Eligibility criteria: measurable disease; Stage IV clearly progressive; ECOG 0-1; ≤ 3 prior systemic therapies for MM; stabilized brain mets allowed; 6 weeks from prior ipilimumab (Ipi), no prior PD-1/PD-L1/PD-L2 blockade. Pts were randomized to 2 dose levels (1.5 or 6 mg/kg IV q2 wk X 27), each with 50 pts and each balance stratified by prior Ipi (yes/no). **Results:** 103 pts were randomized; 75% M1c, 15.5% brain mets, 30% elevated LDH, 33% disease spread to ≥ 3 organs. 77% received prior systemic therapy for MM; 51% prior Ipi, 7.8% prior Braf inhibitor, 44% prior biologics (cytokines). 45% did not respond to most recent therapy. 45% received pidilizumab less than 4 months after prior therapy. ORR using irRC for all pts was 5.9% [90% CI: 2.3, 12.0] and 10.0% [90% CI: 1.8, 28.3] for 1.5mg/kg & prior Ipi. Pts with prior Ipi had higher irSD (53.7% vs 20.5%) and slightly longer median PFS (2.8 vs 1.9 months). Overall Survival at 12 months (12mo survival) was 64.5% (90% CI: 55.6, 72.0), with insignificant differences between strata or doses and irrespective of therapies given before study entry or after study withdrawal; 12mo survival for pts without prior or post-study Ipi (n=26) was 55.7% [90% CI: 35.6, 71.8], 12mo survival for pts with B-RAF V600 WT tumors (n=63) was 69.3% [90% CI: 58.2, 78.1]. 12mo survival for M1c pts (n=77) was 67.2%; [90% CI: 57.0, 75.5]. The most frequent AEs were fatigue (43%), diarrhea (22.5%), arthralgia (21%) and SAEs of pneumonia (5%) and dyspnea (3%). **Conclusions:** Despite low response rates, pidilizumab therapy results in substantial 12mo survival in heavily pretreated pts. The 12mo survival appears comparable to that of other anti- PD-1 MAbs. Treatment is very well tolerated. Further studies of pidilizumab in pts with MM are warranted, preferably in combination with other therapeutics. Clinical trial information: NCT01435369.

**9002** **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Long-term survival of ipilimumab-naive patients (pts) with advanced melanoma (MEL) treated with nivolumab (anti-PD-1, BMS-936558, ONO-4538) in a phase I trial.** *Presenting Author: F. Stephen Hodi, Dana-Farber Cancer Institute, Boston, MA*

**Background:** We have shown that nivolumab, a fully human IgG4 PD-1 immune-checkpoint inhibitor antibody, is tolerable and active in pts with advanced solid tumors in a large phase I trial (Topalian et al. N Eng J Med 366:2443-54, 2012). For the MEL pts in this trial, we report long-term clinical activity, pts' response off therapy, tumor PD-1 ligand (PD-L1) expression associated with survival endpoints, and for the first time, 3-y overall survival (OS). **Methods:** Previously treated advanced MEL pts with no prior ipilimumab therapy received nivolumab (0.1, 0.3, 1, 3, or 10 mg/kg IV) Q2Wk for ≤96 wk and were evaluated for OS and progression-free survival (PFS). PD-L1 tumor cell membrane expression was retrospectively assessed in archival specimens by a Dako immunohistochemistry assay with ≥5% tumor cells designated as PD-L1(+). **Results:** From 2008-2012, 107 MEL pts initiated treatment with nivolumab; 25% had ≥3 prior therapies. Across doses, the 2- and 3-y OS rates were 48 and 41%, respectively (Table). For the 34/107 (32%) pts with objective responses (OR; RECIST), median response duration was 22.9 mo. Twenty-four OR pts stopped nivolumab for reasons other than disease progression; 11 (46%) maintained responses for ≥24 wk off drug (range: 24, 56+ wk). Four (4%) pts had unconventional "immune-related" responses. In a subset of pts with evaluable tumor samples (41/107), pts with PD-L1(+) and (–) tumors (n=18 and 23, respectively) had median OS of not reached and 12.5 mo; median PFS was 9.1 mo and 1.9 mo. Safety has been previously reported (Sznol et al. J Clin Oncol 31:abs CRA9006, 2013). **Conclusions:** In advanced MEL pts, nivolumab demonstrated favorable 2- and 3-y OS rates, durable responses with a number persisting off therapy, and an acceptable safety profile. Additional analyses will be presented by pts' characteristics across the full population, the long-term survival subgroup, and the PD-L1(+/–) tumor subgroups. Ongoing phase III trials are further evaluating nivolumab for MEL pts and PD-L1 as a potential predictive biomarker for response to nivolumab. Clinical trial information: NCT00730639.

| OS rate* n=107 | % (95% CI) | Pts at risk |
|---|---|---|
| 1 y | 63 (53, 71) | 63 |
| 2 y | 48 (38, 57) | 44 |
| 3 y | 41 (31, 51) | 22 |

*September 2013 analysis.

**LBA9003^** **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Survival, response duration, and activity by BRAF mutation (MT) status of nivolumab (NIVO, anti-PD-1, BMS-936558, ONO-4538) and ipilimumab (IPI) concurrent therapy in advanced melanoma (MEL).** *Presenting Author: Mario Sznol, Yale Cancer Center, New Haven, CT*

**The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Monday, June 2, 2014, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2014, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.**

**9004** **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Correlation between pre-existing MEK1$^{P124}$ mutations and clinical and in vitro response to BRAF inhibitors in metastatic melanoma.** *Presenting Author: Matteo S. Carlino, Melanoma Institute Australia; Westmead Institute for Cancer Research & Westmead Millennium Institute, University of Sydney, Sydney, Australia*

**Background:** MEK1 mutations can confer resistance to BRAF inhibitors although pre-existing MEK1$^{P124}$ mutations do not preclude clinical responses to BRAF inhibitor therapy. We sought to determine if pre-existing MEK1$^{P124}$ mutations affected clinical outcome in BRAF inhibitor treated melanoma. **Methods:** Data from three published data sets, and from patients treated at our institutions, were analyzed to determine if pre-existing MEK$^{P124}$ mutations affect radiological response or progression-free survival (PFS) in BRAF$^{V600}$ mutant metastatic melanoma patients treated with vemurafenib or dabrafenib. The effects of MEK1$^{P124}$ mutations on MAPK pathway activity and response to dabrafenib were also investigated in a series of cell models. **Results:** 123 patients with pre-treatment tumors tested for MEK1 mutations were included. Those with a pretreatment MEK$^{P124}$ mutation (n=12) had a poorer RECIST response (33% vs 71% CR or PR in MEK1$^{P124}$ vs MEK1 wild-type, p=0.008), this was associated with a shorter median PFS in those with a MEK1$^{P124}$ mutation (Median 3.1 vs 4.8 months, p=0.004). Introduction of MEK1 P124Q or P124S variants into BRAF-mutant SKMel28 melanoma cells resulted in diminished inhibition of ERK phosphorylation by dabrafenib and enhanced clonogenic survival compared to cells ectopically expressing wild-type MEK1. The impact of MEK1$^{P124}$-variants was significantly less than the effect of MEK1$^{K57E}$, a known mechanism of acquired BRAF inhibitor resistance. Consistent with these data, two BRAF mutant cell lines with endogenous MEK1$^{P124}$ mutations, including a short term culture generated pre-treatment from a patient who responded poorly to combined dabrafenib and trametinib, showed weak sensitivity to dabrafenib (IC50s 21 and 26nM) compared to a panel of MEK1 wild type/BRAF mutant cell lines (median IC50 7nM; range 4-14nM). In contrast, melanoma cell lines showed equivalent sensitivity to ERK inhibition, irrespective of the MEK1 genotype. **Conclusions:** Pre-existing MEK$^{P124}$ mutations are associated with a reduced response to BRAF inhibitor therapy but are unlikely to affect response to ERK inhibitors.

**9005** **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

***BRAF*$^{V600}$ mutation levels and response to vemurafenib in metastatic melanoma.** *Presenting Author: Celeste Lebbe, Hôpital Saint-Louis, Paris, France*

**Background:** Resistance mechanisms acquired during BRAF inhibitor (BRAFi) treatment were shown to involve multiple signalling pathways including MAPK, PI3K pathways and tumor microenvironment. They may also be complicated by intra-tumor heterogeneity of *BRAF* mutational status which paradoxically enhances wild-type *BRAF* cells proliferation. We therefore wanted to evaluate using a quantitative pyrosequencing assay whether the level of *BRAF*$^{V600}$ mutation in tumor tissue could predict clinical response and outcome of *BRAF*$^{V600}$melanoma patients treated with the BRAFi, vemurafenib. **Methods:** melanoma specimen from 44 patients with advanced melanoma treated with vemurafenib were available at abseline. The *BRAF*$^{V600}$ mutation level was defined as the ratio of the *BRAF*$^{V600}$ allele quantification to the percentage of tumor cells in the sample. The main end point were response according to RECIST, progression free survival, overall survival and ratio of the mutated allele to percentage of tumor cells. **Results:** The *BRAF*$^{V600}$ mutation level was significantly associated with the best response rate to vemurafenib (*BRAF*$^{V600E}$ and *BRAF*$^{V600K}$ *P*=0.003; *BRAF*$^{V600E}$ only *P*=0.003). The median PFS and OS for all patients were respectively 4 (95%CI 3 to 6) and 13 (95%CI 6 to 15) months. Interestingly, until 10 months of treatment the PFS of patients with high ratio (≥ 0.5; median) was significantly better than those of patients with a low ratio) but the benefit did not last. Indeed the progression free survival (PFS) benefit in those patients with a high mutation levels (≥ 0.5) gradually decreased during the first 6 months of treatment as the risk of progression increased and, beyond 10 months of treatment, became even lower than in patients with low mutation level. **Conclusions:** We show that quantification of BRAF mutant allele (V600E and V600K) is a predictive marker of BRAFi response in metastatic melanoma patients. This preliminary study constitutes a first step in the identification of surrogate biomarkers of melanoma response to BRAFi and provides a promising tool that might help in the management of metastatic melanoma.

**9006^** **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Metabolic tumor burden for prediction of overall survival following combined BRAF/MEK inhibition in patients with advanced BRAF mutant melanoma.** *Presenting Author: Grant A. McArthur, Skin and Melanoma Service, Peter MacCallum Cancer Centre, East Melbourne, Australia*

**Background:** BRAF mutation is a common and potent oncogenic driver of ERK signalling in melanoma. Abrogation of pERK reduces 18-F-fluorodeoxyglucose (FDG) uptake on PET with recovery in glycolytic metabolism being a hallmark of resistance. FDG-PET also allows accurate quantification of melanoma burden. In a Ph1b trial (BRIM7), combining vemurafenib (vem) with a MEK inhibitor, cobimetinib (cobi), BRAFi-naïve patients (pts) with advanced *BRAF*$^{V600}$-mutated melanoma attained 87% confirmed response rate, by RECIST and median progression-free survival of 13.7 months. We evaluated FDG-PET response as predictor of clinical outcome in BRAFi/MEKi naïve patients (pts) treated with this combination. **Methods:** FDG-PET scanning was performed in cycle 1 (C1) (day 10-15) and in C2 (day 35-49) of BRIM7. The percentage of the injected dose (%ID) of FDG and metabolic tumor volume (MTV), as measures of tumor burden, and maximum standardized uptake value (SUVmax) in up to 5 target lesions, as an indicator of metabolism, were assessed at baseline, C1 and C2. PFS and OS were analysed by the log rank method. **Results:** 35 evaluable BRAFi-naïve pts (mean %ID 1.6±2.9% and mean 'MTV 166±251 ml) demonstrated a mean reduction in %ID, MTV and SUVmax of 86±14%, 72±23% and 76±18% at C1, respectively, and 95±10%, 92±12% and 89±14% at C2, respectively. All pts achieved a partial metabolic response (PMR) (> 30% decrease in SUVmax) by C1 with 5 complete metabolic responses (CMR) (14%) in C1 and 17 CMR (51%) in C2. Pts achieving a CMR in C1 had longer PFS when compared to Pts achieving PMR. Although tumor burden at baseline was not correlated with metabolic response, both %ID and MTV were predictors of OS. Pts with a baseline %ID <median (0.36%) or MTV <median (47.5 ml) had better OS (HR 0.19, p<0.02 and 0.14, p=0.03) compared to pts with >median values. **Conclusion:** Independent of tumor burden, BRAFi/MEKi naïve pts treated with vem/cobi achieved a marked, early and progressive metabolic response on FDG-PET consistent with successful inhibition of ERK-signaling. Tumor burden was a predictor of clinical outcome in this small patient cohort with low baseline %ID or MTV associated with longer overall survival; further validation is warranted. Clinical trial information: NCT01271803.

**9007** **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Comparative health care (HC) costs in patients (pts) with metastatic melanoma (mM).** *Presenting Author: Chun-Lan Chang, IMS Health, Plymouth Meeting, PA*

**Background:** Advances in mM have increased treatment (tx) options, where previously, few therapies were available. This study compares HC and adverse event (AE) costs in a U.S. managed care population of mM pts. **Methods:** This retrospective study used a large claims database comprised of 55 U.S health plans. mM pts who initiated treatment with vemurafenib (VEM), ipilumimab (IPI), dacarbazine (DTIC), paclitaxel (PAC) or temozolomide (TMZ) from 7/2009-9/2012 were identified. A treatment episode (TE) was defined as time from index date to addition or switch to different study drug, or a gap >45 days (>112 days for IPI). Adverse events (AEs) were selected if reported in package inserts (Grade 3/4 occurring ≥5%) and identified by ICD-9 codes occurring within TEs and 30 days after end of TEs. All-cause costs for TEs and AEs were normalized as monthly costs. Multivariate regression models with repeated measures were used to estimate adjusted monthly HC and AE costs. **Results:** The study identified 541 mM pts with mean (SD) age of 57.5 (11.5) years; 62.1% were male; 49.0% had >3 sites of metastases. A total of 809 TEs (VEM:143; IPI:147; DTIC:89; PAC:139; TMZ:291) were identified. Total mean (SD) all-cause costs for VEM were $77,687 (60,329); IPI $153,062 (134,048); DTIC $35,243 (33,641); TMZ $42,870 (41,384); PAC $58,991 ($81,306). Adjusted mean monthly TE costs for VEM was significantly lower than IPI and comparable to other mM drugs. VEM had significantly lower monthly AE costs than all other study drugs (Table). **Conclusions:** HC costs were highest for IPI, followed by TMZ, VEM, PAC and DTIC. This study is amongst the 1st economic analyses to include recently approved therapies in mM. In combination with safety and efficacy findings, these results may assist clinicians, policy makers and managed care organizations with treatment strategies in mM.

| | VEM | IPI | DTIC | TMZ | PAC |
|---|---|---|---|---|---|
| TE length, mean (median) days | 138 (124) | 72 (73) | 69 (54) | 87 (63) | 100 (76) |
| Adjusted monthly costs, mean (95% CI) | | | | | |
| TE | $17,223 ($16,966–$17,480) | $65,313 ($64,338–$66,288) | $16,123 ($15,882–$16,363) | $17,885 ($17,618–$18,152) | $16,941 ($16,688–$17,194) |
| AE | $2,259 ($2,209-$2,309) | $4,628 ($4,526-$4,730) | $9,415 ($9,207-$9,622) | $3,189 ($3,118-$3,259) | $8,261 ($8,079-$8,444) |

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**LBA9008** **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Ipilimumab versus placebo after complete resection of stage III melanoma: Initial efficacy and safety results from the EORTC 18071 phase III trial.** *Presenting Author: Alexander M. Eggermont, Cancer Institute Gustave Roussy, Villejuif, France*

**The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Monday, June 2, 2014, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2014, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.**

**9008a** **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Primary overall survival (OS) from OPTiM, a randomized phase III trial of talimogene laherparepvec (T-VEC) versus subcutaneous (SC) granulocyte-macrophage colony-stimulating factor (GM-CSF) for the treatment (tx) of unresected stage IIIB/C and IV melanoma.** *Presenting Author: Howard L Kaufman, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

**Background:** T-VEC is an oncolytic immunotherapy derived from herpes simplex virus type-1 designed to selectively replicate in tumors and produce GM-CSF to enhance systemic antitumor immune responses. OPTiM is a randomized, phase 3 trial of T-VEC or GM-CSF in patients (pts) with unresected melanoma with regional or distant metastases (NCT00769704). OPTiM met the primary endpoint of a statistically significant improvement in durable response rate (DRR) with T-VEC vs GM-CSF (Andtbacka et al. ASCO 2013). The primary analysis of OS is reported here. **Methods:** Key entry criteria were age ≥ 18 yrs, ECOG ≤1, unresectable melanoma stage IIIB/C or IV, injectable cutaneous, SC, or nodal lesions, LDH ≤1.5X ULN, ≤ 3 visceral lesions (excluding lung), none > 3 cm. Pts were randomized 2:1 to intralesional T-VEC (initially ≤ 4 mL x$10^6$ pfu/mL then after 3 wks, ≤ 4 mL x$10^8$ pfu/mL Q2W) or SC GM-CSF (125 $\mu$g/m$^2$qd x 14 days q28d). The primary endpoint was DRR: partial or complete response continuously for ≥ 6 mos starting within 12 mos. Responses were per modified WHO by blinded central review. The primary analysis of OS (290 planned events) had 90% power to detect a HR of 0.67 with two sided $\alpha$=0.05. **Results:** 436 pts are in the ITT set: 295 (68%) T-VEC, 141 (32%) GM-CSF. 57% were men; median age was 63 yrs. An increase of 4.4 mos in OS with T-VEC vs GM-CSF was observed (p =0.051): HR 0.787 (95% CI: 0.62, 1.00); median (95% CI) OS was 23.3 (19.5, 29.6) mos with T-VEC vs 18.9 (16.0, 23.7) mos with GM-CSF. Objective response rate with T-VEC was 26% (95% CI: 21%, 32%) with 11% CR, and with GM-CSF was 6% (95% CI: 2%, 10%) with 1% CR. DRR for T-VEC was 16% (95% CI: 12%, 21%) and 2% for GM-CSF (95% CI: 0%, 5%), p<0.0001. Most common adverse events (AEs) with T-VEC were fatigue, chills, and pyrexia. No ≥ grade 3 AE occurred in ≥ 3% of pts in either arm. **Conclusions:** In pts with unresectable Stage IIIB-IV melanoma, T-VEC demonstrated a significant improvement in the DRR vs GM-CSF with a tolerable safety profile. An improvement in OS approaching statistical significance was seen in the ITT population. Clinical trial information: NCT00769704.

**9009** **Clinical Science Symposium, Sun, 8:00 AM-9:30 AM**

**A phase 1b/2 study of LEE011 in combination with binimetinib (MEK162) in patients with *NRAS*-mutant melanoma: Early encouraging clinical activity.** *Presenting Author: Jeffrey Alan Sosman, Vanderbilt University Medical Center, Nashville, TN*

**Background:** *NRAS*-mutant melanoma has poor prognosis with no approved targeted therapies. Enhanced MAPK pathway signaling and cell cycle checkpoint dysregulation are frequent in *NRAS*-mutant melanoma. Thus, simultaneous inhibition of MEK and CDK4/6 could further suppress pathway activation. The MEK inhibitor binimetinib (MEK162) showed clinical activity in patients (pts) with *NRAS*-mutant melanoma. In preclinical studies, the selective CDK4/6 inhibitor LEE011 demonstrated tumor growth inhibition, and in combination with binimetinib led to regressions in *NRAS*-mutant melanoma models, warranting clinical study. **Methods:** This is a phase 1b/2, open-label study of LEE011 + binimetinib in pts with *NRAS*-mutant melanoma. The primary objective of the phase 1b part is to estimate the MTD/RP2D of the combination, using a Bayesian logistic regression model (BLRM) with overdose control. Secondary objectives include safety, pharmacokinetics (PK), and preliminary efficacy. LEE011 is administered once daily for 21 days of each 28-day cycle and binimetinib is administered twice daily continuously. **Results:** As of Dec 20, 2013, 14 pts were enrolled (93% stage M1c; ECOG PS 0/1/2 [43%/50%/7%]; median 2 prior lines) and were treated with LEE011 at 200 mg (dose level [DL] 1, n = 8) or 300 mg (DL 2, n = 6) and with binimetinib 45 mg. DLTs occurred at DL 1 (grade 3 acute renal injury, n = 1) and DL 2 (grade 4 asymptomatic creatine phosphokinase [CPK] elevation and grade 3 edema plus grade 4 atrial fibrillation, 1 pt each). Common treatment-related toxicities included CPK elevation, rash, edema, anemia, nausea, diarrhea, and fatigue. Preliminary PK was consistent with single-agent data for either drug, with no evidence of drug-drug interaction. Six pts achieved partial response (43%; 1 confirmed, 5 unconfirmed) and 6 had stable disease (4 with tumor shrinkage > 20%). Several pts experienced early tumor shrinkage with major symptomatic improvement; 8 pts remain on treatment (duration 2-8 mo). **Conclusions:** Combined LEE011 + binimetinib shows promising preliminary antitumor activity in pts with *NRAS*-mutant melanoma. Determination of a phase 2 dose and schedule and PD effects are ongoing. Clinical trial information: NCT01719380.

**9009a^** **Clinical Science Symposium, Sun, 8:00 AM-9:30 AM**

**Randomized, double-blind study of sonidegib (LDE225) in patients (pts) with locally advanced (La) or metastatic (m) basal-cell carcinoma (BCC)** *Presenting Author: Michael Robert Migden, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Pts with advanced BCC have limited treatment options. Sonidegib blocks the hedgehog pathway (overexpressed in ≥ 95% of BCCs) by selective inhibition of smoothened. **Methods:** In this ph 2 study (BOLT; NCT01327053), pts with LaBCC, not amenable to curative surgery or radiation, or mBCC were randomized 1:2 to receive sonidegib 200 or 800 mg daily. The primary endpoint, objective response rate (ORR—histopathologically confirmed complete response [CR] + partial response [PR]—achieved if point estimate ≥ 30% and 95% CI lower bound > 20% [either arm]), and secondary endpoints duration of response (DoR), CR rate, time to tumor response (TTR), and PFS were assessed according to modified RECIST (mRECIST; LaBCC) or RECIST 1.1 (mBCC) by central review. Statistical comparison of arms was not planned. Safety was assessed up to ≈30 days post-last dose. **Results:** Pts (194 LaBCC; 36 mBCC) were enrolled from Jul 2011-Jan 2013. The primary endpoint was met for both arms (Table; median follow-up 13.9 mo). Median exposure was 8.9 (200 mg) and 6.5 mo (800 mg). AEs were less frequent at 200 mg. AEs leading to discontinuation (200/800 mg) included muscle spasms (3.8%/8.7%), dysgeusia (2.5%/4.7%), weight decreased (2.5%/4.7%), and nausea (2.5%/4.0%). **Conclusions:** Meaningfuldisease control with sustained DoR and prolonged PFS were achieved with both doses of sonidegib, with a more favorable benefit-risk profile for 200 mg. Clinical trial information: NCT01327053.

| | Sonidegib (daily) | | | |
|---|---|---|---|---|
| | 200 mg | | 800 mg | |
| | LaBCC n=66 | mBCC n=13 | LaBCC n=128 | mBCC n=23 |
| % ORR[a] | 47.0 | 15.4 | 35.2 | 17.4 |
| 95% CI | 34.6-59.7 | 1.9-45.4 | 26.9-44.1 | 5.0-38.8 |
| % CR | 3.0 | 0 | 0 | 0 |
| % PR | 43.9 | 15.4 | 35.2 | 17.4 |
| % Disease control rate (CR+PR+SD) | 90.9 | 92.3 | 78.2 | 82.6 |
| % ORR[b] | 42.9 | 15.4 | 37.6 | 17.4 |
| 95% CI | 27.7-59.0 | 1.9-45.4 | 27.8-48.3 | 5.0-38.8 |
| % ORR,[a] per investigator | 65.2 | 23.1 | 57.0 | 34.8 |
| 95% CI | 52.4-76.5 | 5.0-53.8 | 48.0-65.7 | 16.4-57.3 |
| TTR[a] | | | | |
| Median, mo | 3.9 | 4.6 | 3.7 | 1.0 |
| 95% CI | 3.6-4.2 | 1.8-7.4 | 2.6-3.8 | 1.0-2.1 |
| DoR[b] | | | | |
| n/N[c] | 4/31 | 0/2 | 3/45 | 1/4 |
| Median, mo | NE | NE | NE | 8.3 |
| 95% CI | | | | NE |
| PFS[a] | | | | |
| n[c] | 7 | 4 | 10 | 10 |
| Median, mo | NE | 13.1 | NE | 7.6 |
| 95% CI | | 5.6-13.1 | | 6.2-11.1 |

[a] Full analysis set (intent-to-treat population) [b] Subset of pts (LaBCC w/tumor fully assessable per mRECIST [n=42, 200 mg; n=93, 800 mg] + mBCC per RECIST 1.1) [c] n=PFS events; N=responders NE, not estimable

**9010^ Clinical Science Symposium, Sun, 8:00 AM-9:30 AM**

**Updated overall survival (OS) for BRF113220, a phase 1-2 study of dabrafenib (D) alone versus combined dabrafenib and trametinib (D+T) in pts with *BRAF* V600 mutation-positive (+) metastatic melanoma (MM).** *Presenting Author: Keith Flaherty, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA*

**Background:** D, a selective BRAF inhibitor, and T, a reversible, highly selective allosteric inhibitor of MEK1/2, are approved monotherapies, and an FDA approved combination therapy for $BRAF^{V600}$mutation + MM. **Methods:** Safety and efficacy of D+T were evaluated in this Phase 1-2 study. $BRAF^{V600E/K}$mutation + MM pts naive to BRAFi and MEKi were enrolled. Part B (Ph 1, n=77 BRAF naive) pts enrolled into escalating cohorts of D mg BID + T mg QD – 75/1, 150/1, 150/1.5 and 150/2 respectively. Part C (Ph 2, n=162) pts were randomized 1:1:1 to D 150 mono, 150/1 and 150/2. Cross-over from D mono to 150/2 was allowed post progression of disease (PD). Primary endpoints were progression free survival (PFS), response rate (RR), duration of response (DoR), and safety; secondary endpoints were OS and PK. **Results:** Updated OS for pts in Parts B and C with median follow-up of 28 and 24 months (mo) presented in Table 1.In Part C, median OS for 150/2 pts is 23.8 mo (HR=0.73 vs. D mono, p-value=0.24); 18-mo OS rate is 63%, reflective of paradigm shifting improvements in OS in this population. OS for D mono is confounded by cross-over to 150/2; 45 (83%) pts crossed over at time of analysis. In 150/1 and 150/2, 43 (80%) and 24 (44%) continued to receive D+T beyond RECIST PD. Subsequent systemic therapies were similar across arms; 38 (23%) pts received immune checkpoint inhibitors (19% ipilimumab and 8% PD-1/PD-L1 13), and 19 (12%) received vemurafenib. **Conclusions:** Updated median OS is 23.8 mo for 150/2. Contribution of treatment beyond PD or post-treatment therapy is unknown. Follow-up continues; updated OS and safety data analysis will be performed in the final analysis after 30 mo follow-up or 75% events. Clinical trial information: NCT01072175.

| Treatment | Number of deaths n (%) | Med OS, mo (95% CI) | Hazard ratio (95% CI) p-value | 12-mo OS rate (%) | 18-mo OS rate (%) |
|---|---|---|---|---|---|
| **Part B** | | | | | |
| 150/2 (N=24) | 8 (33) | NR (12.9, NR) | NA | 73 | 67 |
| **Part C** | | | | | |
| D mono (N=54) | 31 (57) | 20.2 (14.5, 25.9) | NA | 70 | 56 |
| 150/1 (N=54) | 27 (50) | 18.7 (13.7, NR) | 0.96 (0.57, 1.60) 0.8683 | 69 | 51 |
| 150/2 (N=54) | 25 (46) | 23.8 (17.5, NR) | 0.73 (0.43, 1.24) 0.2436 | 80 | 63 |

Abbreviations: NR, not reached; NA, not applicable.

**9011^ Clinical Science Symposium, Sun, 8:00 AM-9:30 AM**

**COMBI-d: A randomized, double-blinded, Phase III study comparing the combination of dabrafenib and trametinib to dabrafenib and trametinib placebo as first-line therapy in patients (pts) with unresectable or metastatic $BRAF^{V600E/K}$ mutation-positive cutaneous melanoma** *Presenting Author: Georgina V. Long, Melanoma Institute Australia, Sydney, Australia*

**Background**: As monotherapies, the BRAF inhibitor dabrafenib (D) and the MEK inhibitor trametinib (T) demonstrated superior progression-free survival (PFS) v chemotherapy in pts with $BRAF^{V600}$ mutant, metastatic melanoma (MM). Resistance develops in most pts, and oncogenic toxicities (e.g., cutaneous squamous carcinoma (cuSCC)) are associated with BRAF inhibition. Simultaneous inhibition of BRAF and MEK mitigated these effects in the Phase I/II study of D+T v D (NCT01072175), with an improvement in overall response rate (ORR), PFS and reduced frequency of cuSCC. This Phase III study (NCT01584648) was conducted to confirm the superiority of D+T over D in pts with $BRAF^{V600E/K}$ mutant MM. **Methods:** Pts were randomized 1:1 to receive D (150 mg twice daily) + T (2 mg once daily) or D+ placebo (P) as first-line therapy. Eligible pts were ≥18 years and ECOG performance status ≤1, with histologically confirmed unresectable stage IIIC or IV, $BRAF^{V600E/K}$ mutant cutaneous melanoma. The primary endpoint was investigator-assessed PFS; secondary endpoints were overall survival (OS), ORR, duration of response, and safety. Cross over was prohibited. The study has 95% power and a one-sided $\alpha$=0.025 to detect a PFS hazard ratio (HR) of 0.59. **Results:** From May 2012 to Jan 2013, 423 pts were randomized (211 to D+T, 212 to D+P). Median follow up was 9 mo (0-16 mo). HR for investigator-assessed PFS was 0.75 (95% CI: 0.57, 0.99; p=0.035), in favor of D+T with a median PFS of 9.3 v 8.8 mo with D+P. The confirmed ORR was 67% (complete response [CR] 10%) for D+T and 51% (CR 9%) for D+P (p=0.0015). HR for interim OS was 0.63 (95% CI 0.42, 0.94; p=0.023), in favor of D+T (40 v 55 deaths). Rates of AEs were similar for both arms. More pts had AEs leading to dose modifications with D+T v D+P. Increased incidence (51% v 28%) and severity (grade 3, 6% v 2%) of pyrexia occurred with D+T v D+P. Fewer cutaneous hyperproliferative events occurred with D+T v D+P (cuSCC 2% v 9%; hyperkeratosis 3% v 32%). **Conclusions:** D+T demonstrated a significant improvement in PFS compared to D+P in pts with $BRAF^{V600E/K}$ mutant MM. Clinical trial information: NCT01072175.

**9012 Poster Highlights Session (Board #27), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Vismodegib in the treatment of patients with metastatic basal cell carcinoma (mBCC) and distant metastases: Survival in the pivotal phase II and phase I studies.** *Presenting Author: Karl D. Lewis, University of Colorado Cancer Center, Aurora, CO*

**Background:** mBCC is rare and poorly characterized. Recent data (McCusker, in press, *Eur J Cancer*) indicated that between 1981-2011, the median overall survival (OS) of patients (pts) with mBCC and distant metastases was 2.0 years (95% CI 1–2.9) from time of diagnosis, with a 1-year survival probability of 58.6% (95% CI 44.6–72.6). Vismodegib (VISMO) is a first in-class Hedgehog pathway inhibitor approved for adults with mBCC or locally advanced BCC that is inoperable. Here we report OS in a pooled aBCC population of pts with distant metastases from the pivotal phase II and phase I studies in the context of survival estimates from the literature. **Methods:** 45 mBCC pts with radiographically measurable distant metastases, present at any site, including soft tissue, other than or in addition to regional lymph nodes, were enrolled in the phase I (NCT00607724; Von Hoff, 2009; n=16) and pivotal phase II (NCT00833417; Sekulic, 2012; n=29) trials. Pts received VISMO 150/270/540 mg/d in the phase I and 150 mg/d in the pivotal phase II trials until disease progression/intolerable toxicity. Analysis of OS in mBCC pts with distant metastases was performed 26 Nov 2013 after primary analysis for the phase I (28 Feb 2009) and the pivotal phase II (26 Nov 2010) trials. OS probability and median OS were estimated with 95% CIs by the Kaplan-Meier method. **Results:** The clinical characteristics of these 45 pts treated with VISMO were similar to those in the McCusker review, including mean age at mBCC diagnosis (58 yrs vs 58.5 yrs), male predominance (72% vs 80%), and mean time from initial BCC diagnosis to detection of metastases (6.3 yrs vs 7.4 yrs). 22 of 45 pts (49%) with mBCC and distant metastases who were treated with VISMO were alive at the last assessment. VISMO therapy resulted in a median OS of 2.8 yrs (95% CI 2.0–not estimable) from first dose of VISMO (vs 2.0 yrs [95% CI 1.0–2.9] in the McCusker review), and 1- and 2-year survival estimates of 84.4 % (95% CI 73.9%–95.0%) and 68.0 (95% CI 54.2%–81.9%), respectively. **Conclusions:** Survival of these 45 pts with mBCC and distant metastases compares favorably to historical reports. VISMO may improve OS of mBCC pts with distant metastases. Clinical trial information: NCT00833417.

**9013 Poster Highlights Session (Board #28), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma: Final update (30-month) of the pivotal ERIVANCE BCC study.** *Presenting Author: Aleksandar Sekulic, Mayo Clinic, Scottsdale, AZ*

**Background:** BCC pathogenesis involves abnormal Hedgehog pathway (HP) signaling. In the ERIVANCE BCC trial, vismodegib (VISMO), the first FDA-approved HP inhibitor (HPI), showed objective response rates (ORRs) by independent review of 30% in metastatic (m) BCC and 43% in locally advanced (la) BCC, with median duration of response (DOR) of 7.6 mo for both. ORRs by investigator (INV) review were 45% (mBCC) and 60% (laBCC), with median DOR of 12.9 and 7.6 mo, respectively. Some patients (pts) continued VISMO treatment >3 yrs after start of therapy. We present safety and INV-assessed efficacy results 30 mo (30 May 2013) after primary analysis (26 Nov 2010). **Methods:** ERIVANCE BCC was a multicenter, international, nonrandomized study in pts (N=104) with radiographically measurable mBCC or laBCC (surgery inappropriate due to multiple recurrence, or substantial morbidity or deformity anticipated) receiving oral VISMO 150 mg daily until disease progression or intolerable toxicity. Key secondary endpoints included INV-ORR, progression-free survival (PFS), DOR, overall survival (OS), and safety. **Results:** At data cutoff, 9 pts (9%) continued to undergo protocol-specified assessments and 69 pts (66%) were in survival follow-up. ORR (INV) was 48.5% (mBCC) and 60.3% (laBCC), comparable with primary analysis. Median DOR (INV) improved from 12.9 and 7.6 mo for mBCC and laBCC (primary analysis) to 14.8 and 26.2 mo, respectively. Median (95% CI) PFS was 9.3 (7.4-16.6) and 12.9 (10.2-28.0) mo in mBCC and laBCC, respectively; median OS for mBCC was 33.4 (18.1-not estimable) mo and not reached in laBCC. Adverse events (AEs) remained consistent with the primary analysis; >30% of pts reported muscle spasm, alopecia, dysgeusia, weight decrease, fatigue, and nausea. 23 (22.1%) pts reported AEs leading to treatment discontinuation. 17 deaths (mBCC=10; laBCC=7) have been reported since the primary analysis and were not considered drug related. 16 deaths occurred in survival follow-up; 1 pt died due to general deterioration of health. **Conclusions:** The 30-month ERIVANCE BCC update confirmed the efficacy of the primary analyses and showed long-term consistent safety of VISMO in pts with aBCC. Clinical trial information: NCT00833417.

**9014 Poster Highlights Session (Board #29), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Adjuvant radiation therapy and chemotherapy in Merkel cell carcinoma: Survival analysis of 6,908 cases from the National Cancer Data Base.** *Presenting Author: Shailender Bhatia, University of Washington/Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance, Seattle, WA*

**Background:** Merkel cell carcinoma (MCC) is an aggressive skin cancer with high risk of recurrence after surgery. Adjuvant radiation therapy (RT) and/or chemotherapy are commonly used, but with limited data regarding their effectiveness. To assess the impact of adjuvant RT and chemotherapy on MCC survival, we performed a retrospective analysis of the National Cancer Data Base (NCDB) that has the largest known cohort of MCC patients (pts). NCDB also collects data on adjuvant chemotherapy and comorbidity status (Charlson/Deyo score) that were missing in a prior study of outcomes with adjuvant RT in 1,487 pts in the Surveillance, Epidemiology, and End Results (SEER) database. **Methods:** 6,908 MCC pts with stage, treatment and survival data available were included in this analysis. Multiple covariate analyses were conducted for overall survival outcomes with various treatment modalities while adjusting for age, sex, comorbidity score, and other therapies. **Results:** In pts with localized MCC (AJCC stage I N=3,369; stage II N=1,474), surgery plus RT was associated with significantly better survival than seen with surgery alone (Stage I HR 0.75 [95% CI 0.67–0.83], p<0.0001; Stage II HR 0.77 [95% CI 0.67–0.90], p=0.0006). In pts with nodal involvement (stage III N=2,065), adjuvant chemotherapy was not associated with improved or worsened survival versus no chemotherapy (HR 1.07 [95% CI 0.93–1.22], p=0.37). Even among a subgroup of stage III pts aged < 65 and with comorbidity score=0, adjuvant chemotherapy was not associated with improved survival. **Conclusions:** This retrospective study analyzed the largest MCC dataset to date for outcomes with adjuvant therapy. These results suggest improved survival with the use of adjuvant RT in stage I-II MCC pts. Adjuvant RT or chemotherapy were not associated with improved survival in stage III MCC pts. Despite the ability to assess comorbidity scores, treatment biases that could have accounted for some of the observed effects cannot be directly addressed, and prospective multicenter evaluations of adjuvant RT and chemotherapy remain warranted. Until then, multidisciplinary evaluation and individualized care is appropriate for all pts with MCC.

**9015 Poster Highlights Session (Board #30), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Sentinel node biopsy in the initial evaluation of 87 patients with Merkel cell carcinoma.** *Presenting Author: Eve Maubec, Assistance Publique–Hôpitaux de Paris, Hôpital Bichat, Paris, France*

**Background:** Merkel cell carcinoma (MCC) is a rare cutaneous neuroendocrine tumor. The objective was to determine the role of sentinel lymph node biopsy (SNB) in the management of patients with MCC. **Methods:** A SNB procedure was proposed to all patients, from 5 hospitals, referred for a MCC without palpable regional lymph node from 1999 to 2013. Features between positive (SNB+) and negative (SNB-) SNB patients (pts) were compared using a Fisher's exact test. **Results:** Eighty-seven pts with a F/M ratio=0.85, a median age =74 yrs (31-90 yrs; 63% aged at least 70 yrs), a stage T1 (N=54), T2 (N=30) or T3 (N=3), a location on extremities (56%), head and neck (32%) or trunk (12%) were included. Among pts, 8% were immunosuppressed. The frequency of SNB metastasis (20/83=24% of successful SNB) did not differ significantly in T1 and T2 stages (p= 0.4). 19/20 SNB+ pts had a radical lymph node dissection and additional positive lymph nodes were found in 6/19 (31%) pts. Adjuvant radiotherapy was delivered to the primary tumour site in 71/87 pts and to the involved lymph node basin in 18/20 SNB+ pts. During a median follow-up period of 25 mths (4-158 mths) (25 mths in SNB+ and 23 mths in SNB- pts) recurrence developed in 23% of all pts within a median period of 13 mths (3-115 mths). Fifteen per cent of pts died of MCC. Although higher in SNB+ pts (20% vs 9.5%) the frequency of specific death did not differ significantly in the 2 groups (p=0.19). SNB- pts who did not received radiotherapy to the primary tumour site had a worse course of the disease with more recurrences (42% vs 14%; p= 0.04) and a trend to a higher death rate (25% vs 6%; p= 0.08). **Conclusions:** SNB positivity is not associated with T stage and is high in T1 stage. All pts without palpable lymph node should be considered for SNB. Negative SNB might predict for better outcome.

**9016 Poster Highlights Session (Board #31), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Plasma vemurafenib concentrations in advanced *BRAFV600*$^{mut}$ melanoma patients: Impact on tumor response and tolerance.** *Presenting Author: Elisa Funck-Brentano, APHP, University of Versailles, Boulogne-Billancourt, France*

**Background:** Vemurafenib (V), a *BRAFV600*$^{mut}$ targeted therapy, improves survival in advanced melanoma pts, but tolerance is often poor and resistance frequently occurs. No predictive factor of intolerance or escape is well known. We searched for a relation between plasma V concentration (PVC) and V intolerance or melanoma resistance. **Methods:** After obtaining informed consent, blood was prospectively collected in 23 successive previously BRAF$^{inh}$ naive pts with AJCC stage IIIc (n=3) or IV (n=20) inoperable *BRAFV600*$^{mut}$melanoma receiving V monotherapy. Blood was harvested when tumor response was evaluated or when toxicity occurred. Tumor response to V was assessed every 2 months blinded to PVC results using RECIST 1.1 and adverse effects were graded using CTCAE 4.0. PVC was measured with liquid chromatography-tandem mass spectrometry (precision: 13%). Herein, we report on PVC at steady state (≥14d after V introduction or dose modification). As V could be continued in slowly progressing pts, samples collected after first melanoma progression were excluded from the response-concentration analysis. All samples were included in the tolerance-concentration analysis, where each adverse event occurrence was linked to the closest sample collected. Wilcoxon rank sum test was used. **Results:** V was first line systemic treatment for 17 pts. Initial V dose was 960 mgx2/d, reduced by 25% (n=6) or 50% (n=1) for intolerance. 12 pts experienced first progression during study after a mean 35 weeks on V. PVC showed high inter-individual variability (13 to 104 $\mu$g/mL, mean 56). Mean PVC was lower at time of first progression (37.8±19.3 $\mu$g/mL) compared to PVC found when tumor was considered stable or in complete or partial response (56.9±20.8 $\mu$g/mL, *p=0,003*). 105 samples were included in the tolerance-concentration analysis: PVC tended to be higher when toxicity occurred, without reaching statistical significance. All pts declared high compliance to treatment. **Conclusions:** PVC at steady state is highly variable, and low PVC was associated with tumour progression, suggesting a new (and simple) path to melanoma resistance to V. This preliminary finding should be confirmed in larger series.

**9017 Poster Highlights Session (Board #32), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**BRAF mutation in circulating DNA of melanoma patients at baseline and intertumor heterogeneity.** *Presenting Author: Marc G. Denis, Department of Biochemistry, Nantes University Hospital, Nantes, France*

**Background:** Determination of the BRAF mutation status is a requirement for treatment selection of metastatic melanoma patients. However, the inter and intra-tumor genetic heterogeneity for BRAF status has been described supporting the need for testing multiple sites for the same patient. Circulating DNA is considered a promising non-invasive tool for cancer monitoring. The objective of our work was to determine the potential of plasma DNA to detect BRAF mutations, particularly in patients presenting discordant BRAF status from different tumor sites. **Methods:** Plasma DNA was extracted using the iPrep PureLink Virus Kit on an iPrep purification system (Invitrogen). BRAF mutations were detected using the Therascreen BRAF RGQ kit (Qiagen). **Results:** Ninety-nine patients were included, and plasma was collected at baseline. Nine stage III melanoma patients presenting a mutant BRAF (6 V600E, 2 V600K and 1 V600D) were tested and for 4 of them we detected the corresponding mutation (including the V600D and both V600K) in circulating DNA (sensitivity 44.4 %). Similarly, 20 stage IV patients were tested (17 V600E, 2 V600K and 1 V600R). The corresponding mutation (including the V600R and both V600K) was detected in 15 of these patients (sensitivity 75.0%). Interestingly, 4 stage IV patients included in our series presented discordant BRAF mutation status on different sites (1 patient with a WT primary tumor (PT) and a V600E lymph node (LN) metastasis; 1 patient with a V600E PT and WT LN metastasis; 2 patients with a V600E PT, V600E LN and WT liver metastasis). We were able to detect the expected BRAF mutation in circulating DNA for all these patients. **Conclusions:** The sensitivity of our procedure, based on approved kits, suggests a high interest for use in clinical practice, even for non-V600E mutations. Plasma DNA might be less sensitive to heterogeneity between tumor samples, and therefore might represent an interesting alternative source of DNA to detect BRAF mutations in clinical setting.

**9018 Poster Highlights Session (Board #33), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Identification of multiple informative genomic mutations by deep sequencing of circulating cell-free tumor DNA in plasma of metastatic melanoma patients.** *Presenting Author: Dave S. B. Hoon, Department of Molecular Oncology, John Wayne Cancer Institute, Santa Monica, CA*

**Background:** We have been assesseing the prognostic utility of genomic changes in circulating cell-free DNA(cfDNA) in melanoma patients. The limitation has been assessing a few selected genomic targets and sensitivity. The approach of cfDNA analysis in melanoma patients offers detection of potential targeted tumor-related genes mutation(mt) without tumor biopsy. **Methods:** AJCC stage IV melanoma patients (n=18; different metastasis sites) plasma and paired metastatic tumor tissues resected after blood draw were assessed. The assay was performed on 2 ml filtered plasma. We employed Guardant360, a single-molecule digital sequencing assay that enables detection of rare genomic abnormalities with ultra high-specificity and sensitivity. Using bioinformatics and single molecule sensitivity, rare variants could be detected in cfDNA. **Results:** In an initial 8 patients, BRAF and TP53 in tumor genomic DNA were sequenced. We found ctDNA with somatic mt in 6/8 matched tumor and plasma specimens(mt allele frequency of 0.2-23.1%) with an overall concordance of 86% for the status of BRAF and TP53 mt in a single bleed. To note known BRAFmt at multiple exons were detectable. Subsequently, matched tumor and plasma from 10 patients were analyzed. We found ctDNA mt in 8/10 cases (mt allele frequency of 0.1-19.1%). Well known frequent melanoma-related mt were detected in patients cfDNA(BRAF, TP53). Other known tumor mt were also detected(CDKN2A, NRAS, PTEN, NOTCH1, EGFR, JAK2) that have not been reported. We established the overall concordance of cfDNA mt with metastatic melanomas across all 54 genes and 80kbps to be 49% whereby, individual single gene concordance were significantly much higher. **Conclusions:** This ongoing study demonstrates that using Guardant360, cfDNA mt can be detected that match with paired melanomas. The approach offers a more comprehensive approach of monitoring metastatic melanoma patients' blood for multiple mt during tumor progression. This unique approach will allow for much more comprehensive blood tumor genetic profiling to provide better treatment decision and monitoring for multiple drugable targeted genes without tissue biopsies.

**9019 Poster Highlights Session (Board #34), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Droplet digital PCR monitoring of BRAF and NRAS plasma DNA as biomarkers of treatment response in stage IV melanoma.** *Presenting Author: David Polsky, The Ronald O. Perelman Department of Dermatology, NYU Langone Medical Center, New York, NY*

**Background:** Management of melanoma suffers from a lack of robust biomarkers of disease activity. In this study, we tested the ability of droplet digital PCR (ddPCR) to quantitatively measure levels of circulating BRAF and NRAS mutant DNA in the plasma of metastatic melanoma patients undergoing treatment with BRAF-targeted therapy or immunotherapy. **Methods:** We analyzed plasma samples from 45 patients with stage IV melanoma prospectively enrolled in the NYU Melanoma Biorepository program. All patients were commercially genotyped for BRAF V600E. SNaPshot assays were used to identify NRAS Q61 mutations in BRAF-WT tumors. Each patient had at least 3 serially collected plasma samples including one drawn prior to treatment, one or more after treatment began and one upon signs of disease progression. ddPCR was used to measure mutant copies/ml of BRAF V600E and NRAS Q61K/L/R DNA in plasma samples. **Results:** Among 45 patients, 28 patients had BRAF and 8 patients had NRAS tumor mutations. We extracted DNA from 151 plasma samples. Our preliminary results include analysis of 50 plasma samples from 10 BRAF-mutant and 5 NRAS-mutant patients. All BRAF V600E patients received BRAF inhibitor therapy and had partial responses followed by disease progression. Levels of circulating V600E DNA decreased with clinical response and/or increased with disease progression in 8/10 patients. In 3 patients with progressing disease, plasma samples drawn in-between imaging visits showed increasing BRAF mutant copies/ml up to 2 months prior to clinical scans. Among NRAS mutant patients, all were treated with Ipilimumab: 3 patients progressed, 1 had a near complete response, and 1 progressed and was then treated with Nivolumab. Levels of circulating Q61 DNA rose with disease progression and/or fell with clinical response in 5/5 immunotherapy treated patients. **Conclusions:** Our results indicate that ddPCR is able to measure clinically meaningful changes in the levels of BRAF and NRAS mutant copies/ml in the plasma of stage IV melanoma patients. This analytical platform has the potential for monitoring disease progression and patient response to both targeted and immune-based therapies, and may be a useful adjunct to imaging studies.

**9020 Poster Highlights Session (Board #35), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Ultrasensitive detection and identification of BRAF V600 mutations in fresh frozen, FFPE, and plasma samples of melanoma patients by enhanced-ice-cold-PCR.** *Presenting Author: Alexandre How-kit, Laboratory for Functional Genomics, Fondation Jean Dausset - CEPH, Paris, F-75010, France, Paris, RI, France*

**Background:** Two BRAF inhibitors have been approved for patients with BRAF V600 activating mutation. However, to date the different tools developed for the detection of BRAF V600 mutations lack sensitivity and/or specificity or do not allow sequencing-based identification of the mutation. Enhanced-ice-COLD PCR is a very sensitive assay, which enables a strong enrichment of the mutation during the PCR where mutant and WT alleles undergo exponential and linear amplification, respectively. **Methods:** Methods: Two melanoma-derived cancer cell lines harboring different heterozygous BRAF codon 600 mutations were used in this study for assay optimization. Molecular analyses were performed on 18 fresh frozen, 17 FFPE melanoma and 17 plasma samples from patients suffering from advanced melanoma were used. E-ice-COLD-PCR was performed using a 96-well real-time thermocycler followed by pyrosequencing and automatic mutation identification and quantification. **Results:** This assay has a large dynamic range as 25 pg to 25 ng can be used as DNA input without any reduction in mutation enrichment efficiency and is ultra-sensitive as it can detect up to 0.01% of mutated alleles in a wild-type background. The assay has been validated on fresh frozen, FFPE and plasma samples of melanoma patients and has allowed the detection and identification of BRAF mutations present in the samples which appear as wild-type using standard pyrosequencing, endpoint genotyping or Sanger sequencing. **Conclusions:** This BRAF V600 E-ice-COLD PCR assay is currently the most powerful molecular diagnostic tool for ultra-sensitive detection and identification of BRAF codon 600 mutations.

**9021 Poster Highlights Session (Board #36), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Development and validation of a gene expression signature to distinguish malignant melanoma from benign nevi.** *Presenting Author: Colleen Rock, Myriad Genetic Laboratories, Inc., Salt Lake City, UT*

**Background:** Histopathologic distinction between benign and malignant melanocytic tumors can be unreliable and may lead to misdiagnosis. Measurement of biomarker gene expression has been proposed as an adjunctive diagnostic method in the evaluation of ambiguous melanocytic lesions with uncertain malignant potential. This study aimed to develop and validate a gene signature capable of accurately differentiating malignant melanoma and benign nevi. **Methods:** Seventy-nine candidate genes were identified based on expression changes previously observed in melanoma or other cancer types. RNA expression in five 5-$\mu$m recut sections from FFPE skin biopsy specimens was measured by qRT-PCR. The panel was refined to 40 genes based on the ability of each gene to differentiate benign from malignant lesions (AUC >70%). Expression of this refined panel was measured in 464 melanocytic lesions and forward selection in a logistic regression model was used to finalize the signature. By applying a weighting algorithm and threshold value to the expression data, the signature was translated into a numeric score capable of classifying melanocytic lesions as benign or malignant. Performance of the assay was clinically validated in a second cohort of 437 melanocytic lesions representing a spectrum of histopathologic types. **Results:** Using the 464 case cohort, a final signature of 23 genes was identified, consisting of 13 genes involved in immune signaling and cell differentiation and 9 housekeeping genes. In the second cohort of 437 lesions, the signature was validated to differentiate benign nevi from malignant melanoma with a sensitivity of 90% and a specificity of 91%. **Conclusions:** The predominance of genes that regulate melanocyte differentiation and immune response in the final signature indicates that these pathways represent critical differences between benign and malignant melanocytic lesions. The performance, objectivity, reliability, and minimal tissue requirements of this diagnostic test make it well-suited for clinical use as an adjunct to histopathology. Integration of this assay into current practice has the potential to enhance patient care through more definitive diagnoses of melanocytic lesions.

**9022 Poster Highlights Session (Board #37), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Gene expression profile test (GEP) prediction of metastasis-free (MFS) and overall survival (OS) in a cohort of cutaneous melanoma (CM) patients undergoing sentinel lymph node biopsy (SLNB).** *Presenting Author: David H. Lawson, Emory University School of Medicine, Atlanta, GA*

**Background:** We recently validated a GEP test that provides accurate prediction of metastatic risk for CM cases. The GEP of 31 genes provides a binary outcome of Class 1 (low risk of metastasis) or Class 2 (high risk). This study evaluated the prognostic. **Methods:** Of 406 patients with successful GEP results and clinical data, 217 had a documented SLNB. All samples and clinical data were collected under an IRB approved, multicenter protocol. Quantitative PCR analysis was performed to assess expression of the gene signature, and Radial Basis Machine predictive modeling was used to determine risk prediction (Class 1 vs. Class 2). **Results:** SLNB+ status (n=58) was associated with greater median Breslow thickness, increased mitotic rate, and ulceration. Metastasis was reported for 37 of 58 (64%) SLN+ cases and 70 of 159 (44%) SLN- cases. While positive predictive values for Class 2 and SLN+ status were comparable (69% vs. 64%, resp.), negative predictive values of 75% and 49% were observed for low risk Class 1 and SLN- cases, respectively. Kaplan-Meier (K-M) analysis revealed 5-year MFS of 34% and 37%, respectively, for GEP Class 2 and SLN+ cases, and OS of 54% and 62% for the two groups, respectively. K-M analysis of MFS and OS for GEP and SLN in combination resulted in outcomes shown in Table 1. Cox multivariate analysis showed that GEP Class 2 and positive SLN status were significant predictors of MFS (HR=4.9 and 1.7, resp., $p<0.01$), but that GEP, in this group of patients, was the only significant predictor of OS (HR=5.1, $p<0.0001$). **Conclusions:** In this study cohort, GEP provided an objective, non-invasive tool that accurately predicted MFS and OS in SLN eligible patients. Importantly, in the discordant Class 2/SLN- group, predicted outcomes more closely reflected Class 2 status. Incorporation of GEP class in treatment planning may enable improved patient management. MFS and OS association with class and SLN status.

| | N | 5-yr MFS | 5-yr OS |
|---|---|---|---|
| **Class1/SLNB-** | 67 | 83% | 91% |
| **Class1/SLNB+** | 9 | 53% | 78% |
| **Class2/SLNB-** | 92 | 35% | 54% |
| **Class2/SLNB+** | 49 | 33% | 57% |

**9023 Poster Highlights Session (Board #38), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Analysis of *TERT* promoter mutations in pediatric melanoma.** *Presenting Author: Armita Bahrami, St. Jude Children's Research Hospital, Memphis, TN*

**Background:** Melanoma is rare in children and adolescents and is divided into a conventional adult-type (CM), a small-cell type, and Spitzoid melanoma/ atypical Spitz tumor (AST). ASTs are a group of melanocytic neoplasms with characteristic morphologic features that often affect patients in the first 2 decades, commonly spread to regional lymph nodes, but rarely metastasize to distant sites. Histological criteria are unreliable at predicting the rare subset of AST that disseminates and to date, genomic changes associated with an aggressive clinical behavior have not been identified. Whole genome sequencing has revealed that most adult melanomas have *TERT* promoter activating mutations that lead to increased telomerase activity. We investigated the frequency of *TERT* promoter mutations in pediatric CM and AST and its correlation with clinical outcome. **Methods:** Genomic DNA was extracted from 12 microns of FFPE sections from 15 CM (all in adolescents) and from 26 AST in 25 patients (18 children; 7 adolescents). A portion of the *TERT* promoter (HG19 coordinates, chr5: 1295151-1295347) was amplified by PCR using conventional methods. The resulting amplicon was Sanger sequenced and analyzed for the presence of heterozygous or homozygous alterations within the amplified region. **Results:** 12 of 15 CM had one of the two most frequently described UV associated *TERT* single nucleotide variants (SNVs) (6 SNVs at position 1295228; 6 SNVs at position 1295250), and 2 were marked as indeterminate. An additional CM had a dinucleotide CC->TT variant at positions 1295242/243. At last follow-up (mean, 30 months), 9 patients had died of disease and 3 were alive with disease. Only 2 of 26 AST samples carried a *TERT* promoter mutation (SNV 1295228) and both patients developed widespread metastasis and died of disease. None of the remaining patients with AST developed extranodal disease spread and all were alive without disease at a mean of 17 months. **Conclusions:** *TERT* promoter UV-signature mutations correlate with aggressive clinical behavior in pediatric patients with melanocytic neoplasms. The findings support a pathogenic role for UV light in pediatric melanoma progression.

**9024 Poster Highlights Session (Board #40), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Clustered genomic variants specific to patients who develop immune-related colitis after ipilimumab for prediction of toxicity.** *Presenting Author: Ahmad A. Tarhini, University of Pittsburgh Medical Center, Pittsburgh, PA*

**Background:** Ipilimumab (Ipi) is approved for metastatic melanoma based on significant survival benefits shown in phase III trials. Ipi can result in immune-mediated effects on various organ systems, leading to adverse events (AE) including diarrhea/colitis reported in 30-40% patients (pts) that can be serious and life-threatening. The ability to predict the risk of this AE may lead to new monitoring and improved management. **Methods:** Targeted, deep sequencing of DNA from the blood of 34 pts who underwent neoadjuvant Ipi for regionally advanced melanoma (*Tarhini et al, PLOS One, 2014*) was performed to detect the 21 pts who experienced diarrhea/ colitis. Sequencing was focused on the coding region of 10 genes and genomic domains surrounding 9 SNPs previously associated with IBS, Crohn's Disease and ulcerative colitis in GWAS studies. Selected amplicon libraries derived from locations on 5 chromosomes were sequenced on Ion Torrent PGM at high base density (318 chip: >1000X) and BAM files interrogated using GATK algorithm (UGT v.2.3, Broad Institute, Boston, MA) to identify SNPs, single base substitutions and INDELs (<5 bases). Variants were selected for specificity to pts with grade 1-3 colitis vs pts without. All calls were verified by manual curation of BAM files using Integrated Genomics Viewer (Broad Institute). **Results:** We identified 132 variants specific to pts with colitis (X =6.1; range=1-20). The most parsimonious variant signature (11 variants, 3 chromosomes) comprised 3 INDELs shared by 13 pts including an intronic 5 base DEL in CDKAL1 gene and 2 INS in KIF21B. While 11 pts were classified by 6 unique INDELs and 2 rare SNPs (rs55770822, rs140589352). Alternatively, a 34Kb chromosome 1 "hot spot" in KIF21B gene captured variants specific to 18 pts including multiple frameshift and other coding mutations predicted to alter protein translation. **Conclusions:** These data suggestthat unique INDELs and SNPs specific to pts with colitis after Ipi may provide a predictive biomarker signature. The predominance of these variants within the KIF21B gene previously implicated in inflammatory bowel disease suggests an important role in Ipi induced colitis. (Supported by NIH award P50CA121973). Clinical trial information: NCT01608594.

**9025^ Poster Highlights Session (Board #41), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Systemic antitumor effect and clinical response in a phase 2 trial of intratumoral electroporation of plasmid interleukin-12 in patients with advanced melanoma.** *Presenting Author: Adil Daud, University of California, San Francisco, San Francisco, CA*

**Background:** Interleukin-12 (IL-12) promotes anti-tumor activity through multiple mechanisms, including augmentation of adaptive and innate immune responses. Intratumoral (IT) delivery of IL-12 via electroporation (EP) avoids systemic toxicity while promoting systemic antitumor immunity. This phase 2 study explores the systemic efficacy, clinical response and safety of IT plasmid IL-12 injection (pIL-12) followed by EP in patients (pts) with advanced melanoma. **Methods:** This single-arm, open-label phase 2 study plans to enroll 30 pts with in-transit or M1a melanoma. One treatment cycle consists of IT pIL-12-EP on days 1, 5, 8 in up to four lesions per cycle. A maximum of four cycles at 12-week intervals are allowed. ORR was assessed by a modification of RECIST for cutaneous lesions with restaging performed every 12 weeks. The primary endpoint is best ORR within 24 weeks of first treatment. Pre- and post-treatment tumor biopsies were obtained in all patients. Ongoing analyses to assess safety and emerging efficacy data are being utilized to inform future studies. **Results:** 29 pts have been enrolled and have received at least one treatment cycle. The ORR is 33% (9/27), with 11% CR (3/27). Regression of non-injected lesions was seen in 62% (13/21) of pts with evaluable lesions. Transient pain (56.5%) and inflammation (17.4%) at the treatment site were the most common grade 1/2 drug-related adverse events (AEs), with no grade 3/4 drug-related AEs. Exploratory analyses indicate a doubling of intratumoral NK cells from pre-treatment through day 11 and at day 39, and increased frequency in activated circulating NK cells. **Conclusions:** Local treatment with pIL-12-EP is well tolerated without severe systemic side effects. Regression of treated and non-treated tumors suggests successful induction of systemic anti-tumor response. Local and systemic increases in NK cells are consistent with the expected pharmacodynamic effect of IL-12. Based on these data, an expansion protocol to evaluate increased treatment frequency is planned for melanoma patients. Clinical trial information: NCT01502293.

**9026 Poster Highlights Session (Board #42), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Patterns of durable response with intralesional talimogene laherparepvec (T-VEC): Results from a phase III trial in patients with stage IIIb-IV melanoma.** *Presenting Author: Merrick I. Ross, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** T-VEC is an intralesional oncolytic immunotherapy comprising a modified HSV-type 1. In the randomized OPTiM phase 3 trial, T-VEC significantly improved DR rate (DRR, continuous partial or complete response for ≥6 mo) by 16% vs 2% and overall RR by 26% vs 6% vs subcutaneous (SC) GM-CSF in patients (pts) with advanced melanoma. We hypothesized that some pts progressed on treatment (tx) prior to DR and sought to determine how such events impacted the durability of response. Here we describe response patterns in T-VEC-treated pts with a DR. **Methods:** 436 pts with Stage IIIB-IV melanoma were randomized 2:1 to receive intralesional T-VEC or SC GM-CSF until clinically significant PD, intolerability, or lack of injectable lesions. Tx was to continue for at least 6 mo during which tx discontinuation for PD was not required. PD prior to response (PPR) was defined as the appearance of a new lesion or >25% increase in baseline tumor burden. Injection of new lesions was allowed. Responders were grouped as 1) PPR or 2) no PPR. PPR was grouped by a) existing lesions (± new lesions) or b) new lesions only. Pts without PPR were grouped by DR onset at ≤6 mo or >6 mo. **Results:** Of 48 T-VEC pts with a DR, 23 (48%) had PPR: 9 (39%) pts had PD in existing lesions (± new lesions) and 14 (61%) had new lesions only. For 25 pts with no PPR, 21 (84%) had a DR beginning within the first 6 mo. 40 (83%) of the DRs remain in remission with a median follow up of over 18.4 mo. **Conclusions:** Similar to other immunotherapies, PPR was common in T-VEC-treated pts. Most PPRs included the development of new lesions, thus T-VEC tx should continue through PD. The quality of DR does not seem to be negatively affected by PPR or the timing of achieving DR. These data reinforce the evolving new paradigm of response criteria when treating pts with melanoma with immunotherapeutic agents. Clinical trial information: NCT00769704.

**DR by PPR Status.**

| | Without PPR (n=25) | With PPR (n=23) |
|---|---|---|
| **Median (Min, Max) time to DR (mo)[a]** | 3.1 (1.2, 9.5) | 5.8 (1.3, 10.6) |
| **Median (Min, Max) duration of DR (mo)** | NE (6.2+, NE) | NE (6.3, NE) |
| **DR maintained at end of follow-up, n (%)[b]** | 22 (88%) | 18 (78%) |

[a]P=0.004, Wilcoxon rank sum test; [b]P=0.27, log rank test; NE, Not evaluable, median not reached; +censored.

**9027 Poster Highlights Session (Board #43), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Efficacy of intralesional Rose Bengal in patients receiving injection of all existing melanoma in phase II study PV-10-MM-02.** *Presenting Author: Sanjiv S. Agarwala, St. Luke's Hospital and Health Network, Easton, PA*

**Background:** The safety and efficacy of intralesional (IL) treatment of refractory cutaneous melanoma with rose bengal disodium (PV-10) was evaluated in an 80 patient international, multicenter, single arm phase II trial (NCT00521053). Overall, PV-10 was well tolerated and 41 of 80 ITT patients (pts) met the primary endpoint of objective response (CR+PR) in their injected target lesions (51% ORR CI 40-63%, 26% CR). **Methods:** Refractory pts (median of 6 previous interventions, 6.3 cm median sum lesion diameter in biopsy confirmed melanoma) received PV-10 into up to 20 cutaneous and subcutaneous lesions up to 4 times over a 16-week period and were followed for 52 weeks. Best overall response rate (BORR) was assessed by RECIST in up to 10 injected target lesions. Secondary endpoints included assessment of duration of response, BORR of untreated bystander lesions, overall survival and adverse events.Confidence intervals for response rates were based on the exact cumulative probabilities of the binomial distribution (95% confidence intervals). **Results:** In the subgroup of 28 pts who received PV-10 into all existing melanoma lesions (i.e., no uninjected lesions), ORR by-patient was 71% (CI 51-87%) with 50% CR (CI 31-69%). In these pts with all disease injected plus 26 pts with uninjected disease limited to bystanders (i.e. 54 pts with all disease monitored), CR was achieved in 232 of the 363 injected lesions (64% CR): 121 lesions required a single injection for CR, 84 required 2 injections, 22 required 3 injections and 5 required 4 injections. Additionally, 10 of 28 uninjected bystander lesions achieved CR. **Conclusions:** Recurrent locoregional melanoma can be a source of persistent morbidity, including disfigurement frequently accompanied with pain, ulceration, bleeding and infection. The high rate of symptom control in refractory patients, manifest in CR of injected lesions after minimal intervention, is the basis for a breakthrough therapy application based on the 28 patient "all treated" subgroup. Although the primary ablative effect is responsible for CR in injected tumors, durability of response and bystander response implicate an immunologic mechanism of action secondary to ablation. Clinical trial information: NCT00521053.

**9028 Poster Highlights Session (Board #44), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Assessment of immune and clinical efficacy after intralesional PV-10 in injected and uninjected metastatic melanoma lesions.** *Presenting Author: Amod Sarnaik, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

**Background:** Intralesional (IL) therapy is under investigation to treat dermal and subcutaneous metastatic cancer. In our murine model, IL injection of PV-10 (10% Rose Bengal) induced regression of injected and uninjected "bystander" melanomas. We observed a consistent increase in anti-tumor T cell responses following IL PV-10 in the mouse model, supporting an immune-based mechanism by which PV-10 mediates regression of uninjected "bystander" tumors. **Methods:** We translated these findings into a pilot clinical trial that enrolled 8 patients with dermal and/or subcutaneous metastatic melanoma. Two study lesions in each patient were sampled by biopsy pre-treatment; one of the two lesions was injected with IL PV-10, then both residual sites were completely excised. We compared tumors before and after treatment with H&E staining to determine pathologic complete response (pCR), and we confirmed results with MelanA immunohistochemistry. Peripheral blood mononuclear cells (PBMC) before and after IL PV-10 were phenotyped for activation markers by flow cytometry. **Results:** Treatment with IL PV-10 led to pCR in the post-treatment biopsies of both PV10-injected and uninjected study lesions in 4 of the 8 patients, and all 8 exhibited at least partial regression of the injected lesion. IL PV-10 was associated with an increase in circulating cytotoxic $CD3^+/CD8^+$ T cells (paired t test, p=0.008). Pre and post PV-10 treated PBMC from one patient were re-stimulated with autologous tumor in vitro. Compared to pre-treatment, PV-10 treatment produced an increase in tumor-specific interferon-gamma release by ELISA. Six of 8 patients had metastatic disease refractory to previous ipilimumab, anti-PD-1 and/or vemurafenib therapy. Four of these 6 patients exhibited pCR to PV10 in both the injected and uninjected lesions. **Conclusions:** IL PV-10 treatment can lead to systemic anti-melanoma immunity and pCR in injected and uninjected lesions including treatment-refractory tumors. Further studies are ongoing to determine the mechanism by which PV-10 increases tumor-specific T cell responses as well as to establish the interaction of intralesional PV-10 with combination checkpoint protein inhibition. Clinical trial information: NCT01760499.

**9029^ Poster Highlights Session (Board #45), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Primary analysis of a phase 1b multicenter trial to evaluate safety and efficacy of talimogene laherparepvec (T-VEC) and ipilimumab (ipi) in previously untreated, unresected stage IIIB-IV melanoma.** *Presenting Author: Igor Puzanov, Vanderbilt-Ingram Cancer Center, Vanderbilt University, School of Medicine, Nashville, TN*

**Background:** T-VEC, an HSV-1 derived oncolytic immunotherapy designed to induce systemic antitumor immunity, showed a ≥ 6 mos higher durable response rate vs GM-CSF in a phase 3 melanoma trial (Andtbacka et al. ASCO 2013). This phase 1b/2 study will determine the safety and efficacy of T-VEC as a priming regimen when added to ipi. **Methods:** Phase 1b studied the safety of T-VEC+ipi. Objective response rate (ORR) was also evaluated with tumor assessments q12w. Blood was collected pre- and post-treatment (tx) for correlative studies. Key criteria: unresected Stage IIIB-IV melanoma, no prior systemic tx, measurable disease, and ≥1 injectable cutaneous, subcutaneous or nodal lesion. T-VEC was given intralesionally at ≤ 4 mL of $10^6$ PFU/mL at wk 1, then $10^8$ PFU/mL at wk 4 and then q2w. Ipi 3 mg/kg q3w was given as 4 infusions starting wk 6. Tx continued until DLT, intolerance, all injectable tumors disappeared, or disease progression (PD) per Immune Related Response Criteria. DLT was any grade (gr) ≥ 4 adverse event (AE) or gr ≥ 3 immune-related AE within the first 6 wks of ipi tx. **Results:** Of 19 patients (pts) enrolled: 42% men, 42% ≥ 65 yrs, 58% Stage IV M1b/c; 18 pts received T-VEC+ipi. No DLTs were reported. Gr 3/4 AEs occurred in 32%. 2 pts had possible immune-related gr 3/4 AEs: 1 pt had gr 3 hypophysitis (attributed to ipi) and gr 3 adrenal insufficiency and gr 3 diarrhea (both attributed to combination), and 1 pt had gr 4 amylase+lipase attributed to ipi. PD (CNS metastases) led to one gr 5 AE. By 15 Oct 13 (data cutoff), median tx duration of T-VEC was 13.3 wks. Of 17 pts with investigator assessed response, ORR was 41% (24% CR, 18% PR); 35% had SD. Median time to response was 2.9 mos. By flow cytometry, activated CD8 T cells significantly increased from baseline 1.8x after T-VEC alone and 2.9x during T-VEC+ipi tx. **Conclusions:** T-VEC+ipi appears to be tolerable with no DLTs. In consideration with published reports, these data, although preliminary, suggest higher CR and OR rates than either agent alone and earlier responses after ipi initiation during T-VEC+ipi than with ipi alone. Additional immunophenotyping and phase 2 (ipi vs T-VEC+ipi) are ongoing. Clinical trial information: NCT01740297.

**9030 Poster Highlights Session (Board #46), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Phase I dose-escalation study of the protein kinase C (PKC) inhibitor AEB071 in patients with metastatic uveal melanoma.** *Presenting Author: Sophie Piperno-Neumann, Institut Curie, Paris, France*

**Background:** Uveal melanoma is characterized by frequent mutations in *GNAQ* or *GNA11* that encode for G-protein $\alpha$-subunits (G$\alpha$) which mediate signaling from G-protein coupled receptors to downstream signaling pathways, including PKC. AEB071 (sotrastaurin) is a potent, selective oral inhibitor of the classical ($\alpha$, $\beta$), and novel ($\delta$, $\varepsilon$, $\eta$, $\theta$) isoforms of PKC. Preclinical data shows selective sensitivity of G$\alpha$ mutant uveal melanoma cell lines to AEB071. **Methods:** An open-label, multicenter, single-arm, Phase I study was performed in pts (WHO performance status [PS] $\leq$1) with metastatic uveal melanoma. Dose escalation and estimation of the maximum tolerated dose (MTD) was guided by an adaptive Bayesian logistic regression model with overdose control. **Results:** 118 pts received AEB071 at total daily doses of 450−1400 mg administered in divided doses either BID or TID. Genomic profiling analysis has been completed in 52 pts, 96% of which were found to have activating mutations in either *GNAQ* or *GNA11*. Dose-limiting toxicities (DLTs) were observed in 12 pts (11%) at doses $\geq$800 mg/day total (nausea [7%], vomiting [2%], and fatigue [2%]). The MTD was 800 mg/day and 1400 mg/day on TID and BID dosing schedules, respectively. The most common AEB071-related adverse events (AEs) (all grades, all cohorts, >25%) were nausea (68%), dysgeusia (58%), constipation (48%), vomiting (42%), diarrhea (36%), chromaturia (35%), and asthenia (26%). AEB071 exposure increased with increasing dose and was approximately 1–2x higher at steady state during BID dosing, with a median Tmax of 1–4 hr. Decreases in the PKC substrate phosphorylated myristoylated alanine-rich C kinase substrate (pMARCKS) of approximately 40%–90% were seen by Cycle 1 Day 15 for both dosing regimens. pMARCKS suppression did not correlate with clinical response or time on study. One pt achieved a PR and 55/118 (47%) pts achieved SD and progression-free survival (PFS) ranging from <1–57 weeks and with a median PFS of 15.4 weeks (95% CI 8.3–15.7). **Conclusions:** Preliminary data suggest clinical activity of AEB071 and manageable toxicity at multiple dose levels, with evidence of PKC inhibition in patients with uveal melanoma. Clinical trial information: NCT01430416.

**9031 Poster Highlights Session (Board #47), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Open-label, multicenter, single-arm phase II study (DeCOG-Trial) to further evaluate the efficacy and safety of ipilimumab in patients with cutaneous melanoma and rare subgroups.** *Presenting Author: Lisa Zimmer, Department of Dermatology, University Hospital, University Duisburg-Essen, Essen, Germany*

**Background:** Ipilimumab is a recently approved immunotherapy that has shown an overall survival benefit in previously treated and treatment-naïve patients with metastatic melanoma in two phase III trials. However, results of registrational trials might not address all questions regarding safety and efficacy of ipilimumab in advanced melanoma patients seen in daily routine. We performed a multicenter, phase II clinical trial of ipilimumab in patients with different subtypes of metastatic melanoma. **Methods:** Pretreated patients with unresectable stage III or stage IV with cutaneous, mucosal, ocular or unknown primary melanoma (MUP) were included into this study (CA184-137; supported by BMS). Treatment-naïve patients with metastatic ocular melanoma were eligible, too. Four cycles ipilimumab should be administered at a dose of 3 mg/kg 3 weeks apart. Tumor assessments according to RECIST 1.1 version were conducted at baseline, weeks 12, 24, 36 and 48. Adverse events (AEs), including immune-related AEs were graded according to National Cancer Institute Common Toxicity Criteria v.4.0. Primary endpoint was the overall survival (OS) rate at 12 months. **Results:** Between May 2011 to December 2013, 156 patients were enrolled in 25 German centers and received at least one dose of ipilimumab, including 83 cutaneous, 7 mucosal, 53 ocular melanomas and 13 MUP. After a median follow-up of 7 months (range 0.1-26.4), 12-month OS rates were 37% for cutaneous, 14% for mucosal, and 22% for ocular melanomas and 27% for MUP. The median OS from the first dose of ipilimumab was 6.9 months (95% CI 5.7-8.1). The overall response rates among 104 evaluable patients were 16% for cutaneous, 17% for mucosal, 9% for ocular melanomas and 11% for MUP. There were one patient with complete response (1%), 13 patients with partial response (13%), and 23 patients with stable disease (22%). Treatment-related AEs were observed in 106 patients (68%), including 39 grade 3-4 events (25%). There was a drug-related death due to pancytopenia. **Conclusions:** Ipilimumab is a treatment option for patients with cutaneous, ocular, mucosal and unknown primary melanoma with manageable toxicity. Clinical trial information: NCT01355120.

**9032 Poster Highlights Session (Board #48), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Phase II multicentric uncontrolled national trial assessing the efficacy of nilotinib in the treatment of advanced melanomas with c-KIT mutation or amplification.** *Presenting Author: Celeste Lebbe, Hôpital Saint-Louis, Paris, France*

**Background:** Three phase II trials have shown an overall response rate (ORR) around 20% with imatinib in melanoma carrying KIT mutations. The aim of this study was to study the interest of nilotinib a Kit inhibitor with pharmacological advantages compared to imatinib. **Methods:** this multicenter uncontrolled open Hern's single-stage Phase II study enrolled patients with advanced melanoma and KIT amplifications and/or mutations and no BRAF and NRAS mutation, nor previous Kit targeted therapy or active brain metastasis.Patients received Nilotinib 400 mg bid. ORR was the primary endpoint. Secondary endpoints included disease control, metabolic response rate and biomarkers associated to response . Based on type I and II error rates fixed at 0.05 and 0.10, respectively, a sample size of 25 patients was required to test the level of response, p$\leq$ 7.5% against > 30%, with at least 5 successes tindicating that the treatment was effective. Analysis was based on intent to treat. **Results:** 25 patients were enrolled from 2010-07-27 to 2012-08-27: 13 females (52%); median age 70 years(range, 43-87); 23 (92%) tumors with KIT mutations, 5 (20%) KIT amplifications, and 3 (12%) both. One patient (4%) had primary unresectable melanoma, 3(12%) unresectable stage III melanoma, 21 (84%) stage IV melanoma .13 (52%) patients were chemotherapy naive, 12 (48%) had previously received dacarbazine or fotemustine, 1 immunotherapy . Median follow-up was 3 months ([IQR: 2-7], range 0.3-12).One patient reached CR and 4 partial responses, concluding to treatment effectiveness with an ORR of 20% (95%CI: 6.8-40.7) all in patients with KIT mutation . Six patients died and 1-year overall survival was 68.3% (95%CI: 46.5-1.00).The 25 patients experienced a total of 236 adverse events , 2/3 imputed to the drug mostly of grade 1 (n=146 in 21 patients) and grade 2 (47 in 13 pts), and less frequently of grade 3 (39 in 18 pts) or grade 4 (3 in 3 pts: 2 dyspnea, 1 renal failure) and 1 death. Five patients had drug withdrawal because of toxicity. **Conclusions:** According to our hypothesis, nilotinib is an effective drug in KIT mutated melanoma in the absence of BRAF and NRAS mutations and should be added to our armamentarium. Clinical trial information: NCT01168050.

**9033 Poster Highlights Session (Board #49), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Phase II study evaluating ipilimumab as a single agent in the first-line treatment of adult patients (Pts) with metastatic uveal melanoma (MUM): The GEM-1 trial.** *Presenting Author: Jose Maria Piulats Rodriguez, Institut Català d'Oncologia de l'Hospitalet, Barcelona, Spain*

**Background:** Uveal melanoma is the most common primary intraocular malignant tumor in adults. Overall survival (OS) at 5 years is 62% due to high incidence of liver metastasis that are fatal within 4 -9 months from diagnosis. No standard treatment exists for MUM. Ipilimumab has demonstrated to improve both overall and long-term survival in patients with advanced cutaneous melanoma (Hodi FS, *et al.*, NEJM 2010; Robert C, *et al.*, NEJM 2011). However, MUM patients were excluded in these trials. **Methods:** GEM-1 (EudraCT 2010-024415-14) is an open label, single arm phase 2 trial that evaluates first line ipilimumab in adult pts with MUM.The study was conducted in 5 centers in Spain, belonging to the Spanish Melanoma Group (GEM). Eligible pts had progressive metastatic disease, ECOG-PS 0 or 1, and no prior systemic treatment for MUM. Treatment consisted of ipilimumab 10 mg/kg iv q3 weeks (wk) for 4 doses (induction) followed by q12 wk (maintenance) until progression, intolerance or withdrawal. Primary end point was OS and secondary PFS, OR and safety using immune response criteria. **Results:** 32 pts were enrolled from July 2011 to May 2013. One patient was ineligible due to absence of metastatic disease at baseline. An interim analysis showed preliminary data from the 31 patients. 18 pts were men, mean age (SD) 60 (10). 64.5% (20) and 35.5% (11) of pts were ECOG-PS 0 and 1 respectively and progressive liver metastasis at baseline were present in 25 pts (80.7%) being frequently multiple and affecting both lobes. Ten pts experienced G3 (abdominal pain, hypophysitis (3), emesis, diarrhoea, asthenia, proctalgia, bone pain and urinary tract infection) and 5 pts had G4 toxicities (hepatotoxicity (2), multi-organ failure, altered state of consciousness, and vascular compression). With a median follow-up of 5.5 (CI 95%: 3.4-11.1) months 13 pts were evaluable for response: 1 PR (7.7%) and 6 pts SD (46.2%). Mature OS and PFS data are expected by April 2014. **Conclusions:** This is the first ipilimumab clinical trial showing preliminary activity in MUM pts. Safety profile is similar to prior reports in cutaneous melanoma. Response rate seems promising while mature OS and PFS results are pending. Clinical trial information: 2010-024415-14.

**9034 Poster Highlights Session (Board #50), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Long-term safety and overall survival update for BREAK-2, a phase 2, single-arm, open-label study of dabrafenib in previously treated metastatic melanoma (NCT01153763).** *Presenting Author: Paolo Antonio Ascierto, Istituto Nazionale Tumori Fondazione "G. Pascale", Naples, Italy*

**Background:** Dabrafenib is a potent inhibitor of mutated BRAF kinase in *BRAF* V600E/K mutation–positive metastatic melanoma ($mut^+$ MM). This multicenter, single-arm phase 2 study assessed safety and clinical activity of dabrafenib in *BRAF* V600E/K $mut^+$ MM. We previously reported the primary endpoint of investigator-assessed overall response rate in *BRAF* V600E $mut^+$ MM patients and overall survival (OS; median follow-up 11.9 months). Here we report long term safety data and updated OS (median follow-up 13 months). **Methods:** 92 patients with histologically confirmed stage IV *BRAF* V600E/K $mut^+$ MM received oral dabrafenib 150 mg twice daily until disease progression, death, or unacceptable adverse events (AEs). Secondary endpoints included safety and OS. AEs were summarized by duration of dabrafenib treatment. **Results:** 76 patients with *BRAF* V600E $mut^+$ MM and 16 with *BRAF* V600K $mut^+$ MM were enrolled from August 2010 to February 2011. As of December 2013, 11 patients (12%) had not experienced a progression event and 9 continued to receive dabrafenib. In the *BRAF* V600K group, median OS was 12.9 months (95% CI, 6.9-17.1); 4 patients (25%) were alive beyond 18.8 months (third quartile OS; 95% CI, 12.9-NR). In the *BRAF* V600E group, median OS was 13.1 months (95% CI, 10.4-21.9); 21 patients (28%) were alive beyond 30 months (third quartile OS, NR). The most common AEs in all patients were arthralgia (35%), hyperkeratosis (33%), and pyrexia (29%). Overall, 33 patients (36%) experienced a serious AE; 13 (14%) had cutaneous squamous cell carcinoma. New primary melanoma and other malignancies occurred in 2 patients (2%). For patients on dabrafenib $>$ 24 months ($n = 11$), hyperkeratosis (64%), arthralgia (55%), and pyrexia (45%) were the most common AEs observed during treatment, and 2 patients (18%) experienced serious AEs during treatment. **Conclusions:** 25 patients were alive as of December 2013, and 9 of those patients were receiving treatment with dabrafenib. Median OS was $>$ 1 year in patients with *BRAF* V600E/K $mut^+$ MM treated with dabrafenib. The most common AEs in patients treated with dabrafenib $>$ 24 months were the same as those in patients treated with dabrafenib $<$ 24 months. Clinical trial information: NCT01153763.

**9035 Poster Highlights Session (Board #51), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Treatment patterns and outcomes in BRAF V600E mutant melanoma patients with brain metastases receiving vemurafenib in the real-world setting.** *Presenting Author: Geoffrey Thomas Gibney, Moffitt Cancer Center, Comprehensive Melanoma Research Center, Tampa, FL*

**Background:** Metastatic Melanoma (mM) patients (pts) with brain metastases (BM) have a poor prognosis and median survival of $<$6 months. Selective BRAF inhibitors may play a role in the treatment of BM, but data from the "real-world" setting is limited. This study aimed to investigate treatment and survival patterns among $BRAF^{V600E}$ mM pts with active BM receiving vemurafenib (vem). **Methods:** Clinical data for $BRAF^{V600E}$ mM pts with active BM treated with vem after 8/2011 were reviewed from a panel of US oncologists. Demographic and clinical characteristics, mM treatment history pre- and post- vem, treatment response, and death were recorded. 6-month survival rate was estimated using Kaplan-Meier (K-M) method. Prognostic factors for death were measured prior to vem initiation and assessed using a Cox proportional-hazards regression model. **Results:** 283 $BRAF^{V600E}$ mM pts who received vem after diagnosis (dx) of BM were analyzed. Mean age was 57 years; 60.8% were male; 67.5% were ECOG 0-1. Median follow-up time from vem initiation was 5.7 months. Prior to vem, 109 (38.5%) pts received local treatment and 23 (8.1%) pts received systemic treatment for BM. Median vem treatment duration among pts who discontinued vem was 5.0 months. 21 (7.4%) pts required a dose reduction of vem. Reasons for vem discontinuation included systemic disease progression (42.9%), intracranial progression (18.1%), death (16.4%), and pt decision (5.6%). 136/283 (48.1%) were reported to achieve overall intracranial response (CR/PR). No new safety issues were identified. K-M survival at 6-month was 85.7% (95% CI: 80.1, 89.8). Pts with $\geq$5 BM (HR 3.8; 95% CI: 1.7, 8.5), progressive extracranial metastases (HR 2.6; 95% CI: 1.4, 4.6), and $\geq$2 sites of extracranial metastases (HR 5.3; 95% CI: 1.4, 20.4) were found to be significant prognostic factors for death. **Conclusions:** In the real world setting, the use of vem treatment is associated with clinical benefit in $BRAF^{V600E}$ mM patients with active BM.

**9036 Poster Highlights Session (Board #52), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**A phase II single-arm study of pazopanib and paclitaxel as first-line treatment for patients with advanced melanoma.** *Presenting Author: John P. Fruehauf, UCI Comprehensive Cancer Center, Orange, CA*

**Background:** We designed a phase II single arm, open label clinical trial evaluating pazopanib in combination with metronomic paclitaxel as first line therapy for subjects with unresectable stage III and stage IV melanoma. We collected PK data to determine if pazopanib blood levels were associated with treatment outcomes. **Methods:** Subjects received paclitaxel at 80mg/$m^2$weekly for 3 weeks in a 4 week cycle and pazopanib at 800mg as a continuous daily oral dose. Patients with treated CNS metastases were eligible. It was predetermined that 44 subjects with measurable disease were sufficient to estimate the response probability to within +/- 15% (95% confidence interval). The primary endpoint was 6-month progression free survival. Secondary endpoints included 1-year survival, TTP and median OS. Outcomes were correlated with pazopanib cycle 2 day 1 pre-dose steady state plasma levels. **Results:** We enrolled 51% M1c, 34% M1b, 13% M1a, and 1 patient was IIIc. Nine patients had previously treated CNS metastases. Forty six patients were fully evaluable for response. Six of 7 unevaluable patient's had clinical progression and were considered to have PD. Response rates were: 1 CR, 20 PR's, 26 SD's, and 6 PD's. The overall RR (CR+PR) was 40%. Disease control rate was 89% (CR+PR+SD). Six-month PFS was 70%, 1-year OS was 43%. Median TTP was 210 days and median OS was 403 days. Grade 3-4 AEs included hypertension (25%), transaminitis (23%), and neutropenia (17%). One patient discontinued for grade 4 transaminitis which subsequently resolved completely. Pazopanib was dose reduced in 30% of patient's. Mean pazopanib serum levels were not significantly different ($p=.2$) in patients with stable disease (43.43 + 32.3 ug/ml) compared with responding patients (31.96 + 20.58). A linear regression for drug levels and best response yielded an insignificant $r = 0.27$. **Conclusions:** This phase II study demonstrated that pazopanib in combination with paclitaxel was well tolerated and resulted in a 40% response rate with 6-month PFS of 70%, indicating that this combination is of further interest. There was no association between pazopanib serum levels and treatment response. Clinical trial information: NCT01107665.

**9037 General Poster Session (Board #241), Sat, 8:00 AM-11:45 AM**

**Incidence and survival of dermatofibrosarcoma protuberans in the United States.** *Presenting Author: Kathryn L Kreicher, Case Western Reserve University School of Medicine, Cleveland, OH*

**Background:** Dermatofibrosarcoma protuberans (DFSP) is a rare cutaneous sarcoma of intermediate malignancy. Information on risk factors, incidence, and survival of DFSP is limited. We sought to describe the incidence of and survival from primary DFSP in the United States. **Methods:** We used data from the 18 registries of the Surveillance, Epidemiology, and End Results (SEER) Program from 2000-2010 to calculate the incidence of and survival from primary DFSP. **Results:** 6,817 cases of primary DFSP were reported from 2000-2010. Overall incidence was 0.41 per 100,000 person years. Incidence remained steady over the study period. The trunk was the most common anatomic site for all age groups except for men over the age of 80. Incidence among women was 1.14 times higher than men (95% CI of rate ratio: 1.07-1.22). Incidence among blacks was almost 2 times the rate among whites (95% CI of rate ratio: 1.8-2.1). 10-year relative survival of DFSP was 99.1% (95% CI: 97.6% - 99.7%). Increasing age, male sex, and black race were associated with higher all-cause mortality. Anatomic location of the upper limb, lower limb, and head were associated with higher mortality as compared to the most common location of the trunk. **Conclusions:** The epidemiology of DFSP differs from most skin cancers. Our data show that incidence of DFSP has not changed over the last decade. Incidence among blacks is almost twice that of whites. This is the first report showing statistically higher incidence among women than men. Worse survival is associated with increased age, male sex, black race and anatomic location of the limbs and head.

**9038 General Poster Session (Board #242), Sat, 8:00 AM-11:45 AM**

**Prognostic significance of PD-L1 expression, angiogenesis, and hypoxia in melanoma brain metastases (MBM): A histopathologic analysis.** *Presenting Author: Stergios J. Moschos, Department of Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

**Background:** We have previously shown that presence of intratumoral hemorrhage and absence of immune infiltrates in craniotomy specimens of MBM are associated with shorter overall survival (OS), defined as time from craniotomy to death (Hamilton Cancer 2013). We hypothesize that immune checkpoint protein(s), angiogenic factors, cytokines, hypoxia, and the density of mature vs. immature blood vessels (MBV, IBV) are important prognostic factors. **Methods:** Clinicopathologically annotated craniotomy tumor specimens were stained for angiogenic/hypoxic factors (bFGF, VEGF, HIF1$\alpha$), blood vessel density (CD31), PD-L1, and for vessels (>50 $\mu$m2) that are IBV (CD31+SMA—) or MBV (CD31+SMA+). The Aperio imaging system and Definiens Tissue Studio were used to analyze expression of each marker in different compartments within the tumor (tumor, reactive glia, normal brain, mononuclear cell clusters). **Results:** An average of 44 cases were analyzed for each of the 7 stains. When each variable was treated as continuous using Cox proportional hazards models, no variable was associated with OS. When survival information was used to define the optimal cut-point for each variable between those with long versus short OS, high tumor expression of PD-L1 and bFGF, and low tumor expression of HIF1$\alpha$ were associated with worse OS (unadjusted $p<0.05$; hazard ratios 1.92, 2.2, 2.1 respectively). PD-L1 expression was significantly higher in tumor compared to normal brain, but insignificantly different between tumor and reactive glia or immune infiltrates. There was a significant inverse association between tumor PD-L1 expression and immune infiltrate. **Conclusions:** This unique dataset suggests that neither the density nor the quality of blood vessels within MBM is a significant prognostic factor nor correlates with tumor hemorrhage. Tumor response to hypoxia by upregulation of HIF1$\alpha$ may paradoxically be a favorable prognostic factor. More important, high expression of PD-L1 in MBM is an adverse prognostic factor, and could be derived from its immunosuppressive effects in the brain microenviroment. Targeting PD1/PD-L1 pathway in patients with MBM is reasonable on the basis of these findings.

**9039 General Poster Session (Board #243), Sat, 8:00 AM-11:45 AM**

**The FAM-GEM-1 study: Frequency and characteristics of familial melanoma in Spain.** *Presenting Author: Ivan Marquez Rodas, Medical Oncology, Instituto de Investigación Sanitaria Gregorio Marañon, Universidad Complutense, Madrid, Spain*

**Background:** Melanoma risk is determined by environmental, phenotypical and familial background. Literature describes a 5-10% of melanoma cases in a familial setting. Familial melanoma (FM) is classically defined as >2 first degree relatives with melanoma in a family. Multiple melanomas (MM), pancreatic cancer (PC) in family and multiple nevi are also risk criteria. In Spain, there are several local studies about epidemiology and characteristics of FM, but there are no studies exploring all the territory **Methods:** FAM-GEM-1 is a national, observational, 2 years-registry study (2011-2013), conducted by the Spanish Multidisciplinary Melanoma Group (GEM), whose principal objective was to assess the rate of patients with FM in Spain. Secondary objectives were to analyze if FM patients are different in terms of clinical, pathological and/or molecular features; and to create a registry of FM for further studies. We present the final results of the 1,049 patients registered. **Results:** In Spanish population, according to this representative sample, 7%patients meet FM criteria**.** In the univariate analysis, FM patients have more frequently MM, and less Breslow index, positive mitosis and positive nodes. No differences in other prognosis factors or characteristics were found (Table). **Conclusions:** Although FM seem to have better prognosis characteristics, it is not clear if these differences are due to a bias (more concern that leads these patients to earlier diagnosis) or to real molecular differences. Further studies are needed to elucidate it.

| * Fisher or t student p< 0.05 vs non-FM (%): for valid data | FM N (%) 73 (7) | Non-FM N (%) 976 (93) |
|---|---|---|
| Age, mean, (SD) | 53.1 (15.5) | 55.2 (16.3) |
| Age < 50 y | 30 (41) | 356 (36.5) |
| Male | 43 (58.9) | 487 (49.9) |
| Phototype I-II | 34 (46.6) | 482 (49.4) |
| Freckles | 18 (25) | 308 (31.6) |
| Multiple nevi | 18 (25.4) | 195 (20.5) |
| Previous nevus | 23 (43.4) | 265 (36.9) |
| MM | 7 (9.6)* | 35 (3.6) |
| Breslow (mm), mean, (SD) | 1.5 (1.7)* | 2.3 (2.7) |
| Breslow>1 mm | 21 (38.2)* | 458 (60.2) |
| Ulceration | 11 (16.7) | 184 (22.9) |
| Mitosis | 20 (37.7)* | 355 (55) |
| Positive Nodes | 14 (19.4)* | 278 (29.5) |
| Metastases | 7 (9.6) | 148 (15.2) |
| BRAF mutant | 5 (71) | 59 (51.8) |
| Other tumor (non-skin) | 8 (11) | 85 (8.7) |
| PC in family (first and second degree) | 4 (5.5) | 37 (3.8) |
| Other tumors in family (first degree) | 32 (43.8) | 439 (44.9) |

**9040 General Poster Session (Board #244), Sat, 8:00 AM-11:45 AM**

**Effect of restoration of microRNA-18a on improvement of imatinib therapy on secondary imatinib-resistance metastatic melanoma.** *Presenting Author: Jun Guo, Peking University Cancer Hospital & Institute, Beijing, China*

**Background:** Imatinib generated remarkable clinical response in melanomas harboring c-kit mutation. However, melanoma resistance to imatinib develops rather quickly in most of the patients. It has been shown that gene mutations, translocations, deletions, amplifications, and epigenetic changes are involved in the process of secondary imatinib-resistance in GI stromal tumor. But imatinib resistance in melanoma has not been well evaluated. **Methods:** The level of miRNAs expression was initially discovered through miRNA profiling using pretreatment and post treatment imatinib resistant melanoma tissues, and then confirmed by quantitative PCR. Scratch wound and in vitro invasion assays were performed to evaluate cell migration and invasion. Luciferase reporter assays, immunoblots, and immunohistochemistry analyses were conducted to examine the association between miR-18a and their targets in imatinib-resistant cell and specimens. **Results:** miR-18a was dramatically down-regulated in secondary imatinib-resistant melanoma tissues. Reintroduction of miR-18a led to imatinib-resistant cells become sensitive to imatinib treatment. Cell cycle and apoptosis analysis indicated that miR-18a overexpression in combination with imatinib treatment resulted in a decrease of cell numbers of S-phase and an increase of apoptotic cells, respectively. Wound healing assay and in vitro invasion assay indicated enforced expression of miR-18a, as well as imatinib treatment dampened the capacity of melanoma cell migration and metastasis. CCND2 and Notch2 were validated as bona fide effectors of miR-18a in melanoma cells. Furthermore, rescued assay was performed to probe the interaction among miR-18a, CCND2/Notch2, and phenotypic alterations, which demonstrated that the sensitivity of imatinib therapy on imatinib-resistant cell line was improved through miR-18a mediated regulation of CCND2/Notch2. **Conclusions:** Targeting of miR-18a is sufficient to enhance the therapeutic effect of imatinib on melanoma treatment, suggesting that restoration of miR-18a may be a promising strategy for the prevention of melanoma patients from developing secondary resistance.

**9041^ General Poster Session (Board #245), Sat, 8:00 AM-11:45 AM**

**Intralesional treatment of stage III metastatic melanoma patients with L19-IL2: Clinical and systemic immunological responses.** *Presenting Author: Dario Neri, Federal Institute of Technology, Zurich, Switzerland*

**Background:** In previous studies, intralesional injection with interleukin-2 (IL2) showed efficacy for the intratumoral treatment of cutaneous/subcutaneous metastases in advanced melanoma patients. Objectives of this multicenter study (ClinicalTrials.gov Id.: NCT01253096) were to investigate whether intralesional delivery of L19-IL2, a targeted form of IL2, would yield similar results with reduced injection frequency and treatment duration and whether systemic immune responses were induced by the local treatment. L19-IL2 is a recombinant fusion protein, consisting of IL2 fused to a single-chain monoclonal antibody (L19) directed against extradomain B of fibronectin, a well-characterized marker of angiogenesis. **Methods:** Twenty-five patients with unresectable Stage IIIB/IIIC melanoma and cutaneous/subcutaneous injectable metastases received intratumoral injections of L19-IL2 once per week at a maximum daily dose of 10 MIU for 4 consecutive weeks. Tumor response was evaluated twelve weeks after the first treatment. **Results:** Twenty-four of 25 enrolled patients were evaluable. Toxicities were mild and comparable to that of free IL2. No serious adverse event was recorded. A complete response of all metastases was achieved in 6 patients (25%), which was long-lasting in most cases (5 patients $\geq$ 24 months). Analysis of progression rates for these patients seems to show an effect of intratumoral injection of L19-IL2 in retarding spread of the disease to distant lymph nodes or appearance of visceral metastases, as compared to historical controls. A significant temporary increase of peripheral regulatory T cells and a sustained decrease of myeloid-derived suppressor cells was observed upon treatment. **Conclusions:** Intratumoral L19-IL2 treatment elicited objective responses in a high percentage of lesions. The targeted form of IL2 yielded results similar to those of the untargeted cytokine, but at lower cumulative doses and more favorable schedule and treatment duration. Analysis of progression and survival rates for these patients indicates a substantial advantage, compared to historical controls, in terms of overall survival and distant metastasis-free survival. Clinical trial information: NCT01253096.

**9042 General Poster Session (Board #246), Sat, 8:00 AM-11:45 AM**

**Incidence and characteristics of melanoma brain metastases appearing during vemurafenib treatment.** *Presenting Author: Lucie Peuvrel, Dermato-Cancerology department, Nantes University Hospital, Nantes, France*

**Background:** Melanoma brain metastases are frequent and severe. We studied their characteristics in a retrospective cohort of patients treated with vemurafenib, a BRAF inhibitor indicated in V600-mutant metastatic melanoma. **Methods:** We included in this study all patients receiving vemurafenib in our department between November 2010 and November 2013 without melanoma brain metastases at initiation of treatment. Brain scans were performed after 2 months, and then every 3 months or in case of neurologic symptoms. RMI could be performed to confirm scan result. Our primary endpoint was the brain metastases incidence. Secondary endpoints were associated risk factors, onset modalities and clinical evolution. **Results:** In our cohort of 86 patients, incidence of brain metastases was 20% after a median follow-up of 9 months (1 to 26 months). They appeared after a mean of 5.3 months of vemurafenib exposure (1 to 15 months). The only identified risk factor was a high number of metastases before treatment (p=0.045). Radiological exams revealed 41% of miliary brain metastases. Occurence of brain metastases was associated with a trend toward a decrease in overall survival from 12.8 months (95% CI: 9.2-16.7) to 8.5 months (95% CI: 4.5-11.5) (p=0.07) and with a significant decrease in progression free survival from 7 months (95% CI: 5-8) to 5 months (95% CI: 3-8) (p=0.04). Among patients with brain metastases, 82% were died at time of analysis after a median of 2.7 months (0.2 to 7.2 months). Comparatively, only 58% of the patients without brain metastases died during the same period. The extra cerebral disease was well controlled in 59% of patients at the time of diagnosis of brain metastases. **Conclusions:** Our study shows that melanoma brain metastases appearing in patients during vemurafenib are frequent in real life conditions and associated with a very poor prognosis. Systematic brain explorations must thus be performed during vemurafenib treatment, even in patients with good extra cerebral responses. RMI should be preferred to scan due to the high frequency of miliary metastases. Specific resistance mechanisms are likely in this location due to the high number of dissociated responses between cerebral and extra cerebral metastases.

**9043 General Poster Session (Board #247), Sat, 8:00 AM-11:45 AM**

**Landscape of genetic alterations in patients with metastatic uveal melanoma.** *Presenting Author: Sophie Piperno-Neumann, Institut Curie, Paris, France*

**Background:** Uveal melanoma (UM) is a rare type of cancer with a mutational profile distinct from skin melanoma and poor prognosis in a metastatic setting. In the context of a dose-escalation clinical trial of the PKC inhibitor AEB071 (sotrastaurin) in UM we conducted genomic profiling of 52 formalin-fixed, paraffin-embedded biopsies from metastatic patients (pts), primarily from liver. **Methods:** Massively parallel sequencing of 288 clinically-relevant cancer genes was performed by Foundation Medicine at high depth (median 646X) to characterize mutations, amplifications (≥6 copies) and homozygous deletions. **Results:** Alterations of known or likely functional significance were frequent only in genes previously implicated in UM but two novel patterns were observed. All but two pts (96%) had a known activating mutation in either GNAQ (63%; Q209P/L/R or R183Q) or GNA11 (33%; Q209L). While this mutually exclusive pattern is a known feature of UM the higher prevalence reported here is likely due to the sequencing depth, as evidenced by low allele frequencies in some pts even after correcting for tumor purity. In addition truncations or splice site mutations in BAP1 were observed frequently (62%), in line with previous reports. The tumors harbored nearly complete mutual exclusivity between partial or putatively complete amplifications of chromosome 8q (52%) and recurrent mutations in SF3B1 (19%; R625C/H or V701F), a pattern previously unreported. In addition BAP1 mutations were frequent in 8q-amplification pts (23/25 [85%]) but rare in SF3B1-mutant pts (2/10 [20%]), suggesting complementary and redundant consequences of these lesions with BAP1 mutations respectively. Mutations of known or likely functional impact were otherwise rare. P53 and SMARCA4 were mutated in two pts each and 15 genes were mutated in a single pt. We then investigated the effect of genetic subtype on the baseline levels of pMARCKS as an indicator of PKC activity. No relationship with any gene or within GNAQ/GNA11 mutant subtypes was observed. However, pMARCKS levels were attenuated upon AEB071 treatment. **Conclusions:** High-depth sequencing of clinical pt metastases sheds new light on the interplay among the small group of genetic alterations observed in uveal melanoma.

**9044 General Poster Session (Board #248), Sat, 8:00 AM-11:45 AM**

**A pilot trial of hu14.18-IL2 in patients with completely resectable recurrent stage III or stage IV melanoma.** *Presenting Author: Mark R. Albertini, University of Wisconsin, Madison, WI*

**Background:** Phase I testing of the hu14.18-IL2 immunocytokine (IC), a mAb reactive with GD2 disialoganglioside, linked to IL2, in patients (pts) with melanoma showed immune activation, reversible toxicities, and a maximal tolerated dose of 7.5 mg/m$^2$/day. Preclinical data in IC-treated tumor bearing mice with low tumor burden documents striking antitumor effects. Thus, we studied IC in melanoma pts in remission but at high risk for recurrence. **Methods:** Pts with completely resectable recurrent stage III or stage IV melanoma were scheduled to receive 3 cycles of IC at 6 mg/m$^2$/d IV over 4 hours on days 1, 2 and 3 of each 28-day cycle. Pts were randomized to surgical resection of all sites of disease either following (Group A) or prior to (Group B) IC cycle 1. Primary objectives were to evaluate histological evidence of IC anti-tumor activity, time to recurrence, and overall survival (OS). **Results:** Twenty melanoma pts (11 recurrent stage III, 8 stage IV, one unknown primary) were randomized to Group A (11 pts) or B (9 pts). Two Group B pts did not receive IC due to persistent disease following surgery. Seven of 18 IC-treated pts remain free of recurrence, with median recurrence-free survival of 5.8 months (95% confidence interval: 2.3 months, not yet reached). Eleven of 18 IC-treated pts are still alive (median follow-up of surviving pts: 34.6 months (range: 19.8-47.5 months)). Toxicities were similar to those previously reported for IC. Immunohistologic evaluations of resected tumors showed variable inflammation and tumor necrosis between pts and no clear differences between Groups A and B. Predominant inflammatory cells were CD3+ T cells and CD163/CD68+ macrophages. Twelve pts had evaluable tumor samples for GD2 analysis and 6/12 showed expression of GD2 on melanoma cells (high (2 pts); low/moderate (4 pts); and undetectable (6 pts)). There was no correlation between GD2 expression (positive vs negative) and time to recurrence (logrank p-value=0.572). **Conclusions:** Prolonged tumor-free survival was seen in melanoma pts at high risk for recurrence who were treated with IC. GD2 expression was detected in 50% of pts. The immunological activation by IC with manageable toxicities suggests potential for combination treatments. Clinical trial information: nct00590824.

**9045 General Poster Session (Board #249), Sat, 8:00 AM-11:45 AM**

**Final overall survival from a phase 3 trial of *nab*-paclitaxel versus dacarbazine (DTIC) in chemotherapy-naive patients with metastatic melanoma.** *Presenting Author: Evan Hersh, University of Arizona Cancer Center, Tucson, AZ*

**Background:** In a phase 3 trial, *nab*-paclitaxel significantly improved progression-free survival (PFS) compared with DTIC (4.8 vs 2.5 months; hazard ratio [HR] 0.792; $P = 0.044$) in chemotherapy-naive patients with metastatic melanoma thereby meeting the primary study endpoint. A trend toward improved overall survival (OS; HR 0.831; $P= 0.094$) at the interim analysis (64% of patients with an event) was also shown. Here we report the final OS analysis. **Methods:** 529 patients with chemotherapy-naive, stage IV melanoma (M1c, 65%; elevated lactate dehydrogenase [LDH], 28%) and an Eastern Cooperative Oncology Group performance status of 0-1 were randomized to receive *nab*-paclitaxel 150 mg/m$^2$ on days 1, 8, and 15 of a 28-day cycle (n = 264) or DTIC 1000 mg/m$^2$ on day 1 of each 21-day cycle (n = 265). The randomization was stratified by metastatic stage, region, and baseline LDH. *BRAF* status was known in 67% of patients; of these, 37% had mutant and 63% had wild-type *BRAF* melanoma. September 20, 2013, was the clinical cutoff date for the final OS analysis. **Results:** At the final OS analysis (median follow-up, ≈ 30 months for censored patients), 427 patient deaths occurred: 215 (81%) in the *nab*-paclitaxel vs 212 (80%) in the DTIC arm. Median OS trended in favor of *nab*-paclitaxel, but did not reach statistical significance vs DTIC (12.6 vs 10.5 months; HR 0.897;95% CI 0.738 - 1.089; $P = 0.271$. OS favored *nab*-paclitaxel vs DTIC across most patient subgroups, including patients aged ≥ 65 years and those with M1c stage disease, elevated LDH, and any *BRAF* status melanoma. The use of poststudy anticancer therapy did not differ by treatment arm, with 77% vs 73% of patients in the *nab*-paclitaxel arm vs DTIC arm receiving poststudy therapy. The use of a BRAF inhibitor (13% vs 10%) or ipilimumab (31% vs 32%) was also similar between treatment arms. As previously reported, the most common grade ≥ 3 adverse events with *nab*-paclitaxel were peripheral neuropathy (25% vs 0% with DTIC) and neutropenia (20% vs 10% with DTIC). **Conclusions:** The study met the primary endpoint with a significant improvement in PFS. At final analysis, *nab*-paclitaxel continued to demonstrate a trend toward improved OS vs DTIC. Clinical trial information: NCT00864253.

**9046 General Poster Session (Board #250), Sat, 8:00 AM-11:45 AM**

**Clinical utility of serum miRNAs for the prediction and early detection of recurrence in melanoma patients.** *Presenting Author: Nathaniel H. Fleming, Ronald O. Perelman Department of Dermatology, NYU Langone Medical Center, New York, NY*

**Background:** The improvement of recurrence risk assessment at the time of primary melanoma diagnosis and the development of better surveillance strategies to monitor recurrence remain critical challenges in melanoma patient care. In the current study, we examine the ability of serum-based miRNAs to 1) improve patient risk stratification and 2) improve early detection of melanoma recurrence. **Methods:** Sera levels of 12 miRNAs were measured using qRT-PCR (Exiqon) in serum prospectively collected at diagnosis from 201 melanoma patients (median FU of survivors 91 months). A multivariate logistic regression model that includes miRNAs in combination with stage was built using the training cohort and evaluated in an independent validation cohort of 82 patients (median FU of survivors 39 months). Sera levels of the most informative miRNA signature were assessed longitudinally in a subset of patients (n=82) with samples drawn pre- and post-recurrence when applicable (n=225 samples). An L1 penalized regression approach (Lasso) was performed on TCGA melanoma data to predict the biological role of the miRNA signature. **Results:** A risk score that included four miRNAs (miR-15b, miR-30d, miR-150, and miR-425) in addition to stage significantly separated recurrence-free and overall survival in both the training and validation cohorts (training RFS and OS $P<0.001$, validation RFS $P<0.001$, OS $P=0.005$). The model improved prediction of recurrence over stage alone, increasing AUC from 0.70 to 0.76 (training) and from 0.76 to 0.79 (validation). Normalized serum levels of miR-15b significantly increased over time in recurrent patients ($P<0.001$), but not in non-recurrent patients ($P=0.17$). Serum levels of miR-15b increased in the three months prior to evident recurrence, peaking at recurrence diagnosis and falling after treatment. In TCGA data, miR-15b was predicted to be associated with mRNAs such as AURKB and CNPA involved in the cell cycle, mitotic regulation, and DNA replication ($P<0.001$ for all). **Conclusions:** The addition of serum-based miRNAs can improve prediction of recurrence at time of primary diagnosis. Our data also revealed that dynamic serum miRNA levels can be useful in informing the timing of imaging studies.

**9047 General Poster Session (Board #251), Sat, 8:00 AM-11:45 AM**

**Biochemotherapy with interleukin-2 for metastatic melanoma: Long-term results in 100 patients.** *Presenting Author: David R. Minor, California Pacific Medical Center Research Institute, San Francisco, CA*

**Background:** As the limitations of new melanoma treatments are seen, we felt an evaluation of long-term results of biochemotherapy (BC) for metastatic melanoma (MM) would be useful. **Methods:** Retrospective single-institution review of 100 consecutive patients (pts) who began therapy between 9/30/2002 and 6/20/2006. Median follow-up is 9 years. Staging: IIIC-1; M1A-17; M1B-35; M1C-47. Patients were treated with the O'Day regimen which is similar to ECOG BC except Temozolomide 150mg/m2 used for DTIC; 6 cycles of BC given, not 4; decrescendo IL-2 dosing 36-18-9-9 miu/day dosing not based on BSA; and patients received maintenance inpatient "pulse IL-2" 108miu/42 hrs monthly for 6-18 months after BC. **Results:** 28 pts are still alive, all without evidence of melanoma (NED). One patient died NED due to a pulmonary embolus, one died from sepsis during BC, and 70 died from MM. 17 pts achieved CR with BC and never relapsed. Two patients achieved PR, had surgery for solitary sites of residual disease, and are NED. 6 pts progressed soon after BC, received ipilimumab (ipi) on various schedules, and are now NED. Two patients had late relapses over 3 years after BC. The first received ipi and is now NED off therapy. The second responded to ipi, progressed, and is now NED on therapy with anti-PD-1. One patient received BC in 2005, relapsed in 2007 and is NED after multiple continuous treatments over 7 years with chemo, RT, surgery, ipi, and vemurafenib. Of the 28 patients alive, only the last two are currently receiving therapy. **Conclusions:** First-line decrescendo BC can give durable remissions in many patients; late relapses are uncommon. Durable responses to ipilimumab may follow progression with BC. Biochemotherapy should now be systematically studied as second line or consolidation therapy.

**9048 General Poster Session (Board #252), Sat, 8:00 AM-11:45 AM**

**microRNA (miRNA) expression profiling predicts clinical outcome of carboplatin/paclitaxel-based therapy (CP) in metastatic melanoma (MM) treated on the intergroup trial E2603.** *Presenting Author: Liza Cosca Villaruz, University of Pittsburgh Cancer Institute, Pittsburgh, PA*

**Background:** Chemotherapy continues to be a commonly used modality in MM despite the recent successes of immunotherapy and targeted therapy. CP with or without sorafenib (S) results in objective response rates of 16-18% in unselected chemotherapy-naïve patients (intergroup trial E2603). Our primary objective was to identify molecular predictors of survival and response to CP-based chemotherapy in MM. **Methods:** E2603 randomized 823 MM pts to CP+S vs CP alone. This analysis was performed on pre-treatment formalin fixed paraffin-embedded (FFPE) tumor tissues from 115 pts balanced across treatment arms, *BRAF* status, and clinical outcome. We used technology optimized for FFPE samples: Nanostring miRNA expression array and DASL/Illumina microarrays (HT12 v4) for mRNA expression. Integrative analysis was performed using a novel Tree-guided Recursive Cluster Selection (T-ReCS) algorithm to select the most informative features/genes; TargetScan Human v6.2 for miRNA target prediction and mirConnX for network inference. **Results:** High quality miRNA and mRNA expression data were generated from legacy samples from 115 MM pts treated in E2603 (median progression-free survival (PFS) 4.4 mos). T-ReCS identified *miR-659-3p* as the primary miRNA associated positively with PFS together with *miR-219-1-3p*, *miR-516a-5p*. *miR-659-3p* was differentially expressed based on PFS but not on treatment arm (CP+S vs CP; $p=0.6$), *BRAF* status ($p=0.3$), or *NRAS* status ($p=0.6$). Dichotomized by PFS $<$ 4 mos vs $>$ 4 mos, higher *miR-659-3p* expression remained prognostic of longer PFS ($p=0.03$). High *miR-659-3p* expression distinguished patients with responsive disease (complete or partial) from patients with stable disease ($p=0.04$.) Predicted gene targets using TargetScan and mirConnX included *BRAF*, *PIK3C2A*, *FGF12*, *FGF18* and *RAC1*. **Conclusions:** Novel integrative analysis reveals *miR-659-3p* as a predictive biomarker in MM pts treated with platinum-based chemotherapy and may serve to improve patient selection. Validation in an independent population is ongoing and functional studies to elucidate the mechanisms underlying this observation are planned.

**9049 General Poster Session (Board #253), Sat, 8:00 AM-11:45 AM**

**Role of platinum-based chemotherapy for Merkel cell tumor in adjuvant and metastatic settings.** *Presenting Author: Shailesh R. Satpute, Indiana University Simon Cancer Center, Indianapolis, IN*

**Background:** Merkel Cell Carcinoma (MCC) is a rare, highly aggressive primary neuroendocrine carcinoma of skin. The tumor always stains positive for CK20. Chemotherapy for metastatic disease has been platinum plus etoposide, based upon small cell lung cancer studies. The role of adjuvant chemotherapy in resected high risk disease is controversial. The principles of adjuvant chemotherapy in solid tumors are demonstration of activity in the metastatic setting and a probability for postoperative relapse. **Methods:** We reviewed, retrospectively, 41 patients with MCC seen and followed at Indiana University Simon Cancer Center from 2000 – 2013. Most of these patients received cisplatin or carboplatin plus etoposide for 4-6 cycles. Demographics, disease variables, treatments and outcomes were analyzed. **Results:** Median age was 68 years with 64% males. Primary sites affected were extremities (21), head and neck (11) or others including lymph node only disease with unknown primary (9). 12 patients received chemotherapy for metastatic disease at presentation. 10 of 12 (83%) achieved a RECIST response to chemotherapy. Median duration of remission with chemotherapy was 4 months. 27 patients initially underwent wide local excision with sentinel lymph node biopsy followed by lymph node dissection, if clinically indicated. 2 did not receive any definitive therapy. 15 of these 27 patients received adjuvant chemotherapy based upon high risk features including lymph node involvement (8), positive surgical margins (2), bulky primary tumor (2) or rapid growth (3). 11 of these 15 patients remain continuously progression free with median of 3 years. 12 patients did not receive adjuvant chemotherapy. 5 of 12 remain disease free. 21 patients received adjuvant radiation either as their only therapy (9) or in addition to adjuvant chemotherapy (12). 21 of 41 patients remain alive and disease free, 3 are alive with disease, 13 died from metastatic MCC and 4 died of unrelated causes. Median follow up was 3 years. **Conclusions:** Platinum-based combination chemotherapy is active in metastatic MCC. We recommend adjuvant chemotherapy for MCC with high risk features.

**9050 General Poster Session (Board #254), Sat, 8:00 AM-11:45 AM**

**Randomized, double-blind phase II trial of NY-ESO-1 ISCOMATRIX vaccine and ISCOMATRIX adjuvant alone in patients with resected stage IIc, III, or IV malignant melanoma.** *Presenting Author: Jonathan S. Cebon, Ludwig Institute for Cancer Research, Melbourne, Australia*

**Background:** The cancer testis antigen NY-ESO-1 (ESO) has been evaluated as a biomarker and a therapeutic immunologic cancer target. Preliminary data from a phase I clinical trial of ESO and ISCOMATRIX adjuvant (ESO vaccine) suggested this treatment could prevent relapse in patients (pts) with high risk resected malignant melanoma (MEL). **Methods:** We compared ESO vaccine to adjuvant alone in a randomized double-blind phase II study in pts with MEL. Pts with resected stage IIc, IIIb, IIIc, or IV melanoma expressing ESO were randomized 1:1 to ESO vaccine or adjuvant x3 q4w followed by a 4th dose at 6m. Primary endpoint was rate of RFS at 18m in the intent-to-treat (ITT) population and two per protocol (PP) populations, consisting of all relapses regardless of location. Secondary objectives included RFS and Overall Survival (OS) over the entire period of observation (study defined plus off-study follow-up), safety and ESO immunity. **Results:** Of 111 pts screened with ESO-expressing MEL, 110 comprised the ITT population, with 56 randomized to the ESO vaccine arm and 54 to adjuvant (96% and 87%, respectively, were at stage ≥IIIa at entry). There were no significant differences between the two arms for the ITT population during the 18m observation period for median time to relapse, 139 vs 176 days($p=0.296$), or relapse rate, 27 (48.2%) vs 26 (48.1%) (HR=0.913; 95% CI, 0.402 to 2.231), respectively. RFS and OS for the entire period of observation were similar between the two arms. After the third immunization, a significantly larger percentage of pts in the ESO vaccine arm developed a strong positive antibody (Ab) & cellular immune response (IR) to ESO ($p<0.001$); this difference remained for the duration of the study. A total of 17 out of the 31 pts (55%) who had a vaccine-induced IR (Ab against ESO) and no pre-existing immunity were relapse-free at the end of 18m on study. **Conclusions:** The ESO vaccine was safe, well tolerated, elicited strong Ab and cellular responses but did not affect relapse free survival. Optimal efficacy may require combining it with other immunotherapy modalities. Clinical trial information: NCT00199901.

**9051 General Poster Session (Board #255), Sat, 8:00 AM-11:45 AM**

**A phase 1b dose-escalation study of BYL719 plus binimetinib (MEK162) in patients with selected advanced solid tumors.** *Presenting Author: Dejan Juric, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA*

**Background:** The MAPK and PI3K pathways share common upstream activators and contribute to cell proliferation, differentiation, and survival. Due to compensatory signaling, only partial tumor growth inhibition may occur when targeting either pathway alone. Preclinically-observed synergistic effects of combined PI3K and MEK inhibitors suggest that dual inhibition may be more effective. **Methods:** This phase 1b, open-label study (CMEK162X2109) is evaluating the PI3K$\alpha$ inhibitor BYL719 combined with MEK inhibitor binimetinib (MEK162) in patients (pts) with *RAS*- or *BRAF*-mutant advanced solid malignancies (> 10 types). The objective for dose escalation was estimation of the maximum-tolerated dose (MTD) and/or recommended dose for expansion (RDE), guided by the Bayesian logistic regression model. **Results:** As of September 2, 2013, 58 pts were enrolled and BYL719 was orally co-administered at 80, 120, 160, 200, 220, or 270 mg once-daily (QD) with binimetinib at 30 or 45 mg twice-daily (BID) in 28-day cycles. Thirty two pts (55%) had ≥3 prior anticancer regimens. Median exposure was 7.4 wks. Common adverse events (AEs), regardless of study drug relationship, were diarrhea (86%), nausea (66%), vomiting (52%), reduced appetite (50%), rash (48%), pyrexia (41%), fatigue (38%), and hyperglycemia (36%). Grade 3/4 AEs occurred in 46 individual pts (79%), most commonly diarrhea (12%) and elevated creatine phosphokinase (10%). Dose-limiting toxicities were observed in 9 pts (19%), out of which 4 had grade 3/4 AEs including gastrointestinal and skin disorders. The MTD of the combination was determined to be BYL719 200 mg QD plus binimetinib 45 mg BID, at which 3/6 pts had grade 3/4 AEs. Of 4 ovarian cancer pts with *KRAS*-mutant status, 3 had confirmed partial responses (PRs). PRs were also observed in 1 pt with *NRAS*-mutant melanoma (confirmed) and 1 with *KRAS*-mutant endometrial cancer (unconfirmed). Stable disease lasting > 6 weeks was reported as best response for 18 pts (31%). **Conclusions:** The MTD/RDE for combined BYL719 and binimetinib was reached, and the preliminary safety and efficacy profile justifies further exploration, particularly in pts with *RAS*-mutant ovarian cancer. Clinical trial information: NCT01449058.

**9052 General Poster Session (Board #256), Sat, 8:00 AM-11:45 AM**

**Analysis of recurrence patterns in acral versus non-acral melanoma: Should histologic subtype influence treatment guidelines?** *Presenting Author: Priyanka Gumaste, Ronald O. Perelman Department of Dermatology, NYU Langone Medical Center, New York, NY*

**Background:** Current surgical treatment of primary melanoma is uniform for all histo-subtypes, although certain types of melanoma, such as acral lentiginous melanoma (ALM), are biologically distinct. To our knowledge, no study has explored the effectiveness of standard melanoma treatment guidelines in ALM compared to non-acral melanoma (NAM). **Methods:** Study subjects were selected from a prospectively enrolled cohort of primary melanoma patients at NYU. All patients received wide local excisions with standard margins and a sentinel node biopsy if indicated by accepted practice guidelines. ALM patients were matched to NAM patients (1:3) by gender and melanoma stage, including substage. Logistic regression models were used to compare recurrence and survival outcomes in both cohorts. **Results:** 244 patients were included in this study (ALM=61, NAM=183; median follow-up: ALM= 33 months, NAM=58 months). ALM histologic subtype was an independent negative predictor of recurrence-free survival (HR = 2.45, $p < 0.001$) and melanoma-specific survival (HR= 2.64, $p = 0.001$) compared to NAM. Recurrence was significantly more common in ALM compared to NAM (49% versus 30%, $p=0.007$). When comparing recurrence rates by tumor thickness in both groups, there was no significant difference in recurrence in tumors greater than 2mm (ALM: 64%, NAM: 47%, $p= 0.12$); in tumors less than 2mm, there was a significantly higher recurrence rate in ALM (28%) versus NAM (10%, $p=0.048$). Of note, the rate of loco-regional recurrence was nearly double in ALM (39%) compared to NAM (19%, $p=0.001$). **Conclusions**: Our data revealed a high rate of loco-regional failure in ALM compared to NAM when controlling for AJCC stage. ALM may require wider surgical margins than non- acral cutaneous melanomas of equal thickness, particularly in tumors less than 2mm thick. Revision of surgical margin recommendations based on larger multicenter cohorts may need to be considered.

**9053 General Poster Session (Board #257), Sat, 8:00 AM-11:45 AM**

**Phase I/II study of weekly LOC-paclitaxel (LOC-pac) injection in patients (pts) with metastatic melanoma (MM).** *Presenting Author: Rodabe Navroze Amaria, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background**: LOC-paclitaxel (LOC-pac) is a covalent conjugate of paclitaxel linked to an omega-6 fatty acid designed to enhance uptake of paclitaxel into tumors leading to higher intra-cellular drug concentrations and potentially enhance anti-tumor activity of paclitaxel. This is a first in human, phase I, open label, dose-escalating clinical study of LOC-pac administered weekly in patients (pts) with metastatic melanoma (MM). **Methods**: Adult MM pts who were refractory to prior systemic therapy or were ineligible for other therapy of higher priority with normal organ function and ECOG PS 0-2 were eligible for this trial. Patients with baseline peripheral neuropathy over grade 1, prior exposure to taxane chemotherapy, hypersensitivity to cremaphor or with serious concurrent medical conditions were excluded. LOC-pac was given intravenously over 1 hour on days 1, 8, 15, 22 and 29 every 42 days. LOC-pac dosing was escalated from 100mg/m2 to 1000mg/m2 after safety of the prior dose level was confirmed in cohorts of 3 pts each. Responses were assessed by RECIST every 6 weeks. Toxicity was evaluated using CTCAE v3. **Results:** A total of 33 patients were treated in phase I. Median age was 69 years, median ECOG PS was 0 and 79% of enrolled patients were male. Tumor stages were IIIc/M1a/M1b/M1c in 3/3/7/20 patients respectively. The MTD is 1000mg/m2 and the recommended phase 2 dose is 880mg/m2. DLTs were primarily related to infection including pneumonia and pyelonephritis. Other common toxicities included fatigue, nausea, vomiting, pruritus, peripheral neuropathy and stomatitis. No alopecia or nail changes were appreciated. Of the 33 evaluable patients for best response, 16 had PD, 14 had SD, and 3 had PR. All 3 PRs were confirmed. One patient with PR completed 8 cycles of therapy and then underwent metastectomy showing no viable residual tumor and remains without evidence of disease over 144 weeks. **Conclusions**: Our phase I study demonstrated that LOC-pac is safe and is associated with milder toxicities including neuropathy, nail changes and alopecia when compared with paclitaxel. An ongoing dose expansion study will further define the anti-tumor activity of LOC-pac in MM. Clinical trial information: NCT01039844.

**9054 General Poster Session (Board #258), Sat, 8:00 AM-11:45 AM**

**Improved median overall survival (OS) in patients with metastatic melanoma (mM) treated with high-dose (HD) IL-2: Analysis of the PROCLAIM 2007-2012 national registry.** *Presenting Author: Gregory A. Daniels, UC San Diego Moores Cancer Center, La Jolla, CA*

**Background:** HD IL-2 has been reported to have a overall response rate (ORR) for mM of 16% and a median OS 11.4 months (Atkins,1999), however, the studies that led to its regulatory approval are >15 years old and were performed in an era predating checkpoint inhibition and targeted therapies. **Methods:** The PROCLAIM registry (www.proclaimregistry.com), a HD IL-2 observational database currently with over 30 participating sites, consists of a retrospective cohort (treated 2007-2012) informing an ongoing prospective cohort (~600 patients). We report on the retrospective mM subjects (n=170, 11 sites) with survival status determined as of 11/2013 and a median follow-up of 30.5 months. Sites were encouraged to enroll patients sequentially. Inclusion criteria required that patients have received at least one dose of HD IL-2. **Results:** The ORR for mM in the database was similar to the historical rates. All 170 subjects were accounted for, 98 were deceased and 72 were known to be alive. Median OS was 21 months for mM compared to a median OS range of 6.4-13.6 months for other single agent FDA-approved drugs (Bhatia, 2009; Kaufman, 2005; Hodi, 2010; Chapman, 2012). Among patients with stable disease (SD), median OS was 36.6 months compared to 15.4 months in patients with progressive disease (PD). Median OS has not been reached for patients with complete response (CR) or partial response (PR). Comparison of patients who received HD IL-2 as 1st or 2ndline (n=138, 32, respectively) showed no significant difference in OS between these patients. No deaths due to IL-2 related toxicity were reported in the retrospective cohort. **Conclusions:** The PROCLAIM registry documents an improvement in OS for patients treated with HD IL-2 as compared to the historical reference standards. Response to HD IL-2 traditionally defined as CR or PR and, according to this data, should also include SD, which can be very durable. The observation that 1st and 2nd line HD IL-2 possessed similar OS raises intriguing hypotheses about the sequencing of immunotherapy and targeted therapy in mM, and the utility of IL-2 as a salvage option - all of which are currently under examination in the prospective database.

**9055 General Poster Session (Board #259), Sat, 8:00 AM-11:45 AM**

**Tumor-infiltrating lymphocytes (TILs) and expression of PD-L1 in melanoma brain metastases (BM).** *Presenting Author: Anna Sophie Berghoff, Institute of Neurology, Medical University of Vienna, Vienna, Austria*

**Background:** The brain is considered as an immuno-privileged organ and little is known about the inflammatory response to melanoma BM. **Methods:** Patients with neurosurgical resected and histologically verified melanoma BM were identified. Investigation of PD1, PD-L1, CD3, CD8, CD45RO and BRAF V600E were performed by immunohistochemistry and analyzed using previously published semiquantitative evaluation criteria. **Results:** Forty-six specimens (28/46; 60.9% BRAF V600E positive) were available. Forty-one/46 (89.1%) specimens presented with TIL infiltration. CD3+ TILs were evident in 35/46 (76.1%), CD8+ TILs in 28/46 (60.9%), CD45RO+ TILs in 32/46 (69.6%) and PD1+ TILs in 28/46 (60.9%) specimens. The Table lists details of TIL infiltration density. PD-L1 expression on melanoma BM tumor cells was observed in 21/46 (45.7%) specimens. Median H-score for PD-L1 was 3 (range 1–90). Eight/21 (38.1%) PD-L1 positive specimens presented with an H score over 5 %. PD-L1 expression on tumor cells was associated with higher density of PD1+ (p=0.002), CD3+ (p=0.024) and CD8+ (p=0.050) TIL infiltration. Furthermore, density of CD3+ TILs was associated with density of CD8+ (p<0.001), PD1+ (p<0.001) and CD45RO+ (p<0.001) TILs, respectively. No association of previous systemic antineoplastic therapy (including chemotherapy and interferon) and expression of PD-L1, PD1, CD3 or CD45RO could be observed (p=n.s). Expression of PD-L1 on tumor cells or density of PD1+, CD3+, CD8+ or CD45RO+ TILs did not correlate with BRAF V600E status (p=n.s.) or survival from first diagnosis of BM (p=n.s.). **Conclusions:** Melanoma BM show considerable inflammatory infiltrates and expression of PD1 and PD-L1. Clinical studies should investigate the value of checkpoint inhibitors in patients with melanoma brain metastases.

| | CD3+ TILs | CD8+ TILs | CD45RO+ TILs | PD1+ TILs |
|---|---|---|---|---|
| **Sparse infiltration** | 11/46 (23.9%) | 13/46 (28.3%) | 12/46 (26.1%) | 13/46 (38.3%) |
| **Moderate infiltration** | 12/46 (26.1%) | 12/46 (26.1%) | 11/46 (23.9%) | 11/46 (23.9%) |
| **Dense infiltration** | 8/46 (17.4%) | 11/46 (23.9%) | 7/46 (15.2%) | 4/46 (8.7%) |
| **Very dense infiltration** | 4/46 (8.7%) | 5/46 (10.9%) | 2/46 (4.3%) | 0/46 (0.0%) |

**9056 General Poster Session (Board #260), Sat, 8:00 AM-11:45 AM**

**Ipilimumab in acral melanoma: A retrospective review.** *Presenting Author: Douglas Buckner Johnson, Vanderbilt-Ingram Cancer Center, Nashville, TN*

**Background:** Ipilimumab (Ipi) improves overall survival (OS) in advanced melanoma. Retrospective studies suggest inferior outcomes for Ipi in atypical cohorts of melanoma (uveal, mucosal) compared to unselected populations. Acral melanoma (AM) is an uncommon subtype of melanoma with a poor prognosis. The clinical activity of Ipi has not been well defined in advanced AM. **Methods:** To assess the activity of Ipi in this cohort, we retrospectively reviewed the demographics, treatment history, and clinical outcomes for all patients (pts) with AM treated with Ipi from two centers between February 2006 and June 2013. Using Cox proportional hazards models, we assessed for factors that correlated with OS. **Results:** Of 35 patients with advanced AM who received Ipi, 28 were Caucasian, 6 were black, and 1 was Hispanic. Primary tumors arose on the volar surfaces in 28 and subungual sites in 7. Of 31 genotyped patients, 3 had mutations in *BRAF*$^{V600E}$, 2 in *NRAS*, and 4 in *CKIT*. Stage IVc disease was present in 19 pts, IVb in 6, IVa in 5, and III in 5; 45% had elevated LDH. Median number of prior therapies was 1 (range 0-3) including targeted agents in 6 pts and immune-based therapies in 5. The median number of Ipi doses received was 4 (33 pts with 3mg/kg dosing and 2 with 10mg/kg). Best response by immune-related response criteria (irRC) was complete response in 1 pt, partial response in 3, and stable disease (SD) in 5 for an objective response rate (ORR) of 11.4% and clinical benefit (ORR + SD) at 24 weeks of 25.7%. Median progression-free survival (PFS) from initiation of Ipi was 2.6 months (mo) (95% CI 2.2-3 mo); median OS was 16.7 mo (95% CI 11-22.5 mo). Normal LDH and absolute lymphocyte count ≥1000 at 7 weeks predicted longer OS; metastatic stage, and timing or site of initial recurrence did not influence OS. Toxicities were similar to previous Ipi trials; 16 pts had an immune-related adverse event (irAE) and 7 pts had grade 3 irAEs (colitis in 2, hypophysitis in 3, and hepatitis and dermatitis in 1 each). **Conclusions:** Ipi induced clinical responses in pts with AM with similar ORR, PFS, and OS compared to unselected populations. Treatment was generally well-tolerated with a comparable toxicity profile to previous trials. Ipi remains an appropriate therapy option for pts with advanced AM.

**9057 General Poster Session (Board #261), Sat, 8:00 AM-11:45 AM**

**Vitamin D level at diagnosis and its variation during follow-up as prognostic factor of cutaneous melanoma.** *Presenting Author: Philippe Saiag, Hospital Ambroise Pare, APHP, University Versailles-SQY, Boulogne-Billancourt, France*

**Background:** Low 25-hydroxyvitamin D3 (25(OH)D3) serum concentration at diagnosis of melanoma might be associated with worse survival. We prospectively studied the prognostic value of 25(OH)D3 at diagnosis and during follow-up. **Methods:** Melancohort is a cohort of patients recruited in Paris hospitals in 2003-08 within 1-3 months after diagnosis of AJCC stage I-II, III or IV invasive melanoma and followed until 06/2011. Blood 25(OH)D3 was measured by mass spectrometry. 25(OH)D3 levels were standardized on month of blood drawn, age, sex and body mass index (BMI). Role of 25(OH)D3 level at inclusion and change through time on disease-free survival (DFS) were analyzed in a time dependent covariates Cox model adjusting for age, sex, BMI and AJCC stage. **Results:** 1,171 patients were included, with 411 first relapses during follow-up and 303 deaths. On average 3.25 measures per patient were performed. Median 25(OH)D3 serum concentration at inclusion was 47.2 nmol/L (interquartile range 30.65-63.18). 25(OH)D3 levels at inclusion were inversely correlated with prognostic factors such as AJCC stage (p<0.0001 Kruskal-Wallis), Breslow's thickness (p<0.0001 spearman correlation), and ulceration (p=0.0004 Kruskal-Wallis), but were not associated with DFS in the Cox model, either as a continuous (p=0.747) or categorical variable. Changes in 25(OH)D3 levels during follow-up were significantly associated with worse DFS: with a third quartile Q3 of average change per year (-0.3;4.6nmol/L/Y) used as reference, HR were for Q1 (<-5.25nmol/L/Y) 1.94 95%CI(1.36-2.76), for Q2 (-5.25;-0.30nmol/L/Y) 1.23 95%CI(0.85-1.78), and for Q4 (>4.60nmol/L/Y) 1.61 95%CI(1.14-2.28). In sensitivity analyses, no changes were observed either by AJCC stage or by number of 25(OH)D3 measures performed. Analyses performed on overall survival yielded similar results. **Conclusions:** We show that 25(OH)D3 variation during follow-up is an independent melanoma prognostic marker, but not its level at diagnosis. The biological significance of this finding should be investigated. Previously reported association between low 25(OH)D3 level at diagnosis and poor prognosis were probably due to insufficient adjustment for prognostic factors. Clinical trial information: NCT00839410.

**9058 General Poster Session (Board #262), Sat, 8:00 AM-11:45 AM**

**Dissecting the effect of age on immune response in melanoma patients.** *Presenting Author: Nathaniel H. Fleming, Ronald O. Perelman Department of Dermatology, NYU Langone Medical Center, New York, NY*

**Background:** Older ageat diagnosis has been shown to be an independent negative prognostic factor in melanoma. Nevertheless, no biological basis for the impact of age on melanoma has been defined. In this study, we examined the impact of patient age on cellular immune response as well as response to immunotherapy treatment in the adjuvant setting in a well-studied cohort of melanoma patients. **Methods:** A prospectively-enrolled cohort of patients presenting with stage III melanoma at NYU was studied. Associations between age at diagnosis and presence of tumor-infiltrating lymphocytes (TILs), response to immunotherapy, and stage IV progression-free survival (PFS) and overall survival (OS) were tested by log rank test. In addition, checkpoint PD-L1 expression was tested in pre-treatment tumor specimens in a subset of patients. **Results:** 316 patients (median follow-up for survivors: 45 months) were studied and categorized into two groups by age at diagnosis: ≤60 years (n=163) and >60 years (n=153). The two groups were well matched by clinical substage at presentation. Patients in the older group had significantly shorter OS compared to the younger group (P=0.039). TILs were absent in a significantly larger proportion of the older compared to younger group (35% versus 21%, respectively; P=0.017). Among patients who received adjuvant immunotherapies (n=86), patients in the older group had significantly shorter OS (P=0.048), with a similar trend for PFS (P=0.059). No significant survival differences were observed among patients who received non-immunotherapy treatments (n=57) or no adjuvant treatment (n=165). We reasoned that PD-L1 expression could explain the difference in response to immunotherapy treatment by age; however, no significant difference was observed in PD-L1 expression by age among 66 cases tested at the time of submission. **Conclusions:** Data suggest that decreased immune response and a consequent lack of response to immunotherapy might be contributing, at least in part, to the worse prognosis of older melanoma patients. PD-L1, a key inhibitory receptor, does not seem to be responsible for the observed impaired immune response. Treatment strategies for melanoma patients may need to account for biological differences by patient age.

**9059 General Poster Session (Board #263), Sat, 8:00 AM-11:45 AM**

**Clinicopathologic characteristics and management trends of cutaneous melanoma among older patients: A National Cancer Data Base (NCDB) analysis.** *Presenting Author: Vijaya Raj Bhatt, University of Nebraska Medical Center, Omaha, NE*

**Background:** The incidence and mortality of elderly melanoma are expected to increase. Prior studies have shown poor outcomes in elderly melanoma patients. **Methods:** This is a retrospective study of adult patients diagnosed with cutaneous melanoma between 2000 and 2011 in the NCDB. NCDB contains ~70% of new cancer diagnosis from >1,500 American College of Surgeons-accredited cancer programs in the US and Puerto Rico. Characteristics and management of elderly melanoma (≥60 years) was compared to younger patients (20-59 years) using Chi-square test. **Results:** Of 476,623 total cases, 54% (n=258,153) were diagnosed among older patients. The annual incidence in the older patients increased by 174% (15,910 in 2000 vs. 27,669 in 2011). The majority were white (96%), males (65%), early-stage disease (75% stage 0-II), superficial spreading melanoma histology (39%), and received care in non-academic centers (70%). Elderly patients, compared to younger patients, were more likely to be male, and have in-situ melanoma, less likely to have nodal metastases, receive care in academic centers, undergo wide excision or major amputation for stage I-III disease and systemic therapy for stage III and IV disease (all p<.0001; Table). **Conclusions:** Our study demonstrates a near-doubling of the incidence of melanoma in elderly in the last decade, which disproportionately affects white men. To our knowledge, this is the largest study to demonstrate that the elderly melanoma patients are less likely to receive care in academic centers, undergo wide-excision for stage I-III disease and receive systemic therapy for Stage III-IV. Particularly, the utilization of systemic therapy was markedly lower. All or some of these health care discrepancies may contribute to decreased survival of elderly patients with melanoma.

**Characteristics of melanoma patients[1].**

| Variables | 20-59 yrs (%) | ≥60 yrs (%) |
|---|---|---|
| **Men** | 49 | 65 |
| **In-situ melanoma** | 21 | 28 |
| **Lentigo maligna** | 4 | 13 |
| **Superficial spreading melanoma** | 26 | 16 |
| **Nodal metastases in stage I-III** | 9 | 7 |
| **Care in academic centers** | 35 | 30 |
| **Wide excision or amputation, stage I-III** | 72 | 68 |
| **Systemic therapy, stage III** | 45 | 18 |
| **Systemic therapy, stage IV** | 50 | 30 |

[1]P-values for all the comparisons are <0.0001.

**9060 General Poster Session (Board #264), Sat, 8:00 AM-11:45 AM**

**Is transhepatic chemoembolization with CPT-11 charged microbeads in combination with systemic fotemustine (f-TACE) effective in uveal melanoma liver metastases? A retrospective analysis of 127 consecutive patients.** *Presenting Author: Sara Valpione, Veneto Research Oncology Institute, Padova, Italy*

**Background:** Uveal melanoma is a rare cancer, it represents 5% to 6% of all melanoma diagnoses (annual incidence approximately 0.5-0.7:100000). Up to 50% of patients with UM will develop metastatic disease within 15 years from the treatment of primary tumor. The preferred spread is hematogenous and the liver is the first or prevalent site of metastatic disease in up to 95% of the recurring patients. The median survival time of metastatic uveal melanoma is generally poor, with reported median life expectancy from 3.6 to 15 months and no standard therapy established so far. **Methods:** We retrospectively reviewed our database of patients treated at Veneto Region Oncology Research Institute for metastatic uveal melanoma, grouped by liver replacement percentage, to evaluate the benefit of treatment with transarterial chemoembolization with CPT-11 charged microbeads combined with systemic fotemustine (f-TACE) in this set of patients. From 1990 to 2013, 156 patients were treated for metastatic uveal melanoma in our Centre. Among them, 147 patients had liver metastases and 127 had enough information recorded to perform the study and were analyzed. **Results:** Among 127 patients with liver metastases, 49 were treated with f-TACE as first line-therapy. The cohort of patients treated with f-TACE and the cohort that did not receive f-TACE were not significantly different for prognostic factors. The treatment with f-TACE conferred a survival advantage (20.6 vs 14.7 months, respectively; p=.050); the advantage was maintained when analysis was performed with stratification for liver metastatic substitution (HR= 0.58, p=.002). The treatment was not affected by severe toxicities. **Conclusions:** F-TACE seems a tolerable regimen that confers an improvement in survival of uveal melanoma patients with liver metastases. Our data prompt for the conduction of perspective comparative studies confirming the efficacy of f-TACE and, in the future, we advise combination treatments with targeted drugs.

**9061 General Poster Session (Board #265), Sat, 8:00 AM-11:45 AM**

**Vemurafenib treatment in patients with BRAF-mutated melanoma failing MEK inhibition with trametinib.** *Presenting Author: Helen Gogas, Hellenic Cooperative Oncology Group (HeCOG), Athens, Greece*

**Background:** Trametinib was shown to improve progression-free and overall survival in patients with metastatic melanoma with a BRAF V600E or V600K mutation as compared with chemotherapy in the METRIC trial. However, the median duration of response was 5.5 months and median progression-free survival was 4.8 months in the Trametinib group. Vemurafenib and Ipilimumab were still investigational when this trial was initiated but were available in clinical trials for post-protocol treatment. **Methods:** In this phase III trial 98 patients out of the 322 patients of the intent to treat population who had metastatic melanoma with a V600E or V600K mutation received Vemurafenib (960mg twice daily orally). We present data of patients with complete information on initiation and discontinuation date of Vemurafenib and investigator reported response. **Results:** With a median follow-up of 18.3 months, the median progression free survival (PFS) was 5.2 months with 95% CI 3.7-5.7 and a range of 0.5-27.5+ months. The 6 months PFS was 40.1%. The median overall survival (OS) was 8.3 months with 95% CI 7.1-10.6 and a range of 0.5-27.5+. The 6 months OS was 68.1%. Nineteen patients achieved a partial response and one a complete response. **Conclusions:** Treatment with vemurafenib had an impact on progression free survival post trametinib treatment in patients receiving a MEK inhibitor in first or second line setting. Sequencing BRAF inhibitors with MEK inhibitors and combinations are currently under investigation.

**9062 General Poster Session (Board #266), Sat, 8:00 AM-11:45 AM**

**Effect of the BRAF inhibitor LGX818 on endoplasmic reticulum stress and sensitivity of NRAS-mutant melanoma cells to the MEK inhibitor binimetinib.** *Presenting Author: Friedegund Elke Meier, University of Tuebingen, Tuebingen, Germany*

**Background:** The BRAF inhibitors vemurafenib and dabrafenib have demonstrated antitumor activity in patients with metastatic BRAFV600-mutant melanoma. However, patients with BRAF wild-type, in particular patients with aggressive NRAS-mutant melanoma, do not benefit. In a phase 2 trial, the MEK inhibitor binimetinib showed activity in patients with NRAS-mutant melanoma with overall response rates of >20%. In a previous study, we showed that the BRAF inhibitor vemurafenib induces apoptosis in BRAFV600-mutant melanoma cells through a mechanism involving induction of endoplasmic reticulum (ER) stress. ER stress induction appeared to be an off-target effect of vemurafenib that remarkably enhances its pro-apoptotic activity in BRAFV600-mutant melanoma. **Methods:** In this study, we investigated whether it is possible to take advantage of ER stress induction to establish effective combination therapies for patients with NRAS-mutant melanoma. **Results:** BRAF-mutant and NRAS-mutant metastatic melanoma cell lines were treated with the BRAF inhibitors vemurafenib, dabrafenib and LGX818, and the classical ER stress inducer thapsigargin, and were subjected to electron microscopy. Of note, LGX818 induced morphological features of ER stress, including a significant dilation of the ER in both BRAF-mutant and NRAS-mutant melanoma cell lines. As expected, LGX818 inhibited phosphorylation of ERK and growth and induced apoptosis in BRAF-mutant but not in NRAS-mutant melanoma cells. However, LGX818 significantly enhanced growth inhibition and apoptosis induced by the MEK inhibitor binimetinib in NRAS-mutant melanoma cells. Moreover, LGX818 in combination with binimetinib induced the expression of the ER stress-related factors p8, ATF4, ATF3, CHOP and TRB3 in NRAS-mutant melanoma cells. siRNA inhibition of ATF4 reduced melanoma cell apoptosis induced by LGX818 combined with binimetinib. **Conclusions:** These data suggest that the BRAF inhibitor LGX818 induces endoplasmic reticulum stress and potentiates the antitumor activity of MEK inhibitors in NRAS-mutant melanoma.

**9063 General Poster Session (Board #267), Sat, 8:00 AM-11:45 AM**

**Effect of pregnant sera and a pregnancy-associated metalloproteinase (PAPP-A) on melanoma in vitro and in vivo: Insights into melanoma progression during pregnancy and potential new therapeutic targets.** *Presenting Author: Prashanth Prithviraj, LUDWIG INSTITUTE FOR CANCER RESEARCH, Heidelberg, Australia*

**Background:** At $45/10^5$pregnancies, Malignant Melanoma (MM) is the commonest cancer diagnosed in pregnant women. An aggressive course & poor outcomes are recognised to occur during pregnancy. IGF1 plays an important role in embryogenesis & cancer progression. IGF1 circulates as a complex with IGFBP4, which is cleaved by Pregnancy-Associated Plasma Protein-A (PAPP-A), resulting in release of IGF1. PAPP-A serum levels increase exponentially during pregnancy. **Methods:** 8 MM cell lines were cultured with pregnant & normal sera. Effect on proliferation (MTS) & invasion/migration (wound healing & matrigel transwell assays) were analysed. PAPP-A expression in human MM & cell lines was analysed by PCR, ELISA & IHC. Transient siRNA knock-down of PAPP-A & downstream gene/protein expression were confirmed. Functional assays were performed after PAPP-A knockdown at 24, 48 & 72hrs. An avian neural crest cell migration assay was used to confirm effects in-vivo. Furthermore, effect of PAPP-A neutralising Ab on cell motility & migration induced by sera was analysed. **Results:** PAPP-A is widely expressed in MM tumors and cell lines. While the proliferation of MM cells did not change with PAPP-A knockdown, migratory & invasive capacity was significantly decreased (>40% $p<0.05$). This effect was confirmed in-vivo. The neutralizing Ab attenuated invasion and migration of MM cells, confirming the knockdown results. PAPP-A levels in pregnant sera were 70-fold higher than in control sera. Treatment of MM cells with this serum led to decreased proliferation, but enhanced migration & invasion of MM cells in-vitro. Using an antibody against PAPP-A to evaluate its role in this, we detected a reversion of pregnant serum-induced invasion and migration. **Conclusions:** Pregnant sera enhances the migratory & invasive behaviour of MM cells in-vitro, which can be effectively attenuated by Ab against PAPP-A. Reduced invasion & migration after PAPP-A knockdown suggests a potential therapeutic target in treatment of MM. This study also gives an indication towards a biological mechanism (PAPP-A) involved in MM progression during pregnancy.

**9064 General Poster Session (Board #268), Sat, 8:00 AM-11:45 AM**

**Is extensive lymphadenectomy necessary for regional control of stage III cutaneous melanoma?** *Presenting Author: Manabu Fujita, John Wayne Cancer Institute, Santa Monica, CA*

**Background:** The extent of regional lymphadenectomy in stage III melanoma is still controversial because most recommendations are not based on statistical analysis of the minimum number of excised nodes necessary to minimize regional recurrence. **Methods:** We used our center's melanoma database to identify all patients diagnosed with stage III neck, axillary or inguinal regional metastasis of cutaneous melanoma between 1971 and 2010. We then excluded cases with multiple tumor-involved nodal basins, multiple primaries, <4 removed nodes, or local/ in-transit recurrence. Univariate and multivariate analyses assessed the prognostic significance of demographic and tumor-related variables, including basin site and number of excised nodes, with respect to rates of 5-year regional recurrence-free survival (RRFS) and 10-year melanoma-specific survival (MSS). **Results:** Of 2,748 patients, 785 with regional neck (N=152), axillary (N=387) or inguinal (N=246) metastasis were eligible for study. These patients underwent removal of 4-79 neck nodes (mean 28.8), 4-65 axillary nodes (mean 18.6), or 4-64 inguinal nodes (mean 16.4). Neck, axillary and inguinal regional recurrence rates were 11.8% (18/152), 6.5% (25/387), and 9.8% (24/246), respectively. By multivariate analysis, 5-year RRFS was significantly improved when 20 or more nodes were removed ($p=0.02$) in neck basins, when 10 or more nodes were removed in inguinal basins ($p=0.01$), or when nodes were not palpable in neck ($p=0.05$) or axillary basins ($p=0.02$). The most significant prognostic factor for 10-year MSS was regional recurrence in any of the three sites ($p<0.01$). **Conclusions:** Removal of at least 10 nodes from groin basins and at least 20 nodes from neck basins should minimize regional recurrence in patients with stage III cutaneous melanoma. Comparable recommendations for the axillary basin will likely require meta-analyses that incorporate extracapsular extension and genomic biomarkers.

**9065 General Poster Session (Board #269), Sat, 8:00 AM-11:45 AM**

**A comparison of cutaneous melanoma patients who recur following a negative sentinel lymph node biopsy to those with a positive sentinel lymph node biopsy.** *Presenting Author: Edward L Jones, University of Colorado, Aurora, CO*

**Background:** Sentinel lymph node biopsy (SLNB) for cutaneous melanoma yields powerful prognostic information. Patients with a negative SLNB who recur experience worse outcomes than those with a positive SLNB based upon subgroup analysis in the Multicenter Selective Lymphadenectomy Trial (MSLT-1). The PURPOSE of this study was to compare our patients who recur following a negative SLNB to those with a positive SLNB. **Methods:** Retrospective chart review of a prospectively created database of patients with cutaneous melanoma undergoing SLNB from February 1995 to January 2013. **Results:** Of 1017 patients who underwent SLNB, 170 (17%) recurred after a negative biopsy: 60 (35%) were local/in-transit recurrences, 33 (19%) regional and 73 (43%) distant at a median 27 months (range 15-50 months). One hundred and fifty-seven (15%) patients had a positive SLNB of which 131 (77%) underwent completion lymph node dissection (CLND). Fifty-six (36%) of those patients recurred a median 14 months later (range 8-30 months). The median length of follow-up for entire cohort was 43 months (range 1-170 months). Patients with recurrence after a negative SLNB were more likely to be male (64% vs. 50%, $p=0.02$) but age, Breslow depth, ulceration, mitotic activity and the use of adjuvant therapy were not statistically different. Twenty-nine (88%) of the 33 patients with regional recurrence after a negative SLNB underwent CLND. These patients had significantly more positive nodes in the CLND specimens than those undergoing CLND for a positive SLNB (69% vs. 22%, $p<0.001$). While disease-specific survival was not significantly different between patients with recurrence after a negative SLNB versus a positive SLNB at 5 years (56% vs.77%, $p=0.14$) this became significant at 10 years (28% vs. 68%, $p<0.001$). **Conclusions:** Patients with cutaneous melanoma who recur following a negative sentinel lymph node biopsy have worse survival when compared to those with a positive biopsy. These findings support the subgroup analysis of the MSLT-1 trial and suggest that patients with recurrence following a negative sentinel lymph node biopsy exhibit aggressive tumor biology.

**9066 General Poster Session (Board #270), Sat, 8:00 AM-11:45 AM**

**A randomized phase II study of ipilimumab (IPI) with carboplatin and paclitaxel (CP) in patients with unresectable stage III or IV metastatic melanoma (MM).** *Presenting Author: Rahima Jamal, Centre Hospitalier de l'Université de Montréal - Hopital Notre-Dame, Montreal, QC, Canada*

**Background:** MM has been one of the most treatment-resistant human malignancies. Recently, IPI, a fully human anti-CTLA4 monoclonal antibody has been widely approved for patients (pts) with MM on the basis of increased overall survival (OS). CP is one of few therapies available to pts with BRAF wild type MM that is progressing rapidly. We hypothesized that cytoreduction by CP might both provide time for IPI response, as well as expose immune cells to tumor antigens. In addition to safety and anti-tumor activity, immune biomarker studies were performed. **Methods:** Thirty pts with no prior treatment or one BRAF targeted regimen were randomized in a 1:2 ratio to either concurrent (arm A) or sequential (arm B) CP (AUC6 + 175mg/m$^2$ x 5) with IPI (3mg/kg x 4) given every 3 weeks either concurrently or delayed by one week. Tumor assessments were conducted at week 8, 16 and 24. **Results:** We enrolled 24 cutaneous, 2 mucosal, 3 ocular and 1 unknown primary melanoma. Median age was 55 years and 6 of 8 BRAF mutated pts previously received vemurafenib. Twenty-five pts (83%) received all 5 cycles of CP while 28 pts (93%) completed IPI induction. Two pts died prior to week 16 of disease progression, while 3 patients discontinued CP because of toxicity. Overall median follow-up was 24 weeks (8-24). Response rates (RR) and disease control rates (DCR) for 14 evaluable patients at 24 weeks were 21.4% and 42.9% by mWHO, and 35.7% and 64.3% by irRC, respectively. There were no treatment-related deaths on trial. Grade 3-4 AEs regardless of causality were seen in 63% of pts. CP-related Grade 3-4 AEs were found in 47% of pts in the form of hepatotoxity, electrolyte imbalances, myelosuppression and infections. Grade 3-4 anemia occurred in 3 pts while thrombocytopenia occurred in 2 pts. The rate of febrile neutropenia was 7% (2/30). Seventeen per cent (5/30) of patients received steroids for an immune-related (ir) AE: 2 pts with Grade 3 colitis, 2 pts with Grade 2 endocrinopathy, and 1 pt with Grade 2 rash. **Conclusions:** Safety results suggest manageable toxicity when CP is added to IPI, with most patients completing the full course of treatment. Updated ORR, DCR, 6 month OS, and immune biomarker studies will be presented. Clinical trial information: NCT01676649.

**9067 General Poster Session (Board #271), Sat, 8:00 AM-11:45 AM**

**Predictive importance of ulceration on the efficacy of adjuvant interferon-a (IFN): An individual patient data (IPD) meta-analysis of 15 randomized trials in more than 7,500 melanoma patients (pts).** *Presenting Author: Stefan Suciu, EORTC Headquarters, Brussels, Belgium*

**Background:** Many randomised trials have evaluated the role of adjuvant IFN in high-risk melanoma, some suggesting benefit and others not. To assess the evidence of IFN vs. no IFN, an IPD meta-analysis of these trials was performed. **Methods:** Standard IPD meta-analysis methods were used to assess event-free (EFS) and overall survival (OS), with odds ratios (OR) and confidence intervals (CI) calculated. Trials were divided by dose of IFN – high (10-20MU/m$^2$), Peg-IFN (3-6$\mu$g/Kg), intermediate (5-10MU flat), low (3MU flat) and very low (1MU). **Results:** IPD was provided for 11 of 15 reported trials of IFN vs. no IFN (for the other 4 trials published data were used). Over 7500 pts were included in the analysis, with over 4700 and 3800 events for EFS and OS. There was benefit for IFN for both EFS ($P$<0.00001) and OS ($P$=0.003) (Table). This translated into increased 5-year OS from 46.1% to 49.1%. There was no evidence of differences according to dose, duration of IFN, gender, Breslow thickness or disease stage, but ulceration status impacted the IFN benefit regarding EFS (interaction test: $P$=0.04) and OS ($P$=0.002) (Table). For the ulcerated melanoma, IFN increased the OS from 38.1% to 46.0%, at 5 yrs, and from 28.0% to 38.5%, at 10 yrs. **Conclusions:** This meta-analysis provides evidence that adjuvant IFN significantly reduces the risk of relapse and improves overall survival. This analysis does not identify the optimal dose or duration of IFN. OS benefit was confined to pts with ulcerated tumours. The biological basis of this action is incompletely defined, and being studied in the ongoing study (EORTC 18081 and ECOG-ACRIN Intergroup Trial E1609).

| | OR (95%CI* or 99%CI**) | |
|---|---|---|
| **Dose*** | **EFS** | **OS** |
| **High (N=1196)** | 0.83 (0.72-0.96) | 0.93 (0.80-1.08) |
| **Peg-IFN (N=1256)** | 0.87 (0.76-1.00) | 0.96 (0.82-1.11) |
| **Intermediate (N=2243)** | 0.84 (0.74-0.95) | 0.91 (0.79-1.04) |
| **Low (N=2732)** | 0.85 (0.77-0.94) | 0.86 (0.77-0.96) |
| **Very low (N=484)** | 0.99 (0.80-1.23) | 0.96 (0.76-1.21) |
| **Overall*** | 0.86 (0.81-0.91) | 0.90 (0.85-0.97) |
| **Ulceration**** | | |
| **Present (N=1443)** | 0.79 (0.66-0.94) | 0.77 (0.64-0.92) |
| **Absent (N=2322)** | 0.95 (0.82-1.10) | 1.02 (0.87-1.20) |
| **Unknown (N=2061)** | 0.88 (0.76-1.01) | 0.91 (0.78-1.06) |

**9069 General Poster Session (Board #273), Sat, 8:00 AM-11:45 AM**

**Detection of BRAF mutations in the plasma of melanoma patients as an early marker of treatment efficiency.** *Presenting Author: Marc G. Denis, Department of Biochemistry, Nantes University Hospital, Nantes, France*

**Background:** Mutant BRAF DNA can be detected in plasma of melanoma patients bearing a mutation in their tumor. Detection of these genetic alterations in circulating DNA has potential clinical applications. We investigated the relationship between mutant BRAF in plasma DNA and treatment response. **Methods:** DNA was extracted from plasma using the iPrep PureLink Virus Kit on an iPrep purification system (Invitrogen). BRAF mutations were detected using the Therascreen BRAF RGQ kit (Qiagen). **Results:** Seventeen patients (1 stage IIIC and 16 stage IV) with a mutated BRAF melanoma (V600E in all cases) were included. Pretreatment plasma samples were available in 10 of them, and the BRAF mutation was detected in 8 samples (80% sensitivity). Twelve patients were treated with a BRAF inhibitor, 4 with a combination of a BRAF inhibitor and a MEK inhibitor, and one patient was treated with chemotherapy (DTIC). After 3 months of melanoma treatment, the BRAF V600 mutation was detected in the plasma of 9 patients (9/17; 53,9%). The presence of mutant BRAF in plasma DNA was compared to the clinical response of patients. The BRAF mutation was present in the plasma of 6 out of the 7 patients who did not respond to treatment. In contrast, mutant BRAF DNA was absent from plasma in 7 out of the 10 patients with partial response to treatment (Fisher's exact test : p = 0.04977). Mutant BRAF in circulating DNA was not associated with the number of metastatic sites at the same time (mean 2.625 in patients with mutant BRAF, and 2.22 in patients without mutant BRAF; p = 0.4266, Wilcoxon's test). **Conclusions:** The sensitive detection of mutant BRAF in plasma would be useful for predicting treatment response to targeted therapy. Supported in part by a grant from Roche.

**9070 General Poster Session (Board #274), Sat, 8:00 AM-11:45 AM**

**RAGE ligand S100A8/A9 as a novel prognostic biomarker for high-risk melanoma patients.** *Presenting Author: Christoffer Gebhardt, German Cancer Research Center (DKFZ), Heidelberg, and University Medical Center Mannheim, Ruprecht-Karl University of Heidelberg, Mannheim, Germany*

**Background:** We have recently demonstrated that the receptor for advanced glycation end-products (RAGE) is a central driver of tumorigenesis by sustaining a chronic inflammatory tumor microenvironment. This study aimed at identifying novel prognostic biomarkers for melanoma by a hypothesis-driven approach linking RAGE signaling-related serum markers with clinical outcome of melanoma patients. **Methods:** Plasma concentrations of the soluble form of RAGE (sRAGE) were analyzed in 173 plasma samples of stage I-IV melanoma patients (cohort 1). Serum concentration of RAGE-related markers sRAGE, S100B, S100A8/A9, and HMGB1 were measured in an independent second cohort of 240 metastasized stage III-IV patients and compared to established prognostic markers including sub-stage and lactate dehydrogenase (LDH). All analyses were performed by enzyme-linked immunosorbent assays. **Results:** sRAGE was strongly associated with overall survival (OS) and progression-free survival (PFS) in cohort 1. A detailed analysis of different RAGE-related serum markers was thereafter performed in cohort 2. Analysis of OS of stage III patients showed that elevated S100A8/A9 independently increased mortal risk in addition to sub-stage IIIB or sub-stage IIIC as compared to sub-stage IIIA. Increased S100B, S100A8/A9, and HMGB1 were independently indicating worse PFS in stage III/IV patients. The analysis of S100A8/A9 and S100B was the best combination to predict PFS and improved the sensitivity to identify patients with later progression from 34.2% (S100B) to 58.2% (S100A8/A9 + S100B). **Conclusions:** The RAGE ligand S100A8/A9 is a powerful independent prognostic marker for OS of stage III patients and contributes substantially to standard biomarker S100B for the identification of patients with high risk for progression.

**9071 General Poster Session (Board #275), Sat, 8:00 AM-11:45 AM**

**Adjuvant therapy with pegylated interferon alfa-2a (PEG-IFN) versus low-dose interferon alfa-2a (IFN) in patients with malignant melanoma in stages IIa(T3a): IIIb (AJCC 2002)—Decog-trial.** *Presenting Author: Thomas K. Eigentler, Department of Dermatology, University of Tübingen, Tübingen, Germany*

**Background:** Adjuvant treatment with IFN improved disease free survival (DFS) and showed a trend for improving overall survival (OS). PEG-IFN has a prolonged half life time and is just given once weekly. This trial was designed to examine if PEG-IFN is superior to IFN in regard to distant metastasis free survival (DMFS), DFS and OS. **Methods:** In this multicenter, open-label, prospective randomized phase III trial, patients (pts) with resected cutaneous melanoma stage IIA(T3a)-IIIB (AJCC 2002) were randomized to receive IFN (3 MU subcutaneously [sc] 3x/week; 24 months) or to PEG-IFN (180 mcg sc 1x/week; 24 months). Randomization was stratified for tumor stage, number of metastatic nodes, patient's age and previous interferon treatment. Primary endpoint was DMFS, secondary endpoints were OS, DFS, quality of life and tolerability. Sample size (880 pts) was calculated on an expected difference of 55% *vs* 45% in the 5 years DMFS rate and assuming 80% power (2-sided, significance level 5%). Non-parametric survival models using log-rank tests and Cox regression models were performed on the ITT population. **Results:** Of 909 pts enrolled, 907 (451 PEG, 458 IFN) were eligible for evaluation after a median follow-up of 5.0 years. Neither DMFS (PEG-IFN 65.1% *vs* IFN 70.2%, p=0.18; HR, 1.16; 95% CI, 0.92-1.5) nor OS (74.2% *vs* 74.8%, p=0.13; HR, 1.05; 95% CI, 0.81-1.37) nor DFS (57.9% *vs* 60.8%, p=0.49; HR, 1.06; 95% CI, 0.86 to 1.31) showed significant differences. Subgroup analyses of PEG-IFN *vs* IFN in pts +/- ulcerated primaries and of different tumor stages did not find differences in DMFS, OS or DFS. 118 pts (26.1%) in the PEG-IFN and 61 pts (13.3%) in the IFN population did not receive the scheduled full dose and length of treatment due to adverse events ($p<0.001$). Leucopenia (CTC grade 2+) and elevation of liver enzymes (grade 2+) were more frequent in the PEG-IFN arm (56% *vs* 23.5% LCP; 19.1% *vs* 9.4 % AST; 33.0% *vs* 16.5% ALT). **Conclusions:** PEG-IFN did not improve the outcome parameters over conventional IFN. CTC grade 2+ toxicity was significantly more pronounced and a higher percentage of pts under PEG-IFN discontinued treatment prematurely. Clinical trial information: NCT00204529.

**9072 General Poster Session (Board #276), Sat, 8:00 AM-11:45 AM**

**Preclinical testing supports combined BET and BRAF inhibition as a promising therapeutic strategy for melanoma.** *Presenting Author: Luca Paoluzzi, NYU Cancer Institute, NYU Langone Medical Center, New York, NY*

**Background:** Manipulation of key epigenetic regulators is emerging as a new therapeutic strategy in cancer. Our group recently reported a role for BRD4, a Bromodomain-containing protein and BET family member, in melanoma maintenance (Segura MF et al, Cancer Research 2013). BET inhibition impaired melanoma cell proliferation in vitro and tumor growth and metastatic behavior in vivo. Here we investigated the effect of combining the BET inhibitor JQ-1 with the B-RAF inhibitor Vemurafenib in in vitro and in vivo models of B-RAF mutated melanoma. **Methods:** We performed cytotoxicity and apoptosis assays, and a xenograft mouse model to explore the in vitro and in vivoactivity of JQ-1 alone or in combination with Vemurafenib in melanoma. We conducted RNA sequencing of xenograft tumors, quantitative RT-PCR and immunoblottings to investigate the mechanisms underlying the effects of combined BET and B-RAF inhibition. **Results:** In vitro, the BET-inhibitor JQ-1 exhibited time and concentration-dependent cytotoxicity against a panel of B-RAF mutant melanoma cell lines. When combined with JQ-1, Vemurafenib showed synergism and significant apoptosis in vitro. In a xenograft mouse model of melanoma, the addition of JQ-1 to Vemurafenib enhanced the ability of either drug alone to suppress tumor growth and significantly improved survival. Tumors treated with BET and B-RAF inhibitors had reduced proliferative index, as revealed by Ki67 immunostaining. Pathway analysis of RNA sequencing data of mouse tumor tissues showed a significant impact on transcriptional programs controlling cell growth, proliferation, angiogenesis, cell-cycle regulation and differentiation. **Conclusions:** Collectively, our data provide a rationale for combined BET and B-raf inhibition as a novel strategy for the treatment of melanoma.

**9073 General Poster Session (Board #277), Sat, 8:00 AM-11:45 AM**

**The Memorial Sloan Kettering Cancer Center (MSKCC) experience of systemic therapy in mucosal melanoma.** *Presenting Author: Christiana Bitas, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Mucosal melanoma (MM) is a molecular and clinical subset of melanoma distinct from cutaneous melanoma (CM). The activity of systemic therapy (tx) in MM has not been rigorously evaluated. We performed a retrospective, single center analysis of MM patients (pts) treated with systemic tx. **Methods:** Using institutional databases, we identified pts with MM who were 1) treated at MSKCC between 1998-2012; 2) developed unresectable or metastatic disease (dz); 3) received ≥1 non-adjuvant systemic tx; 4) had scans available for blinded central radiology review using RECIST 1.1. Pt demographics and clinical outcomes were extracted. **Results:** 61 pts met inclusion criteria. Median age at diagnosis 64 years (range, 35-84); 71% female; primary site: 28 anorectal, 19 vulvovaginal, 13 head/neck, 1 gallbladder. Mutation (mut) status: 8/35 KIT mut (7 exon 11; 1 exon 13); 3/33 BRAF mut (all non V600mut); 3/33 NRAS mut. At time of 1st tx, 55 had metastatic dz (10 M1a, 6 M1b, 39 M1c) and 6 had locally advanced dz. Pts received 106 1st or 2nd-line systemic tx: 81 cytotoxic (24 single-agent alkylators [eg. TMZ, DTIC]; 47 alkylator-based combinations [eg. Cisplatin/Vinblastine/TMZ]; 10 other combinations); 11 immunotherapy [7 ipilimumab, 2 high-dose IL-2, 2 other]; 9 targeted [8 KIT inhibitors, 1 BRAF inhibitor]; 4 biochemotherapy; 1 other investigational tx. Overall response rate (RR) rate to 1st and 2nd-line tx was 16% and 13%, respectively, with no complete responses. 24-week (wk) dz control rate with 1st and 2nd-line tx was 20%, and 9%, respectively. RR in either 1st or 2nd-line to single-agent and combination alkylator tx was 8% (2/24), and 15% (7/47), respectively (p=0.71). RR to targeted tx and immunotherapy was 33% (3/9), and 9% (1/11), respectively. Median time to treatment failure (earlier of date of progression or change in therapy) was 11 wks (95% confidence interval [CI] 8-14 wks) for both 1st and 2nd line tx. Median overall survival (OS) from initiation of 1st-line tx was 11 mo (95% CI 8-13 mo). **Conclusions:** The efficacy of systemic tx in MM is modest and appears similar to that seen in CM. Clinical outcomes for this pt population are poor. Further investigation into the biology and treatment of MM is needed.

**9074 General Poster Session (Board #278), Sat, 8:00 AM-11:45 AM**

**Assessment of overall survival from time of metastastasis in mucosal, uveal, and cutaneous melanoma.** *Presenting Author: Michael Andrew Postow, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Rarer subtypes of melanoma such as mucosal melanoma (MM) and uveal melanoma (UM) are thought to be associated with worse prognoses than cutaneous melanoma (CM). Comparison of OS in pts with MM, UM and CM after diagnosis of stage IV disease, however, has not been rigorously evaluated. **Methods:** We conducted a single-center, retrospective analysis of 2920 pts diagnosed with stage IV melanoma between 2000 and 2013 identified from a prospectively maintained database. Melanoma subtype, date of diagnosis of stage IV disease and date of death were extracted, as were established prognostic variables including age at diagnosis of metastasis, gender and M-stage. **Results:** MM (n=237): median (med) age 66 years (yrs; range 26-91); 65% female; M1a/b/c - 8%/21%/71%. UM (n=286): med age 63 yrs (range 16-86); 46% female; M1a/b/c - 5%/8%/87%. CM (n=2397): med age 62 yrs (range 3-97); 34% female; M1a/b/c - 14%/31%/55%. Differences in age, gender and M-stage were significantly different between groups (p=0.002, $p<0.0001$ and $p<0.0001$, respectively). With a median followup of 46.6 months (mos) and 2192 deaths, the median OS for MM, UM and CM was 9.0 mos (range 0.4-108.1), 13.4 mos (range 0.4-144.0), and 11.7 mos (range 0.1-139.8), respectively. Pts with UM and CM had similar OS (HR: 1.02, p=0.82), but pts with MM had worse OS compared to pts with UM (HR: 1.41, $p<0.001$) and CM (HR: 1.44, $p<0.001$). Pts diagnosed with stage IV melanoma between 2006-2013 (n=1148) had a better OS compared to pts diagnosed between 2000-2005 (n=1773; 13.59 vs. 9.77 mos; $p < 0.001$). In a multivariate model taking into account year of stage IV diagnosis (2000-2005 vs. 2006-2013), age, gender, and M-stage, pts with MM had inferior OS compared to UM and CM. **Conclusions:** MM is an independent poor prognostic factor in pts with stage IV melanoma. Despite distinct tumor biology, similar survivals were observed in stage IV UM and CM. Improved OS in pts treated between 2006-2013 may reflect the efficacy of newer therapies. Stratification by melanoma subtype is warranted in trials including MM.

**9075^ General Poster Session (Board #279), Sat, 8:00 AM-11:45 AM**

**Phase II study of vemurafenib in patients with locally advanced, unresectable stage IIIc or metastatic melanoma and activating exon 15 *BRAF* mutations other than V600E.** *Presenting Author: Sigrun Hallmeyer, Oncology Specialists, SC, Niles, IL*

**Background:** Approximately 50% of metastatic melanoma are activating *BRAF* mutation-positive, most commonly in codon V600. Vemurafenib (VEM), an inhibitor of oncogenic BRAF kinase, has been shown to improve progression-free survival (PFS) and overall survival (OS) in pts with advanced V600E-mutated melanoma (Chapman et al, 2011; NEJM). An open-label phase II trial (NCT01586195) is being conducted to determine the activity and safety of VEM in previously treated or untreated stage IIIC or IV melanoma pts with measurable disease and an activating, non-V600E *BRAF* mutation at exon 15 detected by centralized DNA sequencing. **Methods:** Eligible pts received oral VEM (960 mg bid) until disease progression, unmanageable toxicity, pt request for discontinuation, or other protocol-specified criteria. Tumor responses were evaluated per RECIST v1.1. The primary endpoint was investigator-assessed objective response rate. Time to response, duration of response, PFS and OS, 6- and 12-month survival rates, and safety were additional endpoints. **Results:** As of October 2013, 10 US sites had enrolled 29 pts: 12 with V600K (cohort 1) and 17 with non-V600K mutations (cohort 2 [7 V600R, 3 L597S, 7 others]). Median (range) age was 61 (33-88) years, 86% were male, 45% were stage M1c and 17% unresectable stage IIIC, 28% had brain metastases, and 10% had ECOG PS 2 (the remainder were ECOG PS 0-1). 7% of pts were treatment naive. In pts who had prior therapy for advanced disease, the median (range) number of therapies was 2 (1-6). At this interim analysis, 12/29 pts (41%) had an unconfirmed response (5 V600K, 3 V600R, 4 other). Confirmed responses were observed in 3 pts (all PRs; V600K, V600R, and D594G); there were no CRs. Overall toxicity profile is consistent with the reported experience in melanoma, with the following AEs reported most frequently: fatigue (52%), rash (48%), and arthralgia (38%). 11 pts had ≥1 grade 3-5 AEs, irrespective of causality. We plan to present an updated data cut at ASCO. **Conclusions:** Preliminary results show objective responses in this population of advanced melanoma pts with rarer non-V600E *BRAF* mutations; however, additional follow-up is required. Clinical trial information: NCT01586195.

**9076 General Poster Session (Board #280), Sat, 8:00 AM-11:45 AM**

**Outcome with stereotactic radiosurgery (SRS) and ipilimumab (Ipi) for malignant melanoma brain metastases (mets).** *Presenting Author: Sana Shoukat, Internal Medicine, Emory University School of Medicine, Atlanta, GA*

**Background:** SRS with Ipi for melanoma brain mets has been explored for overall survival (OS). We present the first retrospective analysis to determine if this combination is safe and improves OS, while accounting for lactate dehydrogenase (LDH). **Methods:** Patients with melanoma brain mets who underwent SRS between 1998-2012 (n=176) were compared with those who additionally received Ipi (n=38). The primary endpoint was median OS from time of SRS, calculated using Kaplan-Meier method. Cox proportional hazard model was performed for univariate and multivariable survival analysis. The secondary endpoints were local control (LC), anywhere intra-cranial failure, repeat SRS, and toxicity. Additionally, Propensity Score (PS) method was used to match treatment groups based on patient and disease characteristics, and comparison was made among matched sample. **Results:** Median OS for the cohort was 9.0 months and median follow up was 41.2 months. Patients in the Ipi group had median OS of 28.0 vs. 7.0 months in the non-Ipi group ($p < 0.001$). No difference was noted in LC or anywhere intracranial failures. There was no increased toxicity (radionecrosis, hemorrhage, patient reported memory deficits), or need for repeated SRS in the Ipi group. Multivariate Analysis (Table 1) showed that Ipi independently predicted for improved OS even when taking into account LDH and ECOG performance status. After PS matching, the groups did not differ significantly and multivariable analysis remained unchanged {HR = 2.56 (1.29 – 5.05) ($p = 0.007$)}. **Conclusions:** Use of SRS with Ipi appears to be safe and associated with an increase in OS in patients with melanoma brain mets; this combination should be further investigated.

**Univariate and multivariate OS.**

| | | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|
| | | HR (95%CI) | p-value | HR (95%CI) | p - value |
| KPS | > 80 | ref | <.001 | | |
| | < = 80, > 60 | 1.78 (1.23-2.55) | | | |
| | < = 60 | 2.55 (1.42 -4.59) | | | |
| ECOG | 0 | 0.42 (0.28-0.62) | <.001 | 0.50 (0.32-0.80) | 0.004 |
| | 1+ | ref | | ref | |
| DS-GPA | 4 | ref | 0.013 | | |
| | 3 | 1.19 (0.77-1.84) | | | |
| | 2 | 1.75 (1.09 – 2.80) | | | |
| | 1 | 2.17 (1.25 – 3.76) | | | |
| # of brain mets | 1 | 0.57 (0.37 – 0.86) | 0.015 | | |
| | 2 | 0.55 (0.33 -0.91) | | | |
| | 3+ | ref | | | |
| Ipi | No | 3.21 (1.84 – 5.59) | <.001 | 2.95 (1.65-5.29) | <0.001 |
| | Yes | ref | | ref | |
| LDH | < = 250 | 0.48 (0.30 – 0.79) | 0.003 | 0.52 (0.32-0.86) | 0.010 |
| | > 250 | ref | | ref | |

**9077 General Poster Session (Board #281), Sat, 8:00 AM-11:45 AM**

**Lesion-specific patterns of response and progression with anti-PD-1 treatment in metastatic melanoma (MM).** *Presenting Author: Megan Kate Lyle, Melanoma Institute Australia and University of Sydney, North Sydney, Australia*

**Background:** Anti-PD-1 therapy has demonstrated activity in MM but current data may not fully reflect patterns of response and relapse as discerned by comprehensive lesion-specific analysis. **Methods:** Bidimensional measurements of every metastasis (met) ≥5mm (≥15mm short axis for lymph nodes [LN]) in MM pts enrolled in the MK3475-001 phase 1 trial at a single center were obtained on CT scan at baseline, 12 wks and thereafter. Response of each individual met was determined by change in product of longest perpendicular diameters (POD) and classified as complete (CR, disappearance or <10mm short axis for LN), partial (PR, ≥50% reduction in POD), stable (SD, neither CR/PR/PD) or progressive (PD, ≥25% increase in POD and ≥5mm in 1 axis). Overall pt response was investigator determined using standard immune related response criteria (irRC). **Results:** 27 evaluable pts with med. follow up of 54 wks had a total of 442 discrete mets at baseline (med. 10/pt; range 2-68/pt; med. POD 129mm$^2$). 13/27 (48%) pts had an irRC objective response (OR), 11 (85%) by first scan. Med. time to best response in pts with OR was 24 wks. Although only 1/27 pts had CR (3.7%), 228/442 (52%) individual mets underwent CR and 81% of pts (22/27) had ≥1 CR met at first scan. CR mets were smaller than non-CR [med. POD 80 vs 246mm$^2$($p<0.05$)] but 92/244 mets (38%) ≥100mm$^2$ reached CR. CR rate was highest in lung vs other sites combined ($p<0.05$) (Table). Only 1 CR met subsequently progressed. Of 12 (44%) pts who progressed only 1 had prior OR. 10 (83%) of these pts PD in new and existing mets simultaneously. No site of PD predominated; only 1 pt (8%) PD in brain. 98/442 baseline mets (22%) progressed and most (74%) had PD as best response. Of 80 new or growing mets at first scan, only 4 (5%) subsequently had OR. **Conclusions:** Response to anti-PD1 therapy is rare in mets that are new or growing at first scan. CR in individual mets is common, sustained, and influenced by site and size. These results have implications for the biology of PD-1 inhibition, resistance, biomarker development and patient selection.

| Site of met | CR | PR/SD/PD |
|---|---|---|
| Lung | 141 (64%) | 79 (36%) |
| Liver | 20 (54%) | 17 (46%) |
| Subcut | 26 (42%) | 36 (58%) |
| LN | 14 (41%) | 20 (59%) |
| Soft tissue | 18 (32%) | 39 (68%) |
| Other | 9 (28%) | 23 (72%) |
| Total | 228 (52%) | 214 (48%) |

**9078 General Poster Session (Board #282), Sat, 8:00 AM-11:45 AM**

**Safety and clinical activity of combining systemic ipilimumab with isolated limb infusion in patients with in-transit melanoma.** *Presenting Author: Charlotte Eielson Ariyan, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Isolated limb infusion(ILI) for melanoma results in a limb response(CR + PR) of 50%, with 11% of patients progression free(PFS) at one year. Ipilimumab(10mg/kg) for M0 melanoma has an overall response rate of 8.3% (95% CI, 0.2-38.5). This phase II trial evaluated the safety and efficacy of ILI with melphalan and dactinomycin followed by systemic ipilimumab(IPI). **Methods:** Melanoma patients with regional disease (stage IIIb/c ) alone or in combination with distant disease (Stage IV) underwent ILI (melphalan + dactinomycin,7.5mg and 75 mcg/kg/limb volume). Within a median of 12 days (range 7-15) after limb infusion, patients received systemic IPI(10mg/kg) q3w x 4 doses. Patients received maintenance IPI (q3months x 2 years) if there was disease control and no limiting toxicity. The primary endpoint was PFS at one year, secondary endpoints were limb response and toxicity. **Results:** As of January 2014, 18 patients were enrolled; 88% of patients were stage IIIB/C and 12% were Stage IV. Weiderbink grade 2--3 limb toxicity was seen in all patients; no patient required a fasciotomy or amputation. Related adverse events(rAE) for sequential therapy occurred in 78% of patients (grade1-3). rAE included colitis (n=8, grade 2-3), hypophysitis (n=5, grade 2), and rash (n=6, grade 1-2); all were medically managed. At 3 months, 89% of patients had a limb response, 65% of which were complete (CR) and 24% were partial responses(PR). One patient had SD, and one patient had POD. With a median follow-up of 18 months, OS is 78%, 2 patients died of melanoma, one died of a pulmonary embolus 60 days after ILI, and one died of complications of pneumonia 6 months after ILI. PFS at one year is 57%. Of the 11 patients with a CR in the limb, 1 subsequently progressed in the limb and 1 progressed outside of the limb. The ALC and eosinophils increased in all patients (ALC mean of .99 after ILI to 1.8 after IPI, eosinphils mean 1.5 to 10.3 during therapy with IPI, $p<0.05$). **Conclusions:** Combination treatment with ILI and Ipilimumab is safe , with no limb threatening toxicity. The response rates and progression free survival are encouraging and support further studies of limb infusion in combination with immune checkpoint blockade. Clinical trial information: NCT01323517.

**9079 General Poster Session (Board #283), Sat, 8:00 AM-11:45 AM**

**Treatment with tumor-infiltrating lymphocytes (TIL) in metastatic melanoma and clinical benefit regardless of site of origin, mutation status, or prior checkpoint blockade.** *Presenting Author: Isabella Claudia Glitza, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** In this report we describe the association of specific patient attributes, such as mutation status, prior treatment with checkpoint blockade, and location of primary tumor with treatment response to therapy TIL therapy. **Methods:** Stage IIIc-IV patients (pts) were enrolled and treated in an ongoing non-randomized phase II TIL trial at MD Anderson Cancer Center. Cox proportional hazards regression (overall survival (OS), progression-free survival (PFS)) and logistic regression (response) were used to assess the association between outcomes and covariates of interest. **Results:** 56 (19 female, 37 male) pts were enrolled. Most common site of origin was cutaneous (N=45), while a subgroup of pts had melanoma derived of acral (N=7) or mucosal origin (N=3). Staging (69% MIc), mutational status (BRAF V600, NRAS mutations) or the presence of brain metastasis did not significantly impact the odds of response or survival (OS, PFS). Overall response rate was 44% (2 pts CR, 22 pts PR) in 54 pts available for analysis, while stable disease was observed in 20 pts. 22 pts received prior checkpoint blockade with ipilimumab and/or anti-PD1. Among subgroups of pts, 30% of the acral/mucosal melanoma pts, 30% of the pts with previous checkpoint blockade and 53% of patients with BRAF V600 mutations responded. Higher numbers of CD8+ T-cells infused was significantly associated with greater likelihood of response (p=0.03) and longer PFS (p=0.01). PFS was significantly worse (p=0.01) after prior checkpoint blockade (1-year PFS: 14% versus 27%) and with higher pre-treatment LDH level (p= <0.001) and ECOG PS score (p=0.002). OS was not affected by site of origin (1-year OS: 68% acral/mucosal), BRAF V600 status (62%), or prior checkpoint blockade (61%). Higher ECOG PS score (p=<0.001) and LDH level (p=<0.001) were associated with greater risk of death. **Conclusions:** Patients with BRAF V600 mutations and with mucosal or acral origin do benefit from TIL therapy. Despite shorter PFS**,** patients that had previously failed checkpoint blockade therapy still experience benefit from TIL therapy, arguing its use in this highly refractory population.

**9080 General Poster Session (Board #284), Sat, 8:00 AM-11:45 AM**

**The impact of clinical response to anti-CTLA4 treatment on overall survival (OS) in metastatic melanoma (MM).** *Presenting Author: Xiaolan Feng, Tom Baker Cancer Centre, Calgary, AB, Canada*

**Background:** It is well known that response to anti-cytotoxic T lymphocyte antigen 4 (anti-CTLA4) treatment can be durable in patients with MM. But it is not known whether clinical response to induction anti-CTLA4 treatment would translate into an OS benefit. Furthermore, predictors of response to anti-CTLA4 agents are not well-established. **Methods:** We performed a retrospective analysis on one hundred patients treated with anti-CTLA4 agents from 2006-2013 in two tertiary cancer centers in Alberta, Canada. Clinical and tumor characteristics, treatment response, toxicity, and survival data were collected through chart review. Clinicians evaluated response based on immune related response criteria. We performed Kaplan-Meier survival analysis, log-rank test and cox proportional hazards model to compare variable groups and univariable analysis using logistic regression to look for factors associated with clinical response to anti-CTLA4 agents. All statistical analyses were carried out using SAS software. **Results:** Striking differences in median OS (mOS) were observed in responders, defined as complete response (CR) plus partial response (PR), and non-responders defined as stable disease (SD) plus progressive disease (PD) (not reached; greater than 36.1 versus 6.9 months, 95% confidence interval (CI) 3.6-10.9, p<0.0001, respectively). A 9 fold difference in mOS was seen between patients with disease control (CR+PR+SD) and those with PD on induction treatment: 36.1 months (95%CI: 22.9-51.4) versus 4.0 months (95%CI: 3-6.7), respectively (p <0.0001). Only host-tumor immunological parameters were associated with a response to anti-CTLA4 treatment. Brisk, as opposed to non-brisk, tumor infiltrating lymphocytes in the primary tumor (p=0.003) and immune mediated side effects (p=0.048) were associated with response in univariable analysis. **Conclusions:** Our retrospective study, although limited by small population size, reveals that response to induction anti-CTLA4 agents is a dominant predictor for survival. Host-tumor immunological parameters may be important determinants for response to anti-CTLA4 agents, although these need to be prospectively validated.

**9081 General Poster Session (Board #285), Sat, 8:00 AM-11:45 AM**

**Vismodegib for advanced basal cell carcinoma: Duration of response after vismodegib discontinuation and response to vismodegib retreatment upon disease progression.** *Presenting Author: Aleksandar Sekulic, Mayo Clinic, Scottsdale, AZ*

**Background:** Vismodegib (VISMO) (Erivedge) is a first-in-class Hedgehog pathway inhibitor (HPI) approved for advanced basal cell carcinoma (aBCC). In the ERIVANCE trial, VISMO-treated patients (pts) demonstrated objective response rates (ORRs) by independent review of 30% in metastatic BCC (mBCC; n=33) and 43% in locally advanced BCC (laBCC; n=63). ORRs by investigator (INV) review were 45% (mBCC) and 60% (laBCC). Treatment on VISMO may be prolonged, and a number of pts discontinued treatment prior to progression on therapy. Here we provide results from a survey designed to assess durability of response in laBCC pts from ERIVANCE who discontinued VISMO while experiencing a response or stable disease (SD). We also determined whether they responded to retreatment with VISMO. **Methods:** As of May 28, 2012, we identified 13 pts who did not have progressive disease (PD) at the time of study discontinuation and were still alive and available for follow-up.In Oct 2012, a survey was sent to INVs to determine pt outcome (disease status and additional treatments) based on the most recent pt assessment. **Results:** Of the 13 pts identified, 11 had stopped VISMO with an INV assessment of response; 2 had SD. Reasons for discontinuation were pt decision (n=7), adverse event (n=4), and physician decision (n=2).The INV or the referring dermatologist assessed 12 pts within ≤7 months of Oct 2012; 1 pt visited a primary care physician in January 2009. 6 of 13 pts remain progression free. For the other 7 pts with PD, duration of treatment-free interval ranged from 89 to ~725 days. 5 pts were treated with excision and/or Mohs surgery and 2 were retreated with VISMO. Best responses in the 2 pts retreated with VISMO were SD and unconfirmed partial response. Overall, 8 of 13 pts did not have PD for >1 year after discontinuation of VISMO. **Conclusions:** VISMO discontinuation after achieving tumor stabilization did not lead to rapid tumor recurrence; pts may maintain response for >1 year. Among pts who experience PD after discontinuation, additional treatment (Mohs or surgery) may be possible. Pts who discontinue VISMO prior to disease progression may benefit from retreatment upon progression. Clinical trial information: NCT00833417.

**9082 General Poster Session (Board #286), Sat, 8:00 AM-11:45 AM**

**Quantitative assessment of melanoma spread in sentinel and non-sentinel lymph nodes and survival.** *Presenting Author: Anja Ulmer, Department of Dermatology, University of Tübingen, Tübingen, Germany*

**Background:** We have recently shown that quantification of cancer dissemination from melanoma to sentinel nodes is feasible and can be combined with other characteristics of the primary tumor to improve outcome prediction. Here we asked whether quantitative assessment of cancer spread to non-sentinel nodes could further improve outcome prediction. **Methods:** The study includes 128 melanoma patients with microscopic positive sentinel nodes who underwent complete lymph node dissection at the University of Tübingen. We analyzed 267 sentinel nodes and 1129 non-sentinel nodes from these patients by pathology and by quantitative immunocytology. For immunocytology half of the node was disaggregated mechanically, single cell suspensions were dispensed onto slides, stained with the melanoma specific antibody gp100. For each node we recorded the disseminated cancer cell (DCC) density, defined as the number of gp100 positive cells per million lymph node cells examined. **Results:** Quantitative immunocytology showed melanoma spread in non-sentinel nodes in 101 of 128 patients (79%), pathology was positive in 23 of 128 patients (18%). At a median follow-up of 67 months (range 3 to 136 months) 45 patients (35%) had died from melanoma. DCC densities in the sentinel node predicted outcome by univariable and multivariable analyses. Additional quantitative assessment of DCC densities in non-sentinel nodes did not significantly improve outcome prediction. A model based on DCC density in the sentinel node and thickness of melanoma predicted outcome even more precisely than a model based on the current AJCC staging system that includes information about the total number of histopathologically positive nodes. **Conclusions:** Quantitative reporting of the sentinel node status allows accurate prediction of melanoma outcome without knowledge of the status of non-sentinel nodes. Routine measurement of DCC densities in sentinel nodes may improve patient stratification for clinical trials and facilitate treatment decisions at the time of sentinel node biopsy when the complete nodal status is unknown.

**9083 General Poster Session (Board #287), Sat, 8:00 AM-11:45 AM**

**On-demand Gamma Knife combined with BRAF inhibitors for the treatment of melanoma brain metastases.** *Presenting Author: Caroline Gaudy-Marqueste, Dermatology and skin cancers Department, UMR911 CRO2 Hôpital Timone, Aix Marseille University, Marseille, France*

**Background:** Both Gamma-Knife radiosurgery (GKRS) and BRAF-inhibitors (BRAF-I) have been shown to be useful in melanoma patients with brain metastases (BM), thus suggesting that it could be interesting to combine their respective advantages. However cases of radiosensitization following conventional radiation therapy in BRAF-I treated patients have raised serious concerns about the real feasibility and risk/benefit ratio of this combination. **Methods:** Blind review by 2 independent observers of brain MRI follow-up pictures and survival assessment in all patients who had been treated by GKRS and BRAF-I at a single institution. **Results:** Among53 GKRS performed in 30 patients who ever received BRAF-I and GKRS, 33 GKRS were performed in 24 patients while under BRAF-I treatment, from which only 4 with an interruption of BRAF-I. The 20 other GKRS were performed in 15 patients (including 9 of the 24) before initiation of BRAF-I treatment. Out of the 263 BM treated, only 3 edemas and 3 hemorrhages were detected within 2 months after GKRS and 4 edemas and 7 hemorrhages were detected later. No case of BM radiation necrosis and no scalp radiation dermatitis occurred. Neither the MRI features nor the incidence of the rare adverse events were deemed unexpected in such a population of melanoma BM. Median survival from first GKRS and first dose of BRAF-I was 24.7, and 48.8 weeks, respectively. **Conclusions:** This series does not show immediate radiotoxicity nor radiation-recall, in melanoma patients with BRAF-I whose BM are treated by GKRS. Interrupting BRAF-I for stereotactic radiosurgery of BM seems useless, although it is still advised for other radiation therapies. Overall very favorable survival figures suggest to test the potential benefit of combining stereotactic radiosurgery and BRAF-I.

**9084 General Poster Session (Board #288), Sat, 8:00 AM-11:45 AM**

**Polymorphisms in the apoptosis pathway and prognosis in cutaneous melanoma.** *Presenting Author: Cristiane Oliveira, Department of Internal Medicine, Faculty of Medical Sciences, University of Campinas, Campinas, Brazil*

**Background:** Cutaneous melanoma (CM) is notorious for its poor prognosis and resistance to conventional chemotherapy. Genes involved in the apoptosis pathway, such as *P53*, (tumor suppressor gene), *MDM2* (p53 inhibitor), *BAX* (proapoptotic) and *BCL2* (anti-apoptotic) are important for survival and tumor growth. The polymorphisms *P53* Arg72Pro, *MDM2* T309G, *BAX* G(-248)A and *BCL2* C(-938)A alter the expression of the respective encoded proteins. The aim of this study was to evaluate whether these polymorphisms are associated with overall survival (OS) and relapse free survival (RFS) of CM patients. **Methods:** Our analysis included 185 consecutive CM patients at diagnosis seen at our University Hospital from December 1989 to November 2012. Genomic DNA from peripheral blood of patients was analyzed by polymerase chain reaction followed by enzymatic digestion for discrimination of pertinent genotypes. OS and RFS were calculated using the Kaplan-Meier estimate probabilities, and differences between survival curves were analysed by the log-rank test. OS was calculated from date of first diagnosis until the date of death or last follow-up. RFS was defined as the time to beginning of treatment until the date of the first relapse. **Results:** The median period of observation of patients in study were 61 months (range: 3-283). We observed at 120 months of segment, that the OS in CM patients with the *BAX* GA+AA was higher than in those with the GG genotypes (100% *versus* 79%, $P=0.01$). The OS were also higher with in patients with *BAX* GA+AA plus *BCL2* CC+CA combined genotype than in those with *BAX* GG plus *BCL2* AA (100% *versus* 76.7%, $P=0.02$) and *BAX* GA+AA plus *MDM2* TT+TG than *BAX* GG plus *MDM2* GG (100% *versus* 58.3%, $P=0.006$). No difference in RFS was seen in patients with the distinct genotypes of the above referred genes. **Conclusions:** The data suggest, for the first time, that polymorphism *BAX* gene may independent or jointly with *BCL2* and *MDM2* polymorphisms, modulate OS outcome of CM patients. Additional studies will provide some promising guidance for clinical management and tailored or personalized therapeutics in treating for CM.

**9085 General Poster Session (Board #289), Sat, 8:00 AM-11:45 AM**

**Correlation of tumor-derived circulating cell free DNA (cfDNA) measured by digital PCR (DigPCR) with tumor burden measured radiographically in patients (pts) with $BRAF^{V600E}$ mutated melanoma (mel) treated with RAF inhibitor (RAFi) and/or ipilimumab (Ipi).** *Presenting Author: Parisa Momtaz, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** We hypothesized that tumor-derived cfDNA in plasma may reflect accurately total tumor burden. DigPCR is a quantitative technique that carries out individual PCR reactions simultaneously in thousands of droplets. By utilizing fluorescently-labeled probes specific for a unique tumor-specific mutation (e.g. $BRAF^{V600E}$) it is possible to quantify mutated and wild-type (WT) DNA in plasma with high sensitivity (1 copy of $BRAF^{V600E}$/ml plasma). **Methods:** Plasma from 11 pts with $BRAF^{V600E}$ mutated mel treated with vemurafenib, or dabrafenib, and/or Ipi were collected at various time points. cfDNA extraction from pt plasma was performed and the ratio of the concentration of mutant $BRAF^{V600E}$ to WT cfDNA was determined using DigPCR. The ratio of $BRAF^{V600E}$ /$BRAF^{WT}$ cfDNA was correlated with tumor burden measured radiographically as the sum of target lesion diameters. **Results**: 1 pt had a complete response, 8 had partial responses, and 2 had stable disease. 6 pts progressed after responding. All 4 pts assessed at the time when they were free of disease radiographically had undetectable cfDNA. False negative readings were seen in some samples from 2 pts (radiographic evidence of tumor but no detectable tumor-derived cfDNA despite adequate amount of cfDNA). In 1 pt, cfDNA levels increased despite a decrease in the sum of target lesions but this pt had progression in non-target bone metastases indicating that in some situations, cfDNA may more accurately reflect tumor burden than traditional radiographic measurements. In a pt undergoing resection of bulky metastatic melanoma, we measured the half-life of cfDNA to be approximately 3.5 hours. **Conclusions**: Tumor-derived cfDNA appears to correlate well with tumor burden measured by radiographic imaging. We are currently analyzing our retrospective plasma collection as well as prospectively collecting plasma on $BRAF^{V600E}$mutated mel patients treated with RAFi and/or Ipi to assess more formally the value of cfDNA in reflecting tumor volume. Support: Rohan Melanoma Res. Fund.

**9086 General Poster Session (Board #290), Sat, 8:00 AM-11:45 AM**

**Phase I/II study of resiquimod as an immunologic adjuvant for NY-ESO-1 protein vaccination in patients with melanoma.** *Presenting Author: Rachel Lubong Sabado, Icahn School of Medicine at Mount Sinai, New York, NY*

**Background:** The TLR 7/8 agonist, Resiquimod has been shown to induce local activation of immune cells, production of cytokines, and antigen-presentation by dendritic cells, features desirable for cancer vaccine adjuvants. In this study, we evaluated the safety and immunogenicity of vaccination with NY-ESO-1 protein emulsified in Montanide ISA-51 VG when given with or without Resiquimod in surgically resected stage IIB-IV melanoma patients. **Methods:** This is a two-part study design. Part I represents an open-label dose-escalation with Resiquimod using 2 cohorts treated with 100ug NY-ESO-1 protein emulsified in 1.25mL Montanide (day1) followed by topical application of 1000mg of the 0.2% Resiquimod gel on days 1 and 3 for cohort-1 (N=3) or days 1, 3, and 5 for cohort-2 (N=3). The cycles were repeated every 3 weeks, total of 4 cycles. For part II of the study, patients were blindly randomized to receive 100ug NY-ESO-1 protein emulsified in 1.25mL Montanide (day1) followed by topical application of placebo gel (Arm-A; N=8) or 1000mg of 0.2% Resiquimod gel (Arm-B; N=12) using the dosing regimen established in Part I. Blood samples were collected at baseline, one week after each cycle of vaccination, and at follow-up visit for the assessment of NY-ESO-1-specific humoral and cellular immune responses. **Results:** The vaccine was generally well-tolerated, with no grade 4 adverse events or study-related deaths. Most study participants experienced mild adverse reactions reported as Grade 1 or 2 per CTCAE criteria v. 4. One patient experienced a grade 3 syncopal episode that was unrelated to the study drugs and another patient had a grade 3 injection site necrosis that was possibly related to the study drugs. NY-ESO-1 specific antibody responses were induced in both study arms although higher mean antibody titers were observed in Arm B. NY-ESO-1 specific CD4+ T cell responses were induced in patients in both study arms. However, significant NY-ESO-1 CD8+ T cell responses were detected only in Arm B. **Conclusions:** The current study shows that Resiquimod is safe and contributes to the induction of immune responses in patients. Clinical trial information: NCT00821652.

**9087 General Poster Session (Board #291), Sat, 8:00 AM-11:45 AM**

**A unique gene expression signature in tumor positive or negative sentinel lymph nodes in patients with melanoma.** *Presenting Author: Ahmad A. Tarhini, University of Pittsburgh Medical Center, Pittsburgh, PA*

**Background:** Molecular characterization through gene expression (exp) profiling of node positive and node negative sentinel lymph nodes (SLNs) in patients with clinical stage I-II melanoma may improve the understanding of mechanisms of metastasis and identify gene signatures for SLN+/SLN- that correlate with clinical outcome. **Methods:** Gene exp profiling was performed on SLN biopsies of 48 (24 SLN+, 24 SLN-) patients (T3a/b, T4a/b) who underwent SLN for staging using transcriptome profiling analysis on 5$\mu$ sections of fresh LN. U133A 2.0 Affymetrix gene chips were used. SAMR used to test the association between gene exp level and SLN status. Genes with fold change>1.5 and q value <0.05 were considered differentially expressed. Pathway analysis was performed using Ingenuity Pathway Analysis. Benjamini and Hochberg method was used to adjust for multiple testing in pathway analysis. **Results:** We identified 45 significantly increased transcripts (1.5-27 fold). Upon pathway analysis, 25 genes were commonly significantly expressed among the most significant and biologically relevant canonical pathways. Top pathways and associated genes were notably related to melanoma microenvironment and signaling pathways implicated in immunosuppression and development of cancer. **Conclusions:** Gene exp profiling identified pathways enriched with genes significantly differentially expressed in SLN+ vs SLN-. These findings warrant investigation in relation to diagnosis and prediction of outcome.

**Select top pathways and associated genes.**

| Pathway | Adjusted P value |
|---|---|
| Mitotic roles of polo-like kinase | 0.0000 |
| DNA damage-induced 14-3-3 sigma signaling | 0.0001 |
| G2/M DNA damage checkpoint regulation | 0.0001 |
| Cyclins and cell cycle regulation | 0.0012 |
| Eumelanin biosynthesis | 0.0023 |
| Melanocyte development signaling | 0.0096 |
| Role of CHK in cell cycle checkpoint control | 0.0199 |
| Antiproliferative role of TOB in T cell signaling | 0.0401 |
| p53 signaling | 0.062 |
| Genes: BIRC5, CCL20, CCNA2, CCNB1, CCNB2, CCNE2, CDC20, CDC6, CDK1, CHEK1, DCT, KIF11, KIF23, MCM4, PRC1, RFC3, RRM2, SERPINE2, SGK1, SOX10, TOP2A, TTK, TYMS, TYR, TYRP1 | |

**9088 General Poster Session (Board #292), Sat, 8:00 AM-11:45 AM**

**Sentinel lymph node biopsy among elderly patients with melanoma.** *Presenting Author: Michael S. Sabel, University of Michigan, Ann Arbor, MI*

**Background:** While SLN biopsy is considered standard of care for melanoma ≥1mm in depth, its use among the elderly population is more controversial. To examine this, we reviewed our experience at the University of Michigan with melanoma patients ≥ 75 years of age. **Methods:** A prospective database was used to identify 952 melanoma patients ≥ 75 years of age from 1996 to 2011. In addition to clinicopathologic features and recurrence and survival data, co-morbidity data was collected to calculate the Charlson co-morbidity index (CCI). Univariate and multivariate Cox regression analysis was performed to characterize predictors of outcome. Kaplan Meier analysis was used to generate survival curves. **Results:** Among 553 clinically node negative patients with melanoma ≥1mm in Breslow thickness, 213 had wide excision alone while 340 had excision and SLN biopsy, with 83 (24%) having a positive SLN. Predictors of not performing a SLN biopsy included only older age (p<.0001) and head and neck location (p=.007), but not pathologic features or co-morbidity index. A final multiple variable model predicting SLN involvement included female gender [OR 2.15 (95%CI:1.20-3.85) p=.009], Breslow thickness [OR 1.23 for each 1mm increase (95%CI:1.07-1.42) p=0.004] and satellitosis [OR 4.43 (95%CI 1.61-12.21), p=.004]. Distant disease-specific survival was negatively associated with male gender (OR 1.5 (1.12-2.02), p=.007), increasing age (OR 1.05 per year [1.02-1.08, p<.001]), increasing Breslow thickness (OR 1.07 per year [95% CI 1.01-1.13, p=.013), ulceration (OR 1.51 [95%CI 1.14-2] p=.004), a positive SLN (OR 2.61 [95% CI 1.79-3.82], p<.001) and not having a SLN biopsy (OR 1.72 [1.28-2.33], p<.001). CCI did not predict worse disease-free or melanoma specific survival. **Conclusions:** Among elderly patients with clinically node negative melanoma ≥1mm, 24% harbor SLN metastases. SLN biopsy was not only strongly prognostic, but WLE + SLN biopsy, compared with WLE alone, was associated with improved distant disease-specific survival and a trend towards improved melanoma-specific survival, even after factoring for age and co-morbidities. If otherwise healthy, SLN biopsy should be strongly considered for this population.

**9089 General Poster Session (Board #293), Sat, 8:00 AM-11:45 AM**

**New graded prognostic index (GPI) for melanoma patients with brain metastasis (MBM).** *Presenting Author: Vyshak Alva Venur, Fairview Hospital, Cleveland Clinic, Cleveland, OH*

**Background:** Melanoma is the third most common cause of brain metastasis (BM) and graded prognostic assessment (GPA) is used as a prognostic index for MBM. We evaluated prognostic factors that predict overall survival (OS) in MBM treated at a single tertiary care institution. A preliminary data was presented at ASCO 2013. **Methods:** With IRB approval, the Cleveland Clinic Brain Tumor and Neuro-Oncology Center's database was used to identify MBM treated between 1999 and 2011. OS from the diagnosis of MBM was the primary end point.Cox proportional hazard models were used for data analysis. Stepwise variable selection was used to identify independent prognostic factors. **Results:** 176 MBM charts were reviewed and 159 were included for analysis. Primary site of melanoma was head and neck in 27 (22%), trunk and abdomen in 48 (39%), limbs in 46 (37%) and uvea in 2 (2%) patients. Karnofsky performance scale (KPS) was 90-100 in 67 patients (44%), 70-80 in 70 (46%) and <70 in 15 (10%) patients. Single BM was noted in 48 (31%), 2-3 BM in 52 (34%) and more than 3 was seen in 55 (35%) patients. One hundred, twenty two patients (76%) were symptomatic at diagnosis. One hundred, eight (68%) patients had supratentorial BM, 45 (28%) had both supra-and infratentorial and 6 (4%) had only infratentorial BM. Initial therapy included stereotactic radiosurgery (SRS) in 50 (31%) patients, whole brain radiation (WBRT) in 36 (23%), surgery (S) + WBRT in 30 (19%), WBRT + SRS in 24 (15%) and S + SRS in 9 (6%) patients, while 3 patients underwent only S, 6 patients were observed. Median OS from diagnosis of BM was 5.7 months (95% C.I. 4.4-6.8). The conventional disease specific GPA for MBM that includes KPS and number of brain metastasis was prognostic for survival (p<.0001). On multivariate analysis, the number of extracranial metastasis (ECM) at diagnosis of BM was prognostic for OS. **Conclusions:** A new GPI for MBM with KPS, number of BM and number of ECM is proposed.

| Factor | Median Survival (months) | p value |
|---|---|---|
| KPS | | |
| 90-100 | 7.2 | 0.001 |
| 70-80 | 5.3 | |
| <70 | 2.1 | |
| Number of BM | | |
| 1 | 7.4 | 0.002 |
| 2-3 | 6.7 | |
| >3 | 4.4 | |
| Number of ECM | | |
| 0 | 8.9 | <0.001 |
| 1-2 | 6.7 | |
| 3 | 4.4 | |
| >4 | 2.6 | |

**9090 General Poster Session (Board #294), Sat, 8:00 AM-11:45 AM**

**Efficacy of two ipilimumab (IPI) doses (10 vs. 3 mg/kg) in Alberta, Canada, tertiary cancer centers.** *Presenting Author: Richard M. Lee-Ying, Tom Baker Cancer Centre, Calgary, AB, Canada*

**Background:** The efficacy of IPI for the treatment of metastatic melanoma (MM) has been demonstrated in randomized phase 3 trials. Response rates in the initial dose-finding phase 2 trial indicated the highest overall response rate (ORR) in the 10mg/kg group. Prior studies have identified that the degree of drug exposure during induction is statistically significant in predicting response. The optimal dosing is currently under investigation with a 10 vs. 3mg/kg trial (NCT01515189). **Methods:** Two cohorts were identified in the province of Alberta, one received 10mg/kg, while the second received 3mg/kg inductions. Treatment responses were determined by clinical immune-related response criteria. Fisher's exact test was used to compare response rates. **Results:** A total of 97 patients were identified from 2006-2013, with 31 patients in the 10mg/kg group and 66 patients in the 3mg/kg group. The median follow-up was 15.7 vs. 11.7 months, respectively. The complete response (CR) rate is 19.4% (6/31) and 1.5% (1/66), which significantly favors the 10mg/kg group, p=0.006. The partial response (PR) rates are 19.4% (6/31) and 19.7% (13/66), p=0.97 and the stable disease (SD) rates are 22.6% (7/31) and 12.1% (8/66), p=0.09. Progressive disease (PD) rates are lower in the 10mg/kg group, 32.3% (10/31), vs. 63.6% (42/66) p=0.004. A trend towards improved response rate favored the 10 vs. 3mg/kg group (38.7%, 12/31 vs. 21.2%, 14/66) p=0.07, while the clinical benefit rate (CBR) (CR, PR and SD) was statistically significant, 61.3% (19/31) vs. 33.3% (22/66) p=0.01. An additional 3 patients in the 10mg/kg and 2 patients in the 3mg/kg group are alive with no evidence of disease after subsequent therapy. The frequency of immune-related side effects was not significantly different between groups, despite higher dosing in the 10 vs. 3mg/kg group, p=0.79. **Conclusions:** IPI used at 10mg/kg produces a better CBR than 3mg/kg in this study. This benefit is largely due to marked improvement in CR rates in the 10mg/kg group, and lower rates of PD. These findings are limited by the small sample size, retrospective nature and limited follow-up. Our results support the importance of dose exposure with IPI for MM, and will be explored further in a phase III trial.

**9091 General Poster Session (Board #295), Sat, 8:00 AM-11:45 AM**

**Response rate and durability of chemotherapy for metastatic Merkel cell carcinoma among 62 patients.** *Presenting Author: Jayasri G Iyer, University of Washington, Seattle, WA*

**Background:** Merkel cell carcinoma (MCC) is an aggressive skin cancer with a high propensity to metastasize (> 30%). Distant metastatic MCC is often treated using chemotherapy but its efficacy is unclear because the existing literature: 1) intermingles adjuvant and therapeutic chemotherapy cases and, 2) often includes combined chemo-radiation. **Methods:** To assess the efficacy of chemotherapy on MCC we performed a retrospective analysis of 62 patients in our cohort with distant MCC metastases evaluable for response to chemotherapy alone.Tumor responses were characterized as complete remission (CR), partial remission (PR), stable disease (SD) or progressive disease (PD) per RECIST. Overall survival (OS), durability of response and progression-free survival (PFS) were also analyzed. **Results:** Median age of this cohort was 68 years (range: 47 – 96). Median OS from the start of chemotherapy was 9.5 months. Platinum plus etoposide was the most common first line regimen administered to 69% of the patients. Objective response rate (ORR) with front-line chemotherapy was 54% (34/62) with CR in 15% (9/62) of the patients. 7 of 9 patients with CR eventually progressed. The median progression free survival (PFS) for all patients from start of chemotherapy was 93.5 days with 90% of patients progressing by 290 days. Among responders (CR + PR), median PFS was 161 days, median durability of response was 103 days (range: 12 – 522) and 90% progressed in this subgroup by 428 days. Among 30 patients who received a second line chemotherapy regimen, the ORR was 23% (7/30 with 1 CR, 6 PR). Median PFS from start of second line chemotherapy (n=30) was 61 days (range: 11 – 364). Topotecan was the most commonly used second-line regimen (23%). **Conclusions:** The results of our study suggest that responses to cytotoxic chemotherapy for MCC are frequent but of limited durability. While subject to selection bias in a retrospective study, these data may be useful as a basis for comparison as the "control arm" for trials of new therapeutic modalities in this rare malignancy lacking data from prospective trials.

**9092 General Poster Session (Board #296), Sat, 8:00 AM-11:45 AM**

**Severe skin rash during vemurafenib treatment: A predictive factor of early positive response in metastatic melanoma?** *Presenting Author: Nora Kramkimel, Assistance Publique–Hôpitaux de Paris, Hôpital Cochin, Paris, France*

**Background:** Interindividual variability in pharmacokinetics may influence clinical benefit or toxicity of vemurafenib (VMF) in metastatic melanoma (MM) and identification of predictive factors of response and toxicity are mandatory. **Methods:** From Nov. 2011 to Dec. 2013, VMF plasma concentration was assayed at different times within the first 65 days of treatment, after informed consent, in 55 patients treated with VMF for MM in 3 French Dermatologic Departments. Baseline clinical and biologic characteristics, average VMF plasma concentration per patient for tumor response analysis and absolute exposure at the day of the toxicity, tumor response (PFS, OS, early response rate evaluated after 2 months of VMF) according to RECIST criteria and toxicities (grade ≥2 rash and renal failure, any grade≥3 adverse events) graded using the NCI 4.0 scale, were tested univariately. Candidate variables with p<0.1 were studied in multivariate analysis. **Results:** Mean age was 55 years (25-84). 92.7% had stage IV MM, 25.5% had brain metastasis and 76% were PS 0-1. 90.7% of tumor had *BRAF* V600E mutation and 2.5% V600K. VMF was the first line treatment in 66.7%. Early response rate (i.e CR, PR and SD) was 61.5%. Mean PFS was 5.4 months (0.3-17) and mean OS was 9.0 months (0.3-24+). Mean VMF concentration (n=118) was 47.5 ± 20.4 mg/L. Interindividual variability in dose-normalized VMF exposure was 43%. In multivariate analysis, higher average VMF dose was associated with longer PFS (OR: 0.998 [0.997-0.999], p=0.0025). Grade ≥2 rash, observed in 29.6%, (OR: 5.64 [1.004-31.696], p =0.0495) and daily VMF dose regimen (OR: 1.29 [1.032-1.612],p=0.0256) were associated with early 2-month response. BMI (OR: 0.75 [0.592-0.95], p=0.0173) and VMF plasma concentration (OR: 1.061 [1.017-1.108], p =0.0065) were associated with grade ≥2 rash. **Conclusions:** This is the first study that highlights correlation between grade≥2 rash and early MM response under VMF. Moreover, relationship between PFS and high VMF average dose underlines importance to keep highest VMF dose even after adverse event. Finally, low BMI and high VMF plasma exposure were identified as risk factors for development of grade≥2 rash.

**9093 General Poster Session (Board #297), Sat, 8:00 AM-11:45 AM**

**Efficacy and safety of mechlorethamine (MCH) 0.04% gel in mycosis fungoides (MF) after treatment with topical MCH 0.02%.** *Presenting Author: Youn H. Kim, Stanford Cancer Institute, Stanford, CA*

**Background:** MF, the most common form of cutaneous T-cell lymphoma, is characterized by infiltration of the skin by malignant T cells and can further progress to other organs. Early stage disease (limited/localized skin involvement) is managed with skin-directed therapies. The first FDA approved topical formulation of MCH, MCH 0.02% gel (equivalent to 0.016% w/w MCH, mechlorethamine) was noninferior to MCH-Aquaphor (AP) 0.02% in a 12 mo study (Study 201). In clinical practice, patients (pts) who tolerate MCH 0.02% without complete response (CR) may have their dose increased to maximize response. Study 202 tested the efficacy and safety of MCH 0.04% gel after MCH 0.02%. **Methods:** Pts eligible for this 7 mo phase 2 extension study completed 12 mos of treatment with MCH 0.02% gel or AP without CR. All pts applied a thin layer of MCH 0.04% gel once daily. Application frequency could be reduced for toxicity. Primary endpoint was response rate defined as ≥ 50% improvement in composite assessment of index lesions score (CAILS) of up to 5 lesions, confirmed ≥ 4 weeks later. **Results:** 98 of 100 enrolled pts were treated in Study 202 (MCH 0.04%); 86.7% completed the trial. 26 pts (26.5% [18.6-35.9]) achieved confirmed CAILS response from Study 202 baseline, including 6 CR. Additionally, 14 pts (14.3%) had their first response at final visit—unconfirmed response rate, 40.8% (31.5-50.7). There was no difference in response by age, race, or gender. CAILS response rates were also assessed from Study 201 (MCH 0.02%) baseline for index lesions identified at the start of that trial, with confirmed responses occurring in 74 pts (75.5% [66.3-83.2]). By week 88, 33 pts (84.4%) who had previously received MCH 0.02% gel and 39 pts (67.9%) who had previously received MCH 0.02% AP in Study 201 had responses over the course of these sequential studies. Drug related skin adverse events in Study 202 were mostly mild to moderate and were reported by 31 pts (31.6%); the most common were skin irritation (11.2%), erythema (10.2%), and pruritus (6.1%). **Conclusions:** Pts with stage I or IIA MF who did not achieve CR after 12 mos of daily topical MCH 0.02% had additional clinical benefit with up to 7 mos of treatment with MCH 0.04% gel, which was well tolerated in these pts. Clinical trial information: NCT00535470.

**9094 General Poster Session (Board #298), Sat, 8:00 AM-11:45 AM**

**The genetic variants in interleukin locus at 1q32.1 as markers of melanoma survival.** *Presenting Author: Justin Rendleman, New York University School of Medicine, New York, NY*

**Background:** Interleukins play a critical role in immune regulation of tumor development. Because melanoma is a highly immunogenic cancer, and its progression often correlates with immune-related factors, in this study we have tested whether inherited genetic variants in interleukin pathways affect the clinical outcomes of melanoma patients. **Methods:** We performed a two-stage association analysis of 94 SNPs tagging 32 interleukin genes in 1,200 melanoma patients, ascertained at the New York University Medical Center between 2001-2013. The two stages (discovery and validation) were matched by tumor characteristics, age, and gender. Multivariate Cox regression models tested the associations with recurrence-free and overall survival (RFS and OS, respectively), including age, gender, stage, thickness, ulceration status, anatomic site, and histological subtypes as covariates. **Results:** A region within 1q32.1 containing *IL10*, *IL19*, *IL20*, *IL24* was significantly associated with melanoma OS. Specifically, two SNPs in *IL10* (rs3024493 and rs2222202) showed the strongest associations with OS (HR=5.82, 95% CI=2.08-16.3, p=0.0009; HR=0.47, 95% CI=0.28-0.80, p=0.006 respectively). The association between rs3024493 and OS replicated among both stages (stage 1 p=0.028, stage 2 p=0.017). In addition, SNPs tagging *IL16* were associated with both RFS and OS in the aggregate analysis of both stage 1 and 2 (p=0.04). **Conclusions:** The study has identified novel associations of germline genetic risk variants in an interleukin locus at 1q32.1 with melanoma outcomes (rs3024493), and validated the associations from previous smaller studies that showed germline variants in *IL10* (rs2222202) associate with worse OS. Pending multi-institutional meta-analysis and further genetic and functional investigations, this study strongly suggests that germline variants in the interleukin locus at 1q32.1 should be considered as novel prognostic markers with potential clinical utility.

**9095 General Poster Session (Board #299), Sat, 8:00 AM-11:45 AM**

**Integration of melanoma genotyping in clinical care.** *Presenting Author: Ines Esteves Domingues Pires Da Silva, Ronald O. Perelman Department of Dermatology, NYU Langone Medical Center, New York, NY*

**Background:** Molecularly targeted therapy is improving response rates and overall survival in subsets of melanoma patients. However, targeted therapy for "triple negative" patients (BRAF, NRAS and c-KIT wild type) is not yet defined. In addition, new evidence suggests that germline variants may have an impact in melanoma progression and response to therapy. In this study, we attempt to define the utility of a recently developed clinical assay that encompasses targeted sequencing of 50 genes with known impact on cancer progression. **Methods:** We used the AmpliSeq Cancer Panel HotSpot.V2 from Ion Torrent. The panel targets sequencing of Hotspot regions including 2,800 COSMIC mutations within 50 oncogenes and tumor suppressor genes. Tumor and blood germline DNAs were studied. All identified mutations were independently validated by Sanger sequencing. We then linked the molecular profile to extensive clinicopathological information including treatment and prospective clinical follow-up. **Results:** We examined 35 tumor samples from 33 melanoma patients (2 patients had 2 specimens). 14/35 (40%) had BRAF mutations, 12/35 (34%) had NRAS mutations (one patient had both BRAF and NRAS mutated) and 2 had c-KIT mutant tumor. Eight patients were triple negative and presented with mutations in KRAS (n=2), TP53 (n=5), ERBB4 (n=1), PI3K (n=3), RB1 (n=1), NOTCH (n=1), EZH2 (n=1), APC (n=5) and KDR (VEGFR2; n=2). We detected germline variants in TP53 (40%), KDR (34%), APC (29%), KIT (23%) and PIK3CA (14%) genes. Notably, KDR Q472H has been shown to affect VEGFR2 function. Patients with KDR Q742H had higher microvessel density, higher VEGF production and a shorter survival (15.1 months compared to 54.6 months). **Conclusions:** Sequencing using a validated clinical assay was informative of several targetable mutations in triple negative melanoma. Inhibitors targeting some of these mutations are already FDA approved for non-melanoma and others are currently tested in clinical trials. Our data also revealed a role of germline variant KDR Q472H in melanoma progression, that was not reported before, suggesting that further functional studies are warranted.

**9096 General Poster Session (Board #300), Sat, 8:00 AM-11:45 AM**

**Correlation of absolute and relative eosinophil counts with immune-related adverse events in melanoma patients treated with ipilimumab.** *Presenting Author: Katja Schindler, Memorial Sloan-Kettering Cancer Center, New York, NY*

**Background:** Ipilimumab (ipi) has shown significant improvements in overall survival (OS) for patients (pts) with advanced melanoma in randomized phase III trials. Easily obtainable pre- or on-treatment biomarkers would be helpful to optimize this therapy. In a prior analysis, IL-17 levels correlated with immune-related adverse events (irAEs), and IL-17 and eosinophils are immunologically related. In one prior single institution study of 73 ipi-treated pts, an increase in absolute eosinophil count (AEC) was associated with improved OS. Whether this finding correlates with other clinical outcomes such as immune-related adverse events (irAEs) or is reproducible in larger, multicenter analyses remains unknown. **Methods:** 156 pts with advanced melanoma treated with ipi at the approved standard dose of 3mg/kg in 4 institutions (Medical University of Vienna, University of Zurich, University of Lausanne, and Memorial Sloan-Kettering Cancer Center) between 2010 and 2013 were retrospectively analyzed. Baseline (B/L), week (W) 4 and W7 absolute and relative eosinophil (AEC and REC) counts and occurrence of irAEs were noted. Wilcoxon rank-sum test was performed for analyzing the association of AEC and REC with irAEs. OS was calculated from date of first ipi dose to date of death or last followup. The association between B/L, W4 and W7 levels of AEC and REC and OS was assessed using Cox proportional hazards regression. **Results:** The change in AEC from B/L to W4 and from B/L to W7 was significantly associated with the occurrence of any irAE (p=0.032 and p=0.007, respectively). As continuous variables at W4, AEC and REC were significantly associated with irAEs (p=0.018 and p=0.275, respectively). At W7 AEC was significantly associated with irAEs (p=0.019) but REC was not (p=0.074). Neither AEC nor REC at B/L was significantly associated with irAEs. Neither the change in AEC nor REC from B/L to W4 was associated with OS. **Conclusions:** Eosinophils were associated with irAEs but not OS during ipi treatment. Given functional links between IL-17 and eosinophils, and the correlation of both IL-17 and eosinophils with irAEs, further study of the mechanistic role of this pathway in pts with irAEs is warranted.

**9097 General Poster Session (Board #301), Sat, 8:00 AM-11:45 AM**

**Interobserver variability in ultrasound (US) guided fine needle aspiration cytology (FNAC) of sentinel nodes (SN): Experience in 1,000 melanoma patients.** *Presenting Author: Christiane A. Voit, Charité-Universitätsmedizin Berlin, Berlin, Germany*

**Background:** FNAC is used to determine nature of suspected lesions that are either clinically apparent (palpable) or discovered by imaging (non-palpable) with the same high sensitivity (Voit et al.JNCI 2011). However, there seems to be interobserver variability. **Methods:** Morphology criteria (Voit et al. JCO 2010) were tested in 3 pre-SLNB-US examiners. US criteria, FNAC results were collected in a prospective database.Positive cytology was confirmed by histopathology. Examiner #1 had a long US-FNAC experience, 2 others were learners, #2 with a long US, but not FNAC experience, #3 new to both. **Results:** In 1,000 consecutive prospective patients mean/median Breslow thickness was 2.58/1.57mm. Mean/median follow-up was 56 / 53 months (1 – 132). SN positivity rate was 21%. Overall US-FNAC sensitivity was 71%(US only) and 51%(US-FNAC). Sensitivity of US-FNAC was highest for T4 (76%) and ulcerated melanomas (63%). #1 performed 724(72%), #2 202(20%), #3 74(7%). US validation of #1 was 431/724(59.9%) benign, in 227/724(31.4%) suspicious and in 66/724(9.1%) malignant. #2 estimated in 144/202(71.3%) benign, in 50/202(24,7%) suspicious and in 8/202(4%) malignant; #3 in 57(77%) benign, in 8/75 (10.8%) suspicious and in 9/74 (12.2%) malignant (p<0.001). #1 detects early sign peripheral perfusion(PP) in 32%, #2 in 21% and #3 in 22%. #1 performed FNAC in 291(40%), #2 in 55(25%) and #3 in17(15%)(p<0.001). #1 had sensitivity of 86/157(55%), spec of 99%, PPV of 99% and NPV of 89% (p<0.001). #2 had 34%,100%,100% and 88%,#3 56%, 100%,100% and 89% respectively(p<0.001). Detected sentinel node Tuburden <1mm was successfully FNACed in 45% by #1 and in 20% by #2 and#3 respectively. **Conclusions:** This largest database covering FNACs in SN of melanoma patients showed no difference between ultrasonographists with regard to performing a FNAC if a late sign, baloonshape (BS) or loss of central echoes (LCE), was seen. An examiner experienced in both US and FNAC sees more PP, performs more FNACs and has more positive FNACs. Examiners not used to FNAC tend to not perform FNACS. Interobserver difference is due to a significantly lower detection rate of PP.

**9098 General Poster Session (Board #302), Sat, 8:00 AM-11:45 AM**

**A phase IB study of ipilimumab with peginterferon alfa-2b for patients with unresectable stages IIIB/C/IV melanoma.** *Presenting Author: Ragini Reiney Kudchadkar, Comprehensive Melanoma Research Center, Moffitt Cancer Center, Tampa, FL*

**Background:** Peginterferon alfa-2b (Sylatron) as adjuvant therapy has been shown to benefit patients with resected melanoma and interferon studies have shown that the induction of autoantibodies may correlate with benefit. Ipilimumab (IPI, Yervoy) is an anti-CTLA-4 antibody that induces immune-related toxicity that may correlate with clinical benefit. This abstract is an update of previously presented data. **Methods:** This studycombined IPI at 3mg/kg every 3 weeks for 4 doses along with concurrent peginterferon alfa-2b at 3 mcg/kg weekly for up to 156 weeks or until disease progression, unacceptable toxicity, or patient decision to discontinue. The study was designed to obtain toxicity, tolerability, and autoimmune antibody data and to define a well-tolerated dose of the combination. **Results:** 31 patients were treated with13 female and 18 male subjects. Median age was 65. There were 2 CRs, 9 PRs, 3 with stable disease, and 12 with progressive disease in 26 pts evaluable for response thus far. Five pts have not yet completed cycle 1 and therefore are not evaluable for response at the time of this publication but will be presented. Toxicities from peginterferon alfa-2b 3mcg/kg were dose-limiting with 7 pts requiring dose reduction in peginterferon alfa-2b secondary to toxicity. The grade 3 events leading to dose reductions were nausea and vomiting, leucopenia, dehydration, and hyponatremia. Peginterferon alfa-2b was dose reduced to 2 mcg/kg weekly in future pts after these toxicities were noted. In the subsequent patients grade 3 related events included rash (n = 4), pruritis (2), colitis (1), fatigue (2), and hypothyroidism (1). There was no significant change in the presence autoantibodies (ANA, anti-double stranded DNA, antithyroglobulin, antimicrosomal antibodies, and anticardiolipin antibodies) between responders and nonresponders in the evaluable pts. **Conclusions:** Peginterferon alfa-2b added to IPI results in an excellent response rate of 42.3% in this population. Peginterferon alpha-2b at 2 mcg/kg weekly with IPI at 3 mg/kg every 3 weeks is tolerated well though 20% of patients treated at this dose experienced grade 3 rash. Based on a clinical benefit rate (CR + PR + SD) of 53.8 %, this combination warrants further exploration. Clinical trial information: NCT01496807.

**9099 General Poster Session (Board #303), Sat, 8:00 AM-11:45 AM**

**Association of natural killer (NK) cell exhaustion with melanoma progression.** *Presenting Author: Ines Esteves Domingues Pires Da Silva, Ronald O. Perelman Department of Dermatology, NYU Langone Medical Center, New York, NY*

**Background:** Recent success of immunotherapies targeting the exhaustion markers CTLA-4 and PD-1 has inforced the role of $CD8^+$T cell exhaustion in advanced melanoma patients. T cell exhaustion, has been extensively studied, however little is known about NK cell exhaustion in the same context. In this project, we defined NK cells phenotype in different stages of melanoma to examine its role in melanoma progression. **Methods:** NK cells were purified from the peripheral blood of a prospectively-enrolled cohort of 100 melanoma patients: stage I (n=56), stage II (n=21) and stages III/IV (n=23); in addition to 25 healthy donors. NK cells were characterized for the expression of activating (NKG2D and NKp46) and inhibitory receptors (Tim-3, KIRB1 and KIRNKAT2), function (cytotoxicity, IFN-$\gamma$ production and proliferation) and the intracellular expression of the transcription factors (T-bet and Eomes). We then tested the association between NK cell phenotype and clinicopathological variables associated with melanoma prognosis. Unpaired T test was used to compare two groups, and ANOVA to compare more than two groups. **Results:** NK cells gradually develop a phenotypic and functional profile consistent with progressive exhaustion, from stage I to stage IV characterized by: 1) up-regulation of inhibitory receptors (Tim-3, KIRB1 and KIRNKAT2); 2) down-regulation of activating receptors (NKG2D and NKp46) and transcription factors (T-bet and Eomes); 3) loss of IFN-$\gamma$ production,proliferation and cytotoxicity. Interestingly, the expression of Tim-3 and KIRB1 is higher, while the cytotoxic ability is reduced in patients with melanomas thicker than 1mm (Tim-3 – p=0.007; KIRB1 – p=0.03; cytotoxicity – p=0.05). Higher Tim-3 expression is associated with ulceration (p=0.009) and with mitosis (p=0.001). Moreover, higher expression of Tim-3 and KIRB1, and a lower cytotoxic ability is associated with local or distant metastases (Tim-3 – P=0.002; KIRB1 – p=0.0009; cytotoxicity – p=0.0005). **Conclusions:** Data demonstrate that NK cells become progressively exhausted in the context of melanoma progression. NK cells start acquiring this phenotype in early stages which suggests that targeting them earlier can be be a novel therapeutic strategy.

**9100 General Poster Session (Board #304), Sat, 8:00 AM-11:45 AM**

**Clinical characteristics of patients with non-*V600 BRAF* mutant melanomas.** *Presenting Author: Dae Won Kim, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** *V600E* and *V600K* mutations are the most common *BRAF* mutations in melanoma. We previously showed that non-*V600 BRAF* mutations account for 12% of all *BRAF* mutations in melanoma. Limited clinical data are available for non-*V600 BRAF* mutant melanomas. To better understand non-*V600 BRAF* mutations in melanoma, characteristics of tumor and clinical outcomes were investigated. **Methods:** Clinical and pathologic data were collected retrospectively in patients (pts) with melanoma who had multi-gene mutation analysis (next-gene sequencing) at MD Anderson Cancer Center. Fisher's exact test was used for all comparisons. **Results:** We found 52 pts with non-*V600 BRAF* mutations, among whom 8 had *NRAS*/non-*V600* co-mutations. Common non-*V600* mutations were *K601E* (17.3%), *G469E* (15.4%), *G469R* (7.7%), *D594G* (5.8%), *L597S* (5.8%), and *S467L* (5.8%). Compared with *V600E* mutations as a control (n=82) , the presence of a non-*V600* mutations was significantly associated with older age (median, 58 years vs 50; P=0.001), less superficial spreading type (13.6% vs 32.9%; P=0.02), more lentigo maligna type (20% vs 1.2%; P=0.001), more mucosal subtype (9.1% vs 1.2%; P=0.03), more head/neck primary tumor location (36.4% vs 15.9%; P=0.03), less lower extremity primary tumor location (4.5% vs 24.4%; P=0.003), more co-mutations with *NRAS* (15.4% vs 2.4%, p=0.005) and stage IV disease at initial diagnosis (31.8% vs 7.3%; P=0.0003). Among the 33 pts with non-*V600* mutant metastatic melanoma, 7 received selective BRAF inhibitor (BRAFi). Of the 5 evaluable patients (2 could not tolerate treatment), all had disease progression within 2 months. **Conclusions:** *Non-V600 BRAF* mutant melanomas have more aggressive clinical characteristics, more likely to have co-mutations with *NRAS*, and not responsive to selective BRAFi than *V600E* mutations. A larger cohort and a longer follow-up will better define the prognostic indication of non-*V600* mutated melanoma.

**9101 General Poster Session (Board #305), Sat, 8:00 AM-11:45 AM**

**A phase I trial of BKM120 combined with vemurafenib in $BRAFV600^{E/k}$ mutant advanced melanoma.** *Presenting Author: Alain Patrick Algazi, University of California, San Francisco, San Francisco, CA*

**Background:** Vemurafenib induces transient objective responses in half of $BRAF^{V600E}$mutant melanoma patients and a median PFS of 5.3 months. PTEN loss and PI3K activation are common in BRAF mutant metastatic melanoma, and PI3K activation has been implicated as a cause acquired resistance to BRAF inhibitors. This phase I study tested the safety of combining the BRAF inhibitor, vemurafenib, with the PI3K inhibitor, BKM120, in patients with metastatic BRAF mutant melanoma. **Methods:** Vemurafenib-naïve patients receive a single dose of oral BKM120 (d -7) then vemurafenib twice daily with BKM120 daily (starting on c1d1). Patients with prior progression on vemurafenib received both vemurafenib and BKM120 starting on c1d1 after a vemurafenib washout of at least 14 days. Serial biopsies prior to treatment, on cycle 1 day 15, and at progression were obtained for pharmacodynamics analysis in patients with visible or palpable tumors. 3 + 3 dose escalation was planned starting at vemurafenib 720 mg PO twice daily with BKM120 60 mg daily. **Results:** Four BRAF inhibitor naïve patients andfour BRAF inhibitor refractory patients were treated on study with vemurafenib 720 mg PO bid and BKM120 60 mg PO daily. Two BRAF inhibitor naïve patient experienced DLTs (myalgias, DRESS syndrome). One vemurafenib naïve patient was inevaluable due to non-compliance and had minimal exposure to study drug. Two of four BRAF inhibitor refractory patients experienced DLTs (myalgias, febrile neutropenia). One BRAF inhibitor-resistant patient had a mixed response to treatment with a 35.9% reduction in target lesions and two new small subcutaneous lesions. **Conclusions:** Combination therapy with vemurafenib and BKM120 in BRAF-V600E/K mutant melanoma was not tolerated in either BRAF inhibitor naïve or BRAF inhibitor resistant patients. Clinical trial information: NCT01512251.

**TPS9102 General Poster Session (Board #306A), Sat, 8:00 AM-11:45 AM**

**NEMO: A phase 3 trial of binimetinib (MEK162) versus dacarbazine in patients with untreated or progressed after first-line immunotherapy unresectable or metastatic *NRAS*-mutant cutaneous melanoma.** *Presenting Author: Keith Flaherty, Massachusetts General Hospital, Boston, MA*

**Background:** Melanoma tumors often harbor mutations in the mitogen-activated protein kinase-signaling pathway family members BRAF or NRAS. *NRAS* mutations, observed in about 15% of patients with melanoma, are associated with higher tumor proliferation and poorer prognoses. A large retrospective analysis (n = 677) demonstrated that *NRAS* mutations are independently predictive of poor survival in patients with cutaneous melanoma (Jakob *et al.*, 2011). With no approved targeted therapies for melanoma patients with *NRAS*-mutant tumors, treatments are currently limited to chemotherapy and/or immunotherapy. Binimetinib (MEK162), a potent and selective inhibitor of MEK1/2, has demonstrated promising phase 2 clinical activity in this patient subset. Here we describe the "NRAS mElanoma and MEK inhibitOr" (NEMO) trial, an ongoing phase 3 study designed to compare the efficacy of binimetinib vs dacarbazine in patients with metastatic *NRAS*-mutant cutaneous melanoma (NCT01763164). **Methods:** NEMO is a 2-arm, open-label, 2:1 randomized trial of binimetinib vs dacarbazine. Eligible patients must have advanced unresectable or metastatic cutaneous melanoma with a documented *NRAS* Q61 mutation (by central molecular screening) that was previously untreated or has progressed after 1 line of immunotherapy. Patients are stratified by stage, performance status, and prior immunotherapy. The primary endpoint of the study is progression-free survival, and secondary endpoints include overall survival, overall response, disease control rate, safety, and quality of life. Binimetinib is administered orally at 45 mg twice daily and dacarbazine is dosed intravenously at 1000 $mg/m^2$ once every 3 weeks, until disease progression or unacceptable toxicity. Patient crossover from the dacarbazine arm to the binimetinib arm is not permitted. This phase 3 trial is designed to enroll 393 patients and is currently recruiting patients at more than 150 centers worldwide. Clinical trial information: NCT01763164.

**TPS9103^ General Poster Session (Board #306B), Sat, 8:00 AM-11:45 AM**

**A phase II study of intratumoral application of L19IL2/L19TNF in melanoma patients in clinical stage III or stage IV M1a with presence of injectable cutaneous and/or subcutaneous lesions.** *Presenting Author: Riccardo Danielli, Medical Oncology and Immunotherapy, University Hospital of Siena, Siena, Italy*

**Background:** Preclinical studies in three different murine models of subcutaneous tumors have shown that a single intratumoral injection of a combination of two immunocytokines, L19-IL2 and L19-TNF is more effective than each immunocytokine in monotherapy and is curative in 100% of animals. Furthermore, in the clinical setting intralesional delivery of L19-IL2 elicited objective responses in >50% of Stage III melanoma patients, with a possible benefit in terms of distant metastases-free survival rates for these patients and evidence of systemic immune responses in most evaluable patients. L19-IL2 and L19-TNF are recombinant fusion proteins, consisting of the single-chain monoclonal antibody (L19) directed against extradomain B of fibronectin, a well-characterized marker of angiogenesis, fused to IL2 or TNF cytokines, respectively. **Methods:** A Phase II, uncontrolled, multicenter, prospective study is ongoing at two centers in Italy (EudraCT Number: 2012-001991-13). Twenty patients with unresectable Stage IIIC/IVM1a melanoma and cutaneous or subcutaneous injectable metastases will receive intratumoral injections of L19-IL2 (10 Mio IU maximum daily dose) in combination with L19TNF (312 $\mu$g) once per week for 4 consecutive weeks. Primary objective is the assessment of efficacy measured as the rate of patients with complete response (CR) of L19IL2/L19TNF-treated lesions at week 12. Secondary objectives include ORR and DCR of treated lesions at week 12, and ORR and disease control rate (DCR) at weeks 12, 24 and 36 of treated and non-treated lesions. Additional secondary endpoints include duration of OR and DCR of treated and treated-non treated lesions, median overall survival (mOS) and safety of study drugs. Tumor assessment is performed according to RECIST vs 1.1 and modified (m) mRECIST criteria at baseline and at weeks 6, 12, 24 and 36. Adverse events will be collected according to the CTCAE v. 4.02. The study is ongoing and fifteen patients have been enrolled so far. Clinical trial information: 2012-001991-13.

**TPS9104 General Poster Session (Board #307A), Sat, 8:00 AM-11:45 AM**

**A phase II study to assess vismodegib in the neoadjuvant treatment of locally advanced basal cell carcinoma (laBCC): The Vismodegib Neoadjuvant (VISMONEO) study.** *Presenting Author: Laurent Mortier, Dermatology, CHRU of Lille, Lille, France*

**Background**: BCC is the most common skin malignancy. Surgery cures most cases, but a few patients may exhibit progression to life-threatening, unresectable, locally advanced disease or metastatic tumors and there is no standard therapy for this condition. Vismodegib is a small molecule antagonist of the Hedgehog signalling pathway newly approved in this indication. It showed in a phase II study (ERIVANCE BCC), a tumor response rate of 43% (95%CI: 31 to 56; p<0.001) in laBCC (complete responses 21%). We intend to assess vismodegib in the neo-adjuvant treatment of BCC aiming at reducing the BCC size which will allow a lower surgical stage and preserve the functional and the aesthetic appearance of the affected area. **Methods:** This is an open-label, non-comparative, multicenter, phase II study of vismodegib in patients with laBCC conducted in 33 centers in France. Main eligibility criteria are: age≥ 18 years, histologically confirmed diagnosis of laBCC, BCC with a diameter ≥ 3 cm in areas of intermediate risk of tumor recurrence and ≥ 2 cm in areas of higher risk of tumor recurrence, measurable and/or non-measurable disease, adequate liver and hematological functions. Enrolled patients receive vismodegib 150 mg once-daily po continuously. One cycle of therapy is defined as 28 days of treatment. All patients receive study drug until best overall response, within a maximum treatment period of 10 months. The primary endpoint is the proportion of BCC patients with a down-staging of the initial surgical stage following vismodegib neoadjuvant treatment. Surgical stage, validated by the Reconstructive Surgery teams of three University Hospitals in France, includes tumor size and surgical procedure planned. Secondary endpoints are safety, clinical benefit (assessed by an independent panel of experts), quality of life (Skindex-16 Questionnaire at baseline, after Cycle 1, Cycle 3, Cycle 6, end of treatment), and medico-economical assessment. A total of 50 patients will be recruited; they will be followed-up for 3 years after surgery. Clinical trial information: 2013-004338-13.

**TPS9105 General Poster Session (Board #307B), Sat, 8:00 AM-11:45 AM**

**Phase I-II study of the combination vemurafenib plus peg-interferon in advanced melanoma patients harboring the V600BRAF mutation.** *Presenting Author: Paolo Antonio Ascierto, Unit of Melanoma, Cancer Immunotherapy and Innovative Therapy, Istituto Nazionale Tumori Fondazione, Naples, Italy*

**Background:** Preliminary evidence in the literature suggests that interferon receptor subunit IFNAR1 is down-regulated in melanoma cells harboring a mutated active BRAF. This possibility is supported by our own finding that inhibition of the BRAF-MAPK signaling pathway by vemurafenib up-regulates IFNAR1 expression in BRAF mutated melanoma cells. Moreover, vemurafenib and IFN$\alpha$-2b combination enhances HLA class I antigen expression which is associated with an increased recognition of melanoma cells by cognate T cells. A preclinical study has also showed the ability of vemurafenib and IFN$\alpha$-2b combination to significantly prolong the survival of mice grafted with BRAF mutated melanoma cells. These findings have provided the rationale for designing a novel clinical trial. The study end-points include the evaluation of safety and efficacy of vemurafenib/PEG-interferon (PEG-IFN) combination. **Methods:** VEMUPLINT is an open-label, single-arm, phase I/II trial. Advanced melanoma patients with BRAF V600 mutation will be treated with vemurafenib and PEG-IFN combination (NCT01959633). Eligible patients include unresectable or metastatic melanoma, who have either not been treated or have received no more than 1 line of treatment. The primary end-point is the maximum tolerated dose (MTD) for the phase I study, while is the efficacy, assessed as durable response rate lasting > 32 weeks, for the phase II study. Primary end-points include also evaluation of IFNAR1 up-regulation. Secondary end-points are incidence of grade 3-4 toxicities, disease control rate, time to response, time to progression of brain metastases and overall survival. In the phase I study, groups of 3 patients for each cohort (9 patients) will be entered at each dose level (vemurafenib 960 mg b.i.d. + PEG-IFN 1/2/3 micrograms/Kg). The MTD will be considered the recommended dose for the phase II study. The phase II study will be conducted in approximately 10 investigational sites located in Italy; a total of 42 patients will be enrolled (including 3 patients from the phase I study). This phase I-II trial is currently recruiting patients for the phase I study at the Istituto Nazionale Tumori of Naples, Naples, Italy. Clinical trial information: NCT01959633.

**TPS9106 General Poster Session (Board #308A), Sat, 8:00 AM-11:45 AM**

**Phase II, open-label study of dabrafenib plus trametinib in patients with BRAF mutation-positive melanoma brain metastases: A GSK-sponsored trial.** *Presenting Author: Michael A. Davies, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Data from BREAK-MB (phase II, metastatic melanoma, BRAF V600 mutation positive, with brain metastases, dabrafenib monotherapy) demonstrated a 39.2% overall intracranial response rate and a 81.1% intracranial disease control in cohort A (no prior local therapy), and a 30.8% overall intracranial response rate and a 89.2% intracranial disease control in cohort B (previous local therapy). Median survival was 33.1 and 31.4 weeks for cohorts A and B, respectively. [Long G, et al. *Lancet Oncol*. 2012;13:1087-95]. Data from BRF113220 (phase I/II, metastatic melanoma, BRAF V600 mutation-positive, brain metastasis patients excluded, dabrafenib + trametinib) reported a median progression-free survival (PFS) of 9.4 months with dabrafenib 150mg BID and trametinib 2mg QD combination therapy (150/2), and 5.8 months with dabrafenib monotherapy (HR 0.39, $p$<0.0001). [Flaherty K, et al. *N Engl J Med*. 2012;367(18):1694-703] The median overall survival for the 150/2 therapy was 23.8 months compared with 20.2 months for dabrafenib monotherapy (HR 0.73, not significant). [Daud A, et al. Presented at the Society for Melanoma Research Congress, 2013]. This trial is expected to build the body of evidence regarding the safety and efficacy of dabrafenib plus trametinib combination therapy in patients with BRAF V600 mutation positive, unresectable melanoma brain metastases (MBM). **Methods:** This study will evaluate the safety and efficacy of 4 cohorts. A) V600E, asymptomatic MBM, no prior local therapy; B) V600E, asymptomatic MBM, prior local therapy; C) V600D/K/R, asymptomatic MBM, with or without prior local therapy; D) V600D/E/K/R, symptomatic MBM, with or without prior local therapy. Patients will receive dabrafenib 150 mg BID + trametinib 2 mg QD therapy. 120 patients will be enrolled beginning in January 2014. The primary objective of the study is intracranial response in cohort A patients. Secondary endpoints include; intracranial response in patients in cohorts B, C and D; intracranial disease control; extracranial response; overall response; duration of intracranial, extracranial and overall response; PFS; overall survival; and safety. Clinical trial information: NCT02039947.

**TPS9107 General Poster Session (Board #308B), Sat, 8:00 AM-11:45 AM**

**Targeted modified IL-2 (NHS-IL2, MSB0010445) combined with stereotactic body radiation in advanced melanoma patients after progression on ipilimumab: Assessment of safety, clinical, and biologic activity in a phase 2a study.** *Presenting Author: Howard L Kaufman, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

**Background:** Advanced melanoma patients (pts) can benefit from IL-2 therapy, but treatment is often limited by severe toxicities. The immunocytokine NHS-IL2 is a fusion protein composed of genetically modified IL-2 that preferentially binds to the high-affinity IL-2 receptor, and of a human IgG2 antibody targeting DNA exposed in necrotic tumor regions (NHS76). In preclinical studies, NHS-IL2 showed antitumor activity; in phase 1 trials it was biologically active and well tolerated, both as a monotherapy and in a sequential combination with radiotherapy (Gillessen et al. *Eur J Cancer* 2013; van den Heuvel et al. submitted). This phase 2a, open-label, parallel-group dose-escalation trial investigates safety, clinical and biologic activity of NHS-IL2 following stereotactic body radiation(SBRT) in pts with advanced melanoma (NCT01973608). **Methods:** The primary study objective is to determine the maximum tolerated dose of NHS-IL2 combined with SBRT. Exploratory study objectives are safety, biologic and clinical activity of the combination, and immunogenicity and pharmacokinetics of NHS-IL2. Pts with advanced unresectable or metastatic melanoma that has progressed after ipilimumab as immediately preceding treatment are eligible. Main exclusion criteria: active brain metastases and concurrent systemic immunosuppressive therapy. Up to 86 pts will be enrolled to receive $\leq$3 SBRT (up to 20 Gy on max. 3 lesions or up to 16 Gy if irradiated lesion is located in the thorax), followed by NHS-IL2 iv every 3 weeks in 3 arms: fixed doses of 0.3 mg/kg and 1.0 mg/kg; and dose escalation at 1.8–3.6 mg/kg (standard 3+3 design). If safety allows, up to 14 pts per arm will be enrolled to assess biologic activity, defined by the changes in infiltration of $CD8^+$ and regulatory T cells into the tumor before and during therapy. Depending on the biologic activity, trial arms will be expanded or pooled to determine objective response in 40 pts treated with an active dose. Combination treatment will be continued until disease progression, unacceptable toxicity, or withdrawal of consent. As of Jan 31, 2014, 2 pts are enrolled. Clinical trial information: NCT01973608.

**TPS9108 General Poster Session (Board #309A), Sat, 8:00 AM-11:45 AM**

**Phase 1 study of MEDI4736, an anti-PD-L1 antibody, in combination with dabrafenib and trametinib or trametinib alone in patients with unresectable or metastatic melanoma.** *Presenting Author: Michael S. Gordon, Pinnacle Oncology Hematology, Scottsdale, AZ*

**Background:** Greater understanding of tumor immunology in melanoma has led to the development of targeted treatments with improved outcomes in patients (pts) with metastatic melanoma (MM). Dabrafenib, a V600E BRAF inhibitor, combined with trametinib, a MEK inhibitor, resulted in high response rates, progression-free survival (PFS) of 9.4 mo in *BRAF* mutation-positive melanoma and is now an FDA-approved combination. Adding an immunomodulator may further improve outcomes. MEDI4736, a highly potent anti-PD-L1 antibody, showed clinical activity in a phase 1 study of pts with solid tumors including MM and is being evaluated in combination with dabrafenib/trametinib or trametinib alone in *BRAF* mutation-positive or *BRAF*mutation-negative melanoma. **Methods:** This global, multicenter, open-label phase 1b study (NCT02027961) is enrolling adults with unresectable or MM and ECOG performance status 0-1 into 3 cohorts. In cohort A, *BRAF* V600E or V600K mutation-positive (*BRAF*-MP) pts receive dabrafenib orally (PO) twice daily, trametinib PO once daily (QD) and MEDI4736 intravenously (IV) every 2 wks (q2w), given concomitantly followed by continued dabrafenib/trametinib until progressive disease (PD). In cohorts B and C, *BRAF* V600E or V600K mutation-negative (*BRAF*-WT) pts receive trametinib PO QD and MEDI4736 IV q2w according to 2 different treatment schedules until PD. Primary objectives are determination of maximum tolerated dose (dose-limiting toxicity) and safety profile (adverse events, laboratory evaluations, physical exams, echocardiograms/electrocardiograms) of MEDI4736 in combination with dabrafenib/trametinib or trametinib alone. Secondary objectives include antitumor activity (objective response based on RECIST, duration of response, PFS, and overall survival), pharmacokinetic profile, and immunogenicity of the combination. Exploratory objectives include biomarkers, patient-reported outcomes, and tumor growth parameters. Recruitment is ongoing (target: 69 pts). Clinical trial information: NCT02027961.

**TPS9109 General Poster Session (Board #309B), Sat, 8:00 AM-11:45 AM**

**BeyPro1: A phase II single-arm study for the treatment after recurrence of advanced melanoma patients harboring the $^{V600}$BRAF mutation and pretreated with vemurafenib, with the association of vemurafenib plus fotemustine.** *Presenting Author: Paola Queirolo, Department of Medical Oncology A, National Institute for Cancer Research, Genoa, Italy*

**Background:** BRAF-inhibitor Vemurafenib achieves high response rate and a statistically significant improvement in overall survival (OS) in patients (pts) with unresectable stage III and IV melanoma. However, clinical resistance to this agent eventually arises in most pts. In a Phase I study of Vemurafenib, among 48 pts with progressive disease (PD), 18 pts were treated beyond progression (TBP) $>$ 30 days after local therapy of PD lesions: median OS had not been reached at a median follow-up of 15.5 months from initiation of Vemurafenib, with a median treatment duration beyond initial PD of 3.5 months. Conversely, in pts who were not TBP, median OS was 1.4 months (Kim et al. ASCO 2011). In a series of 112 patients treated with BRAF-inhibitors (Chan et al. ASCO 2013), 36/92 were TBP: median OS from commencement of BRAF-inhibitors in those TBP was longer than those not TBP (15.0 vs 6.5 months, $p<0.001$), as was OS from PD (7.4 vs 1.9 mo, $p=0.001$). These findings suggest that one possible approach to improve the prognostic outlook in pts progressing during Vemurafenib treatment may be continuing the drug in combination with chemotherapy: resistance is not caused by acquisition of secondary BRAF mutations but rather by up-regulation in some cell populations of other proliferative signals with the creation of heterogeneous cell populations partly resistant to BRAF inhibition, and a cytotoxic drug such as Fotemustine (FTM) might act on those proliferating clones. FTM was chosen because it has shown an effect on brain metastases: in a phase III study (Avril et al. JCO 2004) comparing FTM with dacarbazine, the median time of occurrence of brain metastases was longer in the FTM group (22.7 months) than in the dacarbazine group (7.2 months). **Methods:** Thirty pts progressing while on Vemurafenib were enrolled in the study between January and October 2013. The primary objective is to assess the activity of Vemurafenib plus FTM in pts harboring the $^{V600}$BRAF mutation and recurred while on treatment with Vemurafenib. The primary endpoint is PFS. Treatment with FTM plus Vemurafenib will be continued until PD or unacceptable toxicity. Clinical trial information: NCT01983124.

**TPS9110 General Poster Session (Board #310A), Sat, 8:00 AM-11:45 AM**

**Dose-seeking and efficacy study of combination BRAFi and high-dose IFN (HDI) for therapy of advanced melanoma.** *Presenting Author: Diwakar Davar, University of Pittsburgh, Pittsburgh, PA*

**Background:** New immunotherapies and BRAF inhibitors (BRAFi) have improved the prognosis of advanced melanoma. Although BRAFi induce regression in ~50% of patients (pts), responses are incomplete and progression typically occurs at 6 months. Intrinsic/acquired resistance mechanisms represent limitations to single agent BRAFi use. Conversely, immunotherapies benefit only 18-30% of patients. In vitro and in vivo studies suggest that treating BRAF mutated melanoma cells with BRAFi increases sensitivity to IFN. We planned a dose-selection and dose-expansion study to evaluate the novel sequential combination of BRAFi followed after 2 weeks by concurrent BRAFi/IFN$\alpha$. **Methods:** Study will enroll pts with BRAF V600E recurrent/inoperable stage III/IV melanoma. Primary objectives are to evaluate safety/toxicity, identify a phase II dose (RP2D) of combination, and improve progression free survival (PFS). Secondary objectives include improving response rates and documenting evidence of immune modulation. Pts will initially receive vemurafenib at 960 mg twice daily with a 2 week lead-in to exploit immunomodulatory effects. HDI will commence in week 3 with standard induction (4 weeks) and maintenance (48 weeks) schedules employed for adjuvant therapy. Intravenous IFN will be administered 5 days weekly for 4 weeks at 3 escalating dosage levels - 10, 15, and 20 MU/m2/d. Subcutaneous IFN will be administered thrice weekly for 48 weeks at 3 dose levels - 5, 7.5, and 10 MU/m2/d. As combination has not previously been evaluated, HDI will be escalated in 3 fixed dose levels using Storer's modified "up and down" scheme to minimize toxicity. Accrual target in the dose expansion phase is 36 patients treated at RP2D. Prior to study and at serial points during, biopsies of accessible lesions will be obtained. We expect that this combination will increase immune recognition of melanoma cells by CD8+ tumor-infiltrating T cells (TILs) through: 1) upregulation of IFN-$\alpha$R1 and HLA class I APM component expression; 2) inhibition of STAT signaling pathways; and 3) modulation of PD-L1 expression by melanoma cells. Clinical trial information: NCT01943422.

**TPS9111 General Poster Session (Board #310B), Sat, 8:00 AM-11:45 AM**

**The influence of a gene expression signature on the diagnosis and recommended treatment of melanocytic tumors by dermatopathologists.** *Presenting Author: Loren E Clarke, Myriad Genetic Laboratories, Inc., Salt Lake City, UT*

**Background:** Many studies have documented suboptimal accuracy and reproducibility in the diagnosis of melanocytic lesions by histopathology, even by experienced dermatopathologists. Therefore, adjunctive methods that provide objective and reliable data have been sought. Recently, a 23-gene expression signature that assesses immune signaling and cell differentiation and uses quantitative reverse-transcription polymerase chain reaction was developed using a cohort of 464 melanocytic neoplasms. (*J Cutan Pathol.* 2014; 41:144-275 [abstr 292263]) The assay has been clinically validated to differentiate benign nevi from malignant melanoma with a sensitivity of 90% and a specificity of 91% in a second, independent cohort of 437 melanocytic lesions representing a broad spectrum of histopathologic types. (*Pending publication*) This study aims to quantify the impact of this assay on diagnosis and management recommendations made by dermatopathologists. **Methods:** Forty-nine dermatopathologists submitted 821 representative histological sections of difficult to diagnose melanocytic lesions encountered during routine practice to a clinical laboratory for gene expression testing. Currently, 513 cases are eligible for study inclusion based upon completed pre- and post-test surveys accompanying each case. Surveys document the physician's diagnosis, predicted biologic behavior (benign, malignant, or indeterminate), level of confidence, and recommendations for management. Study endpoints include the measured level of change in diagnosis, confidence, and treatment recommendations between the pre- and post-test surveys.

**TPS9112 General Poster Session (Board #311A), Sat, 8:00 AM-11:45 AM**

**Pharmacokinetic and pharmacodynamic analysis of preoperative therapy with dabrafenib alone and in combination with trametinib in patients with BRAF mutation–positive melanoma with metastases to the brain (BRV116521).** *Presenting Author: Michael A. Davies, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Dabrafenib (D) has clinical activity in patients (pts) with *BRAF* V600E/K mutation–positive melanoma brain metastases (MBM). The combination of D and trametinib (T) has increased activity in pts with *BRAF*V600E/K mutation–positive melanoma with extracranial metastases (ECM). It is not known whether the activity of D in MBM pts is due to blood-brain barrier penetration of the D parent compound or 1 (or more) of its active metabolites. In addition, the relationships between drug levels (parent compound and metabolites) achieved in MBM, and (1) peripheral exposure and (2) target inhibition in plasma and ECM are unknown. **Methods:** This international, open-label study will enroll up to 30 evaluable pts with stage IV *BRAF*V600E/K metastatic melanoma with untreated, resectable MBM (1-4 cm) and accessible ECM. Pts will be treated with D 150 mg twice daily (BID) for 7-14 days (cohort A, n=15) or D 150 mg BID + T 2 mg once daily for 7-14 days (cohort B, n=15), followed by resection of intracranial lesion(s) and biopsy or resection of accessible ECM(s). Blood (mandatory) and cerebrospinal fluid (CSF; optional) will also be collected on the day of surgery. If clinically indicated, pts in both cohorts will be treated with D + T starting 72 hours postsurgery until disease progression. MBM and ECM tumor tissue will be studied for levels of D (parent and metabolites) and T; expression and activation of pharmacodynamic markers and oncogenic signaling networks (protein, mRNA); DNA mutations and methylation; and immune cell infiltrates. Plasma and CSF will be studied for pharmacokinetics (PK). Blood will also be studied for circulating immune cells and cytokines. The primary objective is to assess PK in MBM, ECM and peripheral blood. Safety and efficacy will also be evaluated. The trial is currently open for accrual in the United States and Australia. Clinical trial information: NCT01978236.

**TPS9113^ General Poster Session (Board #311B), Sat, 8:00 AM-11:45 AM**

**The GERMELATOX DeCOG-trial: German melanoma patients and their attitude toward toxicity during adjuvant interferon treatment.** *Presenting Author: Katharina C. Kaehler, Department of Obstetrics and Gynecology, University Hospital Kiel, Kiel, Germany*

**Background:** Although trials of adjuvant interferon alfa-2b (IFN alpha-2b) in high-risk melanoma patients suggest improvement in disease-free survival (DFS), a metaanalysis could only show a marginal OS survival benefit (OS). Widespread use of adjuvant IFN alpha-2b has been decreased by its significant toxicity.In 2001 Kilbridge et al. (J Clin Oncol 2001) asked US-patients about the degree of improvement in 5-year DFS they would expect to tolerate IFN. At least half of the patients were willing to tolerate mild to moderate and severe IFNa-2b toxicity for 4% and 10% improvements of DFS. On average, patients rated quality of life (QoL) with melanoma recurrence much lower than even severe IFNa-2b toxicity.To date, no data exist on willingness of German melanoma patients to be treated with IFNa-2b. In Germany, melanoma patients are managed by specialized skin cancer units mainly located in certified skin cancer centers and core university hospitals. The willingness of dermatologists to use IFN depends strongly on their experience and capacity to manage IFN-related side effects.A comparison between a German cohort and the US-cohort of Kilbridge would allow new insights into country specific treatment differences. So far no direct comparison has been made between willingness of patients compared to their physicians. **Methods:** In this multicenter non-interventional trial ("GERMELATOX trial") of the Dermatologic Cooperative Oncology Group we assessed preferences and utilities for health outcomes associated with adjuvant IFN among 200 melanoma patients not eligible for IFN due to the low-risk features of their melanoma and 100 dermatooncologists from 10 different melanoma units using the standard gamble technique supported by the willingness to pay mode. The trial described four typical IFN alpha-2b toxicity scenarios and the following three posttreatment outcomes: disease-free health and melanoma recurrence (with or without IFN alpha-2b) leading to cancer death. We also asked patients the improvement in 5-year disease-free survival they would require to tolerate IFN toxicities.The recruitment of the study will be completed in mid 2014.

**TPS9114^ General Poster Session (Board #312A), Sat, 8:00 AM-11:45 AM**

**Biomarker study evaluating the combination of dabrafenib (D) with trametinib (T) versus the combination after 8 weeks of monotherapy with dabrafenib or trametinib in patients with metastatic and unresectable stage IIIC or IV melanoma: GSK study 116613.** *Presenting Author: Christine Mateus, Gustave Roussy Institute, Villejuif, France*

**Background:** Both D and T have demonstrated clinical activity as monotherapies and in combination in *BRAF* mutation–positive melanoma. However, the mechanism of acquired drug resistance and toxicity are not fully understood. We plan to investigate the sequential effects of BRAF and MEK inhibition on skin, blood, and tumor biomarkers, as well as to study correlations between biomarkers and response to treatment and toxicity. **Methods:** This is a 3-arm, open-label, randomized, phase 2 biomarker study in France, comparing the upfront combination of D with T versus their combination after 8 weeks of monotherapy treatment with D or T. As of the end of January 2014, 1 patient was randomized. Approximately 54 eligible patients, ≥ 18 years of age, with histologically confirmed stage IIIc or IV cutaneous melanoma and *BRAF* V600E/K mutation-positive disease will be randomized 1:1:1 to one of three treatment arms. In the monotherapy arms, treatment will be given for 8 weeks continuously (D 150 mg BID or T 2 mg QD) before other drug is dosed. In the combination arm, both drugs, at the respective doses above, will be given upfront. All treatments will be given until disease progression, death, or unacceptable toxicity. The primary objective of this trial is to evaluate biomarkers linked to treatment response, resistance, and toxicity when D and T are given as monotherapy and/or in combination. The secondary objectives are to evaluate the clinical response (overall response rate), as well as the exposures of the 3 arms in connection to clinical response and toxicity, and to characterize the safety profile of D and T in monotherapy and/or in combination. In addition, exploratory objectives are to evaluate changes in inflammation, the impact of the 2 drugs, separately and in combination, on the immune system, progression-free survival, and duration of response. The primary endpoint will be analyzed with a descriptive intent only. Hence, no hypothesis testing will be performed. Clinical trial information: EudraCT number 2012-004577-12.

**TPS9115 General Poster Session (Board #312B), Sat, 8:00 AM-11:45 AM**

**NLG-0304: A phase 2B study of ipilimumab with or without dorgenmeltucel-L (HyperAcute-Melanoma) immunotherapy for patients with stage IV melanoma.** *Presenting Author: Adam I Riker, Advocate Christ Medical Center, Advocate Cancer Institute, Oak Lawn, IL*

**Background:** Dorgenmeltucel-L immunotherapy consists of allogeneic melanoma cells that have been genetically modified to express the carbohydrate $\alpha(1,3)$Gal, to which humans have an inherent pre-existing immunity. It is $\alpha$Gal that is primarily responsible for the hyperacute rejection of foreign tissue via this potent immune defense mechanism in humans. Dorgenmeltucel-L leverages this mechanism to educate the immune system towards components of the patients' own tumor cells. In prior Phase 1 and 2 studies of dorgenmeltucel-L, there have been no grade 3 or higher immunotherapy related adverse events. In the Phase 2 study in combination with pegylated interferon, all evaluable patients developed autoimmune antibodies and 4 developed vitiligo which correlated with either CR or durable post resection NED state. Ipilimumab has now become standard therapy for advanced melanoma patients, particularly those that are BRAF negative. Preclinical data has demonstrated synergy between therapeutic vaccination and anti-CTLA-4 therapy. This study is designed to determine if there is benefit to adding dorgenmeltucel-L to standard ipilimumab therapy. **Methods:** This is a randomized Phase 2B study for patients with stage 4 metastatic melanoma. 100 patients will be randomized to receive either standard ipilimumab therapy (3mg/kg q 3 weeks x 4) or standard ipilimumab plus dorgenmeltucel-L 300 million cells per each immunization, given weekly x 4, then biweekly for 5 months, monthly for 6 months, and every 3 months for an additional year. Patients receiving dorgenmeltucel-L and ipilimumab will start ipilimumab with the $4^{th}$ dose of dorgenmeltucel-L. Primary endpoint is the overall clinical response rate. Secondary endpoints include Disease free survival (DFS), Progression-free survival (PFS), and Overall survival (OS), Duration of Complete Response (CR), Duration of Stable Disease (SD), and immunologic correlates. Clinical trial information: NCT02054520.

**TPS9116^ General Poster Session (Board #313A), Sat, 8:00 AM-11:45 AM**

**A phase II, single-armed, multicenter trial of neoadjuvant vismodegib in patients with large and/or recurrent basal cell carcinoma: NICCI.** *Presenting Author: Ulrike Leiter, Department of Dermatooncology, University of Tuebingen, Tuebingen, Germany*

**Background:** Vismodegib is useful to treat locally advanced or metastatic basal cell carcinoma (BCC) but has not been evaluated for use in a neoadjuvant setting to shrink BCCs before surgery. This multicenter, non-randomized, single-armed phase II clinical study is performed to evaluate the efficacy of neoadjuvant vismodegib in patients with large or large recurrent basal cell carcinoma (BCC). **Methods:** The primary endpoint is to evaluate the efficacy of vismodegib as measured by the percentage of basal cell carcinomas that reach complete remission (CR, as determined by histopathology), partial remission (PR), or stable disease (SD) versus progressive disease (PD) after 12 weeks of treatment. Secondary endpoints include the assessment of i) size-reduction of BCC in $cm^2$ as intended for excision (baseline vs. 12 weeks of treatment by planimetrics), ii) treatment-induced changes assessed by non-invasive imaging techniques (optional: in vivo confocal laserscan-microscopy, optical coherence tomography, high resolution ultrasonography) in correlation with histopathology, and iii) toxicity and tolerability including health-related quality of life questionnaire (Skindex-16) Study design: 75 patients with a BCC or recurrent BCC ($\geq$ 2 cm in diameter in head/neck region, $\geq$ 5 cm for trunk/extremities plus at increased risk for cosmetic disfigurement or functional defects) will be enrolled. After 12 weeks of treatment with vismodegib 150mg/d all patients will receive micrographic excision of the remaining tumor area. Patients will be observed for one year. Documentation of the two-dimensional tumor size (in $cm^2$) as intended for excision will be performed by planimetrics at the time of study inclusion, at week 13 before surgery and at the end of study. Clinical trial information: 2013-004767-31.

**TPS9117 General Poster Session (Board #313B), Sat, 8:00 AM-11:45 AM**

**Phase 1/2 trial of the indoleamine 2,3-dioxygenase pathway (IDO) inhibitor indoximod plus ipilimumab for the treatment of unresectable stage 3 or 4 melanoma.** *Presenting Author: Eugene Kennedy, NewLink Genetics, Ames, IA*

**Background:** IDO is an enzyme that catalyzes the initial and rate limiting step in the conversion of tryptophan to kynurenine. Tryptophan depletion enhances the number and function of the Treg (suppressive) arm of the immune system and inhibits the effector T cell (stimulatory) arm. In addition, it has been shown that kynurenine metabolites may augment the suppressive effects on inflammation and immune responses. The main function of IDO is the regulation of acquired local and peripheral immune tolerance in normal and pathological conditions. In cancer, IDO can either be expressed directly by the tumor cells themselves, or induced indirectly in host antigen presenting cells by the presence of tumor. In these settings, IDO mediates an acquired immune tolerance towards tumors, allowing tumors to thwart an immune response by the host. Therefore, IDO is an attractive target. Ipilimumab is a monoclonal antibody that blocks the immunosuppressive receptor CTLA-4 on T cells, thus enhancing immune responses against tumors. Tumor models have shown synergistic effects with anti-CTLA-4 treatment in combination with indoximod providing a rationale for combination therapy for the treatment of melanoma. **Methods:** This is a Phase 1/2 study of indoximod dose escalation in combination with ipilimumab (3mg/kg q3 weeks x 4 doses) in a standard 3+3 design during the Phase 1 portion. Eligible patients will have unresectable Stage 3 or 4 melanoma. Up to 12 patients will be enrolled in the Phase 1 portion. Indoximod will be administered concurrently with ipilimumab as a twice daily oral dose, continuously for each 21 day cycle. Treatment with indoximod will continue beyond treatment with ipilimumab (halted either due to reaching 4 doses or toxicity) until disease progression or toxicity. The Phase 2 portion will enroll up to 80 patients in a non-randomized study. Patients will receive ipilimumab at the standard dose with concurrent indoximod at the dose determined in Phase 1. Primary endpoints for the Phase 1 portion include safety, toxicity, and determination of a Phase 2 dose. Primary endpoints for the Phase 2 portion will be to evaluate safety and efficacy. Clinical trial information: NCT02073123.

**TPS9118^ General Poster Session (Board #314A), Sat, 8:00 AM-11:45 AM**

**BRIM8: A phase III, randomized, double-blind, placebo-controlled study of vemurafenib adjuvant therapy in patients with surgically resected, cutaneous BRAF-mutant melanoma at high risk for recurrence (NCT01667419).** *Presenting Author: Karl D. Lewis, University of Colorado Cancer Center, Aurora, CO*

**Background:** Approximately 50% of melanomas carry a mutation in the *BRAF* gene. The oral BRAF inhibitor vemurafenib (VEM) has demonstrated meaningful clinical benefit in $BRAF^{V600}$ mutation-positive, locally advanced/unresectable or metastatic melanoma. For patients (pts) with resected melanoma, interferon alfa-2b represents the only widely approved adjuvant therapy; however, its use is limited by a modest improvement in disease recurrence and a high incidence of severe adverse effects that lead to treatment discontinuation in up to a third of pts. BRIM8 is a phase III, international, multicenter, double-blind, randomized, placebo-controlled study designed to evaluate the safety and efficacy of VEM in pts with resected cutaneous melanoma at high risk (>50%) for recurrence (stage IIC and III disease). **Methods:** Pts aged ≥18 yrs with histologically confirmed stage IIC or III $BRAF^{V600}$mutation-positive (by cobas testing) melanoma of cutaneous origin that has been completely resected are eligible. Pts without clinical or radiologic evidence of regional lymph node involvement must undergo sentinel lymph node biopsy, and those with evidence of regional or sentinel lymph node involvement must undergo complete regional lymphadenectomy. Pts with a history of systemic therapy for treatment or prevention of melanoma (including interferon alfa-2b) are ineligible. Two cohorts (C) will enroll ~ 725 pts: C1—500 pts with completely resected stage IIC, IIIA (one or more nodal metastasis >1 mm in diameter, per Rotterdam classification), or IIIB cutaneous melanoma; C2—225 pts with stage IIIC cutaneous melanoma. Pts will be randomized 1:1 to receive VEM (960 mg bid) or placebo for 52 weeks with randomization stratified by pathologic stage and region (C1) and by region (C2). Primary efficacy outcome measure is investigator-assessed disease-free survival. Secondary efficacy outcome measures include overall and distant metastasis-free survival. Safety, pharmacokinetic, and pt-reported outcomes will also be assessed. As of 13 Jan 2014, 179/196 sites are active and 154 pts have been randomized (C1: 89; C2: 65). Clinical trial information: NCT01667419.

**TPS9119 General Poster Session (Board #314B), Sat, 8:00 AM-11:45 AM**

**Phase I/II study of the TLR3 agonist poly-ICLC as an adjuvant for NY-ESO-1 protein vaccination with or without Montanide ISA-51 vg in patients with melanoma.** *Presenting Author: Rachel Lubong Sabado, Icahn School of Medicine at Mount Sinai, New York, NY*

**Background:** Poly-ICLC is a synthetic dsRNA complex which directly activates DCs and also triggers NK cells to kill tumor cells. Compared to LPS and R848, Poly-ICLC is the most potent TLR adjuvant due to its induction of cytokines such as IL-12 in the absence of IL-10, and maintenance of high levels of CD80 and CD86 in DCs. This study assessed the therapeutic potential of TLR3 activation by adding Poly-ICLC to a NY-ESO-1 protein vaccine with and without Montanide in surgically resected stage IIB-IV melanoma patients. **Methods:** In Phase I of the study, patients received subcutaneous injection of 100$\mu$g NY-ESO-1 protein and 1.1mL Montanide emulsified in escalating doses of Poly-ICLC: 0.35mg (cohort 1; N=3), 0.70mg (cohort 2; N=3), or 1.4mg (cohort 3; N=3). The cycles of vaccination were repeated every 3 weeks for a total of 4 cycles. In Phase II of the study, patients were randomized to subcutaneous vaccination of 100$\mu$g NY-ESO-1 protein with 1.4 mg Poly-ICLC, the dose established in the Phase I of the study, (Arm A; N=12) or with 100$\mu$g NY-ESO-1 protein, 1.4mg Poly-ICLC and 1.1ml Montanide (Arm B; N=12). The cycles of vaccination were repeated every 3 weeks for a total of 4 cycles. Blood samples were collected at baseline, one week after each cycle of vaccination, and at follow-up visit for the assessment of NY-ESO-1-specific humoral and cellular immune responses. Clinical trial information: NCT01079741.

**TPS9120 General Poster Session (Board #315A), Sat, 8:00 AM-11:45 AM**

**NCI 8628: A randomized phase II study of ziv-aflibercept (Z) and high-dose interleukin-2 (HD IL-2) or HD IL-2 alone for inoperable stage III or IV melanoma—Efficacy and biomarker study.** *Presenting Author: Madeeha Ashraf, University of Pittsburgh Cancer Institute, Pittsburgh, PA*

**Background:** IL-2 plays a central role in immunity affecting the proliferation and survival of effectors of antitumor response. IL-2 at high bolus IV dosage gives a 16% response rate and durable responses in 4-5% of patients (pts) with metastatic melanoma. VEGF plays a critical role in angiogenesis and host innate and adaptive immunity. VEGF blocks maturation of dendritic cells and inhibits priming of T cell responses. High baseline serum VEGF was reported to be a predictor of non-response to HD IL-2. We developed a strategy to deplete VEGF prior to HD IL-2 to reverse the immunosuppressive impact of VEGF and enhance antitumor T cell response. Z (known as aflibercept outside the US) is a high-affinity soluble decoy VEGF receptor and potent angiogenesis inhibitor. Our phase II study of Z alone for advanced melanoma showed median OS of 16.3 months and PFS 3.7 months. **Methods:** NCI 8628 is a phase II trial of Z and HD IL-2 (Arm A) versus HD IL-2 alone (Arm B) randomized 2:1 respectively with accrual goal 105 pts. Arm A: consists of 3 courses (maximum) and each course consists of 2 cycles of HD IL-2 at 600,000 IU/kg IV every 8 hours for up to 14 doses (1$^{st}$ cycle), followed by a rest period of 1-2 weeks' (wk) rest and readmission for HD IL-2 (2$^{nd}$ cycle). Z is given concurrently at 3 mg/kg IV every 2 wk, starting 2 wk prior to IL-2 in course 1. In the absence of disease progression, maintenance Z is given at 4 mg/kg every 2 wk after completion of IL-2. Arm B: patients receive HD IL-2 alone for a maximum of 3 courses (6 cycles). Eligible pts: Stage III inoperable or Stage IV (any M) melanoma . ECOG performance status of 0/1 and adequate organ function for HD IL-2. Up to two prior regimens for metastatic melanoma are allowed, and stable treated brain metastases. Response assessment follows RECIST v.1.1. Blood and tumor specimens are being collected prospectively for biomarker and mechanistic studies. Clinical trial information: NCT01258855.

**TPS9121 General Poster Session (Board #315B), Sat, 8:00 AM-11:45 AM**

**MIKIE: A randomized, double-blind, regimen-controlled, phase II, multicenter study to assess the efficacy and safety of two different vismodegib regimens in patients with multiple basal cell carcinomas.** *Presenting Author: Rainer Kunstfeld, Medical University of Vienna, Vienna, Austria*

**Background:** Vismodegib, a Hedgehog signaling pathway inhibitor, is FDA and EMA approved for patients (pts) with advanced basal cell carcinoma (BCC) who are not candidates for surgery or radiotherapy. While vismodegib reduces BCC tumor burden and blocks growth of new BCCs in pts with basal cell carcinoma nevus syndrome (BCCNS), further studies are required to optimize the therapeutic index of long-term (chronic) therapy. The MIKIE study (NCT01815840) assesses the efficacy and safety of 2 intermittent vismodegib dosing regimens in pts with multiple BCCs. **Methods:** MIKIE is a randomized, double-blind, regimen-controlled phase II study, in adults with multiple BCCs (including BCCNS) ≥18 years with ≥1 histopathologically confirmed BCC and ≥6 clinically evident BCCs (at least three ≥5 mm in diameter). 200 pts are planned to be randomized (1:1) to regimen A or B and stratified by BCCNS status, geographic region, and immunosuppression status. In regimen A, pts receive 3 courses of vismodegib (150 mg/d) for 12 weeks followed by placebo for 8 weeks, followed by a final 12-week course of vismodegib. In regimen B, pts receive vismodegib (150 mg/d) for 24 weeks, followed by 3 alternating courses of placebo (8 weeks) followed by vismodegib (8 weeks). Total duration of treatment will be 72 weeks in both arms, with 52 weeks of follow up. Major inclusion criteria include ECOG performance status 0–2; adequate hematopoietic, hepatic, and renal function; and signed written informed consent. Major exclusion criteria include inoperable metastatic or locally advanced BCC. Primary objective includes the percentage reduction from baseline in the number of clinically evident BCCs after 72 weeks of treatment in the 2 regimens. Secondary objectives include the percentage reduction in overall size of 3 largest BCCs, the proportion of pts with a 50% reduction in BCCs, the number of pts with new BCCs, recurrence rate, and safety and tolerability (including dropout rate due to tolerability). Skindex-16 quality of life and pharmacokinetic assessments will be conducted at selected sites. The first patient was enrolled in March 2013; the study is ongoing. Clinical trial information: NCT01815840.

**LBA9500^** **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Efficacy and safety of continued zoledronic acid every 4 weeks versus every 12 weeks in women with bone metastases from breast cancer: Results of the OPTIMIZE-2 trial.** *Presenting Author: Gabriel N. Hortobagyi, The University of Texas MD Anderson Cancer Center, Houston, TX*

**The full, final text of this abstract will be available at abstracts.asco.org at 2:00 PM (EDT) on Friday, May 30, 2014, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2014, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.**

**9501** **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Effect of denosumab versus zoledronic acid (ZA) in preventing skeletal-related events (SREs) in patients with metastatic bone disease: Subgroup analyses by baseline characteristics.** *Presenting Author: Allan Lipton, Penn State Hershey Medical Center, Hershey, PA*

**Background:** There is an interest in identifying patients at risk for SREs who may benefit most from treatment with bone-targeted agents (BTA). Previous results from a subgroup analysis of three phase 3 trials demonstrated denosumab was superior to ZA in preventing SREs (pathologic fracture, radiation or surgery to bone, or spinal cord compression) regardless of baseline clinical pain symptoms or prior SRE status. This analysis assesses if denosumab is superior to ZA in delaying patients' time to SREs across relevant baseline characteristics. **Methods:** Patients with metastatic bone disease were randomized 1:1 to receive either SC denosumab 120 mg + IV placebo (n=2,862) or IV ZA 4 mg (adjusted for CrCl) + SC placebo Q4W (n=2,861) in double-blinded phase 3 studies. Time to first on study SRE and time to first and subsequent SRE were evaluated in patients by several baseline variables: location of skeletal metastases (mets) (axial vs appendicular), presence of visceral mets (yes/no), urinary N-telopeptide (uNTx) level (median; ≥43.5 vs <43.5 nmol/mmol), number of bone mets(<2 or ≥2), and ECOG performance status (0 or ≥1). **Results:** Denosumab significantly delayed time to first SRE compared to ZA regardless of patients' baseline characteristics. Similar results were noted in preventing first and subsequent SREs in all subgroups. **Conclusions:** Denosumab significantly delayed patients' time to SREs compared to ZA regardless of patient's baseline status. Clinical trial information: NCT00321464, NCT00330759, NCT00321620.

**Benefit of denosumab vs ZA on time to first on-study SRE.**

| Baseline characteristic | HR (95% CI) | *P*-value |
|---|---|---|
| Axial bone mets only (n=1,422) | 0.83 (0.70,1.00) | 0.046 |
| Appendicular bone mets only (n=753) | 0.78 (0.61,0.99) | 0.042 |
| Both axial & appendicular bone mets (n=1,695) | 0.83 (0.71, 0.97) | 0.022 |
| ≥2 bone mets (n=2,234) | 0.81 (0.71,0.93) | 0.003 |
| <2 bone mets (n=3,489) | 0.84 (0.74,0.94) | 0.003 |
| Visceral mets (n=2,341) | 0.80 (0.69,0.93) | 0.003 |
| No visceral mets (n=3,382) | 0.84 (0.75,0.94) | 0.002 |
| High uNTx (n=2,553) | 0.86 (0.76,0.98) | 0.028 |
| Low uNTx (n=2,553) | 0.75 (0.65, 0.86) | <0.001 |
| ECOG 0 (n=2,312) | 0.82 (0.71,0.94) | 0.006 |
| ECOG ≥1 (n=3,398) | 0.84 (0.75,0.94) | 0.002 |

**9502** **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Phase 3 study of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting during repeated moderately emetogenic chemotherapy (MEC) cycles.** *Presenting Author: Matti S. Aapro, Clinique de Genolier, Genolier, Switzerland*

**Background:** Antiemetic guidelines recommend co-administration of targeted prophylactic medications aimed at inhibiting several molecular pathways involved in emesis. NEPA is a novel, fixed-dose combination of a new $NK_1$ receptor antagonist (RA), netupitant (NETU 300 mg), and palonosetron (PALO 0.50 mg), a pharmacologically distinct 5-$HT_3$RA. NEPA was previously shown to be superior to PALO after a single chemotherapy (CT) cycle in this study; maintenance of efficacy/safety over continuing cycles has been evaluated as a secondary objective. **Methods:** This multinational, randomized, double-blind, parallel group study assessed the efficacy/safety of single oral doses of NEPA versus PALO in chemotherapy-naive patients (pts) receiving multiple cycles of anthracycline-based CT. All pts also received oral dexamethasone (DEX) 12 mg (NEPA) or 20 mg (PALO) on Day 1. Efficacy endpoints were complete response (CR: no emesis, no rescue medication) and no significant nausea (<25 mm on 100 mm VAS). **Results:** 1,455 pts were randomized; 1286 participated in the multiple cycle extension. Patients participated in 5969 total CT cycles; 76% completed at least 4 cycles. Treatment groups were comparable; female (98%), white (80%), mean age of 54 yrs. The superiority of NEPA over PALO for overall (0-120 hr) CR during Cycle 1 was maintained over multiple CT cycles. A greater proportion of NEPA-treated pts also had no significant nausea over repeated cycles. Most frequently reported study drug-related adverse events (AEs) for NEPA included headache (3.5%) and constipation (2.0%) during the multiple cycle extension. The type/incidence of AEs were similar for NEPA and PALO. **Conclusions:** NEPA, a novel, fixed-dose combination targeting dual antiemetic pathways, is highly effective and safe over multiple cycles of MEC. A single dose of NEPA + DEX on Day 1 of CT offers guideline-based prophylaxis with a convenient, single-day treatment. Clinical trial information: NCT01339260.

| Overall CR rates (% patients) | NEPA | PALO | P value |
|---|---|---|---|
| Cycle 1 | N = 724<br>74.3% | N = 725<br>66.6% | 0.001 |
| Cycle 2 | N = 635<br>80.3% | N = 651<br>66.7% | <0.0001 |
| Cycle 3 | N = 598<br>83.8% | N = 606<br>70.3% | <0.0001 |
| Cycle 4 | N = 551<br>83.8% | N = 560<br>74.6% | <0.0001 |

**9503** **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Aprepitant versus metoclopramide, both combined with dexamethasone, for preventing cisplatin-induced delayed emesis: A randomized, double-blind study.** *Presenting Author: Fausto Roila, Oncologia Medica, Ospedale S. Maria, Terni, Italy*

**Background:** A combination of aprepitant, a 5-HT3 receptor antagonist, and dexamethasone is recommended for the prophylaxis of cisplatin-induced nausea and vomiting in acute phase, and aprepitant+dexamethasone (A+D) in delayed phase. Aim of this study was to verify if A+D is superior to metoclopramide plus dexamethasone (M+D) in preventing delayed emesis in cancer patients receiving the same prophylaxis for acute emesis. **Methods:** A randomized double-blind study comparing A+D versus M+D was completed in previously untreated cancer patients. Before chemotherapy, all patients were treated with intravenous palonosetron 0.25 mg, dexamethasone 8 mg, and oral aprepitant 125 mg. On day 2-4 patients randomly received oral dexamethasone 8 mg qd plus aprepitant 80 mg qd (days 2-3) or metoclopramide 20 mg qid plus dexamethasone 8 mg bid. Primary endpoint was rate of complete response (no vomiting, no rescue treatment) in day 2-5 after chemotherapy. **Results:** Of 303 enrolled patients 288 were evaluable, 147 receiving A+D, 137 M+D. Day 1 results were similar inboth arms. On day 2-5, complete response rate was not significantly different (80.3% with A+D versus 82.5% with M+D, p<0.38, respectively), and all secondary endpoints were also similar (complete protection, total control, no vomiting, no nausea, score of Functional Living Index-Emesis; p<0.24). Adverse events incidence was not significantly different between the two treatments. **Conclusions:** In cancer patients submitted to cisplatin-based chemotherapy, receiving the same antiemetic prophylaxis foracute emesis, A+D is not superior to M+D in preventing delayed emesis, and both treatments present similar toxicity. Clinical trial information: NCT00869310.

**9504 Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Long-term risk of heart failure associated with adjuvant trastuzumab in breast cancer patients.** *Presenting Author: Hart Goldhar, University of Toronto, Toronto, ON, Canada*

**Background:** The late cardiac effect of adjuvant trastuzumab (T) and its potential interaction with anthracycline in the general population have not been well studied. The purpose of this retrospective population-based cohort study was to determine the long-term risk of heart failure (HF) associated with adjuvant T and chemotherapy, compared to chemotherapy alone. **Methods:** Female breast cancer patients in Ontario, diagnosed between 2003 and 2009 were identified by the Ontario Cancer Registry and linked to administrative databases to ascertain demographics, cardiac risk factors, comorbidities, and use of adjuvant T and other chemotherapy. Patients with pre-existing HF were excluded. The main endpoint was new diagnosis of HF, obtained using an algorithm of admission and physician claims data. Group differences were assessed by the Kaplan-Meier (KM) method and multivariable piecewise Cox regression. Competing risk analysis using the Fine and Gray method and propensity score matching analysis were performed. **Results:** 19,074 women with breast cancer treated with adjuvant chemotherapy were identified, of whom 3 371 (17.7%) also received adjuvant T. Anthracycline use was 84.9% overall. The groups did not differ significantly in demographics, comorbidities, or cardiac risk factors. After a median follow-up of 5.9 years, patients treated with T and chemotherapy were more likely to develop HF than patients on chemotherapy alone (5-year KM estimates of 5.3% vs. 2.6%; $p<0.0001$ (log-rank)). After adjusting for confounders, adjuvant T remained independently associated with incident HF in the first 1.5 years (HR=5.77, 95% CI 4.38-7.62, p=0.0004), but not thereafter (HR=0.87, 95% CI 0.57-1.33, p=0.53). Anthracycline did not increase the risk of HF with T synergistically (interaction p=0.23). Competing risk and propensity score analyses revealed similar results. **Conclusions:** In this large population-based cohort study of breast cancer patients with long-term follow-up, adjuvant T was associated with increased risk of HF in breast cancer survivors, within the first 1.5 years of initiating treatment, but not thereafter. This provides reassurance about the long-term cardiac safety of adjuvant T in the general population.

**9505 Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Cardiovascular diseases after Hodgkin lymphoma treatment: 35-year disease risk and sequence of events.** *Presenting Author: Frederika A. van Nimwegen, Department of Psychosocial Oncology and Epidemiology,The Netherlands Cancer Institute, Amsterdam, Netherlands*

**Background:** Hodgkin lymphoma (HL) survivors are known to be at increased risk of cardiovascular disease (CVD), causing excess morbidity and mortality. It is unclear, however, whether the increased risk persists after 35 years and whether there are specific patterns in the sequence of multiple CVDs in individual patients. **Methods:** A cohort study was performed including 2,528 5-year HL survivors, diagnosed before age 51 and treated between 1965-1995. We assessed CVD endpoints (ischemic heart disease [IHD], congestive heart failure and cardiomyopathy [HF] and valvular heart disease [VHD]) up to October 2013 through questionnaires to GPs and cardiologists. Cumulative incidence of CVDs was estimated accounting for death as a competing risk. Risk factors were evaluated using Cox regression. Standardized Incidence Ratios (SIRs) were estimated to compare CVD risk with the general population. **Results:** We identified 1,419 CVDs in 752 patients, after a median follow-up of 21 years. Following mediastinal radiation (medRT), 35-year cumulative incidence of CVD was 46.3% (95%CI: 43.5%-49.1%), compared to 18.6% in patients not treated with medRT (14.3%-23.4%). The most frequently diagnosed first cardiac event was IHD (49%), followed by VHD (40%). 49% of CVD patients developed multiple CVDs; 92% of these patients received medRT; among patients with one CVD and patients without any CVDs, this was 90% and 77%, respectively ($p<0.001$). HF was mostly diagnosed as last CVD (67% of HF). Both medRT (Hazard Ratio (HR): 3.6, 95%CI: 2.8-4.7) and anthracycline-containing chemotherapy (HR: 1.6, 95%CI: 1.3-1.9) increased the risk of any CVD independently. More than 35 years after HL diagnosis, our patients had a 2.1–fold increased SIR of primary IHD or HF (95%CI: 1.1-3.7), compared to the general population, corresponding to 126 excess cases per 10,000 person years. 9.4% of patients who died, died from CVDs. Median survival time after a first CVD was 5.1 years. **Conclusions:** The risk of CVD is strongly increased for at least 35 years following HL treatment, especially after medRT. Multiple CVDs are frequently observed. Physicians should be aware of the persistently increased risk of CVDs and the increased risk of developing subsequent CVDs.

**9506 Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Increasing cardiovascular screening in at-risk adult survivors of pediatric malignancies: A randomized controlled trial.** *Presenting Author: Melissa M. Hudson, St. Jude Children's Research Hospital, Memphis, TN*

**Background:** Adults treated with anthracycline chemotherapy and/or chest radiation for pediatric malignancies are at increased risk of cardiomyopathy. Left ventricular function (LVF) screening provides opportunities for early detection and intervention that may preserve heart function. The objective of the ECHOS study was to determine whether the addition of advanced practice nurse (APN) telephone counseling to a print survivorship care plan (SCP) significantly increases the proportion of at-risk survivors who complete cardiomyopathy screening. **Methods:** Survivors currently age $>$ 25 years participating in the Childhood Cancer Survivor Study who received cardiotoxic therapy and reported no history of cardiac screening during the past 5 years were eligible for enrollment. The 472 participants (mean age 40.1, range 25.0-59.0; 53.3% females) were randomized to: 1) standard care consisting of SCP summarizing cancer treatment and cardiac health screening recommendations (n=234) or 2) standard care plus two APN telephone counseling sessions (n=238). The primary outcome, completion of a LVF assessment within 1 year, was validated by medical records and compared between the two arms using adjusted relative risks (RR) with 95% confidence intervals (CI). **Results:** Participants in the standard and APN counseling groups did not differ by demographic or clinical characteristics. At the time of 1-year follow-up (411 participants completing the study), 107/205 (52.2%) of the survivors in the APN group completed screening compared to 46/206 (22.3%) in the non-APN group ($p<0.0001$). With adjustment for gender, age ($<30$, $30+$) and Children's Oncology Group recommended screening frequency group (annual, 2 years, 5 years), survivors in the APN-group were more than two times more likely than the control group to have the recommended cardiovascular screening (RR 2.31; 95% CI: 1.74-3.07). **Conclusions:** The addition of telephone counseling to a SCP with cardiac health screening recommendations increases cardiac screening in at-risk survivors. These strategies can be adapted to support other types of health-protective screening in other at-risk survivor populations. Clinical trial information: NCT01003574.

**9507 Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Impact of vaginal dehydroepiandosterone (DHEA) on vaginal symptoms in female cancer survivors: Trial N10C1 (Alliance).** *Presenting Author: Debra L. Barton, Mayo Clinic, Rochester, MN*

**Background:** Impaired sexual satisfaction is a prevalent and distressing issue for female cancer survivors. The aim of this study was to evaluate the impact of vaginal DHEA on vaginal atrophy symptoms and sexual function. **Methods:** A controlled, randomized trial evaluating 3.25 versus 6.5 mg of DHEA vaginally was conducted. Postmenopausal women with previous breast or gynecologic cancer were eligible if they reported $\geq$ moderate vaginal dryness or pain. DHEA was compounded in a bioadhesive vaginal moisturizer. Women inserted the bioadhesive moisturizer with or without DHEA using a pre-filled syringe daily x 12 weeks before going to sleep, after any sexual activity. The most bothersome vaginal symptom (dryness or pain) was evaluated with a single item Likert scale, and sexual function with the Female Sexual Function Index (FSFI). Side effects were graded by providers using the Common Terminology Criteria for Adverse Events (CTCAE) and self-report. Laboratory tests to assess systemic absorption were done. Analysis of change from baseline to 12 weeks (primary endpoint) included independent t-tests, comparing each DHEA treatment arm with plain moisturizer. **Results:** 441 women from 82 institutions were randomized, 147 in each arm. Women in all 3 arms reported significant improvement in their most bothersome symptom. Cohen's d effect size for severity decrease was 1.4, 1.6 for DHEA 3.25, 6.5 mg respectively and 1.3 without DHEA. Compared with no DHEA, women receiving DHEA 6.5 mg reported statistically significant improvements in sexual function at 12 weeks, based on the FSFI full scale score as well as all sexual domain scores except orgasm (p-values $<.0001$ to 0.03.). Effect sizes ranged from 0.3 to 0.6. There were no significant differences in grade 2/3 toxicities. Two self-reported side effects, voice changes and headaches, were worse for DHEA arms compared to no DHEA. Lab data demonstrated no evidence of clinically important systemic estrogenic activity. **Conclusions:** These data support use of a daily vaginal moisturizer to improve vaginal atrophy symptoms. Vaginal DHEA significantly improves sexual desire, arousal, pain and overall sexual function, compared to this bioadhesive moisturizer alone. Clinical trial information: NCT01376349.

**9508 Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**NCCTG N10C2 (Alliance): A double-blind, placebo-controlled study of magnesium supplements to reduce menopausal hot flashes.** *Presenting Author: Haeseong Park, Virginia Commonwealth University, Richmond, VA*

**Background:** Hot flashes (HFs) are a common symptom in female breast cancer survivors that can negatively impact quality of life. Preliminary data suggest that magnesium may be an effective, low-cost treatment for HFs causing minimal side effects. **Methods:** A four-arm, double-blinded, placebo-controlled randomized trial was conducted. Postmenopausal women with a history of breast cancer and bothersome HFs were randomized into treatment groups of 800 mg or 1200 mg of magnesium oxide per day, or a corresponding placebo group in 2:2:(1:1) ratios. HF frequency and scores (number times severity) were measured using a validated HF diary. A one-week baseline period preceded initiation of study medication. The primary endpoint was the intra-patient difference in average hot flash score between baseline and at the end of the treatment period, comparing each magnesium arm to the combined placebo arms using a gate-keeping procedure. With a sample size of 80 patients per arm, there was 80% power to detect a difference of 8.6 points in HF score (on 0-100) using a two-sided 5% type I error rate. **Results:** 289 women were enrolled between 12/2011 and 03/2013. The study arms were well balanced. Results were analyzed using a repeated measures model on weekly HF score, based on a modified intent-to-treat principle. Mean HF scores, frequencies, and associated changes at the end of the treatment period for each arm are show in the table. An increased frequency of diarrhea was reported in magnesium arms compared to placebo. No statistically significant difference in other toxicity or quality of life measures occurred. **Conclusions:** The results of this trial do not support the use of magnesium oxide for HFs. Clinical trial information: NCT01439945.

| | Placebo (N=90) | 1,200 mg (N=91) | P value** | 800 mg (N=88) | P value** |
|---|---|---|---|---|---|
| **Mean baseline HF score (SD)** | 17.3 (10.8) | 15.4 (10.5) | 0.09 | 16.0 (9.6) | 0.48 |
| **Mean HF score reduction* (SD)** | 5.9 (8.6) | 5.4 (6.6) | 0.84 | 4.2 (5.8) | 0.31 |
| **Mean baseline HF frequency (SD)** | 8.9 (4.5) | 7.6 (3.9) | 0.03 | 8.5 (4.3) | 0.49 |
| **Mean HF frequency reduction* (SD)** | 2.6 (3.3) | 2.3 (2.6) | 0.88 | 2.0 (2.3) | 0.38 |

* Change at the end of treatment period compared to baseline. ** Kruskal-Wallis p value compared to placebo group.

**9509 Clinical Science Symposium, Sat, 3:00 PM-4:30 PM**

**Decline of cognitive functions among elderly localized breast cancer patients after adjuvant treatment: COG-AGE study.** *Presenting Author: Florence Joly, Unité de Recherche Clinique, Centre François Baclesse, Caen, France*

**Background:** Cognitive deficits (CD) have been reported among patients receiving chemotherapy (CT) for cancer.Despite their increased propensity for age-related CD that may worsen during CT, elderly patients have been poorly studied. We assessed the impact of adjuvant treatment as compared to objective and subjective cognitive functions at baseline among elderly localized breast cancer (LBC). **Methods:** Women >65 years-old with LBC were recruited and compared to a sample of healthy women matched on age and education. Episodic and working memories, executive functions and information processing speed were assessed with neuropsychological tests at baseline and at the end of adjuvant treatment (or at the same interval for healthy women). Questionnaires were used to assess subjective CD, anxiety, depression and fatigue. Geriatric assessment was also performed. Longitudinal neuropsychological scores were analysed with Reliable Change Index of Iverson to control practice effects. **Results:** Concern 119 elderly LBC (71±4 years) (58 received CT and 61 received only radiotherapy (RT)), and 62 healthy women (71±5 years). Patient characteristics are: mastectomy (28%), stage (I-II: 87%), positive hormonal receptor (88%), positive Her2 (17%); and Activities Daily Living (ADL) and Instrumental ADL means were 6(±0.09) and 0.24(±0.79). After adjuvant treatment, 49% of patients had objective cognitive decline compared to the performances of the healthy women. The main objective CD concerned working and verbal episodic memories (25% and 15%, respectively). No significant difference on CD was observed between CT and RT groups. Only patients treated with CT developed more cognitive and quality of life complaints and fatigue than healthy women (p=0.002, p=0.04 and p=0.008). **Conclusions:** This is the first large longitudinal study assessing cognitive function after adjuvant treatment in elderly LBC patients. Patients are more at risk to develop objective cognitive impairments during treatment than healthy women. Cognitive and quality of life complaints and fatigue were mainly reported among patients after CT. However we did not find deleterious impact of CT on objective cognitive functions.

**9510 Clinical Science Symposium, Sat, 3:00 PM-4:30 PM**

**Standardized, progressive exercise program (EXCAP) to reduce psychological distress and improve inflammatory cytokines of distress among prostate cancer survivors.** *Presenting Author: Charles Stewart Kamen, University of Rochester Medical Center, Rochester, NY*

**Background:** Psychological distress (a negative emotional, social, or spiritual response to cancer) is among the most common side effects of cancer diagnosis and treatment. Brief and palatable interventions are needed to ameliorate distress in diverse cancer populations, including men with prostate cancer, who may be unwilling to engage in traditional and time-intensive forms of psychotherapy. EXCAP(Exercise for Cancer Patients), a standardized, 6-week, home-based, progressive aerobic and resistance training program, has proven efficacious in improving fatigue among cancer survivors, but its effect on distress and on inflammatory cytokines associated with the pathophysiology of distress are unknown. **Methods:** In this Phase II RCT, 58 older prostate cancer survivors (age M=67) were randomized either to Arm 1) standard care (control) or Arm 2) EXCAP(intervention). Psychological distress (from the Profile of Mood States) and inflammatory cytokines (IFN-γ, IL-6, IL-8, IL-10, sTNFR-1) were measured at baseline and post-intervention (6 wks later). We used ANCOVA to assess the effect of EXCAPon distress and inflammatory cytokines at post-intervention, controlling for baseline values. We used Pearson correlations to evaluate mechanistic associations between change in distress and change in inflammatory cytokines from pre to post. **Results:** Among men with prostate cancer, the EXCAPintervention significantly improved psychological distress relative to standard care, as measured by the POMS Total score (EXCAP M=-5.17, SD=14.02; control M=2.43, SD=8.06; F(4,51)=3.34, p=.02). Decreases in distress among EXCAPparticipants were associated with decreases in IFN-γ ($r$ = .40, p = .03) and IL-10 ($r$ = .39, p = .04). This pattern was not seen in the control arm. **Conclusions:** This study supports the use of EXCAPfor reducing psychological distress and suggests a potential biological mechanism by which this improvement occurs, namely by reducing systemic inflammation. Future, confirmatory research is needed to replicate these findings in larger and diverse samples of cancer survivors. Clinical trial information: NCT00815672.

**9511 Clinical Science Symposium, Sat, 3:00 PM-4:30 PM**

**Predictive factors of early death during 100 days after a comprehensive geriatric assessment in older patients with cancer: A prospective cohort study of 576 patients.** *Presenting Author: Rabia Boulahssass, UCOG PACA EST CHU de Nice, Nice, France*

**Background:** The purpose of this study is to analyse predictive factors of early death in older patients with cancer during 100 days after a geriatric comprehensive assessment (CGA) in order to help oncologist in the therapeutic decisions. **Methods:** 576 older patients with cancers are enrolled, 29 cases could not be analyzed because of difficulties of language (aphasia, mutism) finally in the study. This study is a cohort and prospective study approved by an ethics committee. A geriatric comprehensive assessment (CGA) has been done before the treatment decision. Geriatric data (MMSE, MNA, BMI, grip hand grip strength ,ADL, IADL, CIRSg, Gait speed, QLQC30, Charlson, G8 and Balduccci classification) are collected . Characteristics of the cancer, social and demographic data are also collected. During 100 days of follow up, the rate of death, treatments made and geriatric interventions are collected. **Results:** 22% of the patients have died during the follow up of 100 days. Mean age of the patients is 82 years old (70-96). In univariate analyzes, Patients with lower gait speed (HR=4,2 (2,7-6,2)), loss of autonomy in the ADL (HR=2,6(1,7-3,8) and in the IADL (HR=2,8(1,8-4,5), metastatic cancers (HR=2,1 (1,5-3,1)), poor nutritional status with MNA <17 (HR 8,2 (2,6-29)), home confinement (HR=3,3 (2,3-4,8)), Worse quality of life (HR=4(2,3-7,4)), G8<14 (HR=1,6(1,1-2,4)), Charlson pondered >6(HR=2,2(1,1-4,3)) and higher state score on Balducci's classification had significantly more risk to die.In multivariate analyses poor nutritional status with MNA<17 (HR=2,6(1,1-6,8)),metastatic cancers (HR=2,2(1,4-3,5)) and gait speed<0,8m/s (HR=2(1,1-3,7)) had significantly more risk to die. **Conclusions:** This study confirms the importance of the geriatric comprehensive assessment in oncogeriatric patients to predict risk factors of worse outcomes. It's necessary to screen potential deficiencies to introduce geriatric interventions like care plan for nutrition or physiotherapy and could help oncologists in making therapeutic decisions.

**9512 Clinical Science Symposium, Tue, 9:45 AM-11:15 AM**

**The ENABLE III randomized controlled trial of concurrent palliative oncology care.** *Presenting Author: Marie Bakitas, The University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL*

**Background:** Evidence from randomized controlled trials (RCTs) supports integration of oncology and palliative care; how soon after diagnosis to initiate palliative care has not been defined. **Methods:** We conducted a 'fast track' RCT of patients with advanced cancer in a rural, NCI-designated cancer center, VAMC, and community clinics in NH and VT to determine the effect of immediate vs. delayed (3 months after diagnosis) entry patients into the ENABLE concurrent oncology palliative care intervention on primary outcome measures: QOL (FACIT-pal), symptom impact (Symptom impact subscale of the QUAL-E, mood (CES-D), at 3 and 6 months and survival at 1 year (from enrollment to death or study completion). Other outcomes included: resource use (hospital and ICU days and ER visits-measured by chart review), and quality of EOL care. **Results:** Participants (immediate n=104; delayed=103) were mean age 65; 52% male; 65% married; 96% white; 42% lung; 46% newly diagnosed with advanced disease; 17% with brain metastases. The estimated treatment effects (TE) using a terminal decline model (Cohen's d; immediate minus delayed) for patients from randomization to 3 months were: (mean [SE]: .13 (21.39) for QOL ($P$=.34), -.21 (3.63) for symptom impact ($P$=.09), and .04 (3.91) for depressed mood ($P$=.33). 104 participants died (immediate n=49; delayed n=55) during the study. Compared to delayed entry patients, the risk of death (hazard ratio [HR] (95% CI)) was lower for immediate participants at 1 year 0.72 (95% CI, 0.57-0.89) ($P$=0.003). Median survival for immediate entry patients was 18.3 months (95% CI, 13.2, 28.0) and 11.8 months (95% CI, 9.0, 24.1) for delayed entry patients (P=0.17). Overall median hospital days (3), ICU days (0), and ER visits (1) were identical. 55% (27) of 49 deaths in immediate and 49% (27) of delayed deaths occurred at home. **Conclusions:** Immediate vs delayed entry patients experienced a significant survival advantage at 1 year; however longitudinal TE were not statistically different. Future research is needed to define mechanisms of survival advantage in palliative care trials. Clinical trial information: NCT01245621.

**LBA9513 Clinical Science Symposium, Tue, 9:45 AM-11:15 AM**

**Benefits of immediate versus delayed palliative care to informal family caregivers of persons with advanced cancer: Outcomes from the ENABLE III randomized clinical trial.** *Presenting Author: J Nicholas Dionne-Odom, The University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL*

**The full, final text of this abstract will be available at abstracts.asco.org at 2:00 PM (EDT) on Friday, May 30, 2014, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2014, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.**

**LBA9514 Clinical Science Symposium, Tue, 9:45 AM-11:15 AM**

**Managing comorbidities in oncology: A multisite randomized controlled trial of continuing versus discontinuing statins in the setting of life-limiting illness.** *Presenting Author: Amy Pickar Abernethy, Duke University Medical Center, Durham, NC*

**The full, final text of this abstract will be available at abstracts.asco.org at 2:00 PM (EDT) on Friday, May 30, 2014, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2014, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.**

**9515 Poster Highlights Session (Board #1), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Health and functional status of long-term adult medulloblastoma/PNet survivors: A report from the Childhood Cancer Survivor Study.** *Presenting Author: Allison A. King, Siteman Cancer Center, Washington University School of Medicine in St. Louis, St. Louis, MO*

**Background:** Medulloblastoma is the most common malignant childhood CNS tumor. Survival rates increased from 40% to 70% during the past 30 years. The long-term risks of chronic medical conditions, adverse health status, and reduced psychosocial functioning in aging survivors of childhood medulloblastoma/PNET are not known. **Methods:** Using the Childhood Cancer Survivor Study cohort, we analyzed the long-term outcomes of 380 5+ year survivors of medullobastoma/PNET (median age at last follow-up: 30 years, range 7-53), diagnosed between 1970-1986. A sibling cohort (n=4031) served as a comparison population. Neurological outcomes and cataracts were analyzed as time-to-event data with cumulative incidence, with Cox regression models used to calculate hazard ratios (HR) and 95% confidence intervals (CI). Memory complications, educational status, marital status, independent living, employment status, income, and fertility were assessed cross-sectionally using generalized linear models. Comparisons were adjusted for age and sex. **Results:** By 30 years post diagnosis, mortality was 29% (CI 23-36). Cumulative incidence of second malignant neoplasm was 8% (CI 5-12), and recurrence of the original cancer 18% (CI 14-22) at 30 years. Cumulative incidence for hearing loss was 37% (CI 31-44), seizures 34% (CI 29-39), balance problems 72% (CI 67-77), tinnitus 30% (CI 23-37) and cataracts 14% (CI 9-18). Relative to siblings, survivors reported a higher risk of hearing loss (HR=36.0, CI 23.6-54.9), seizures (HR=12.8, CI 9.0-18.1), poor balance (HR=10.4, CI 6.7-15.9), tinnitus (HR=4.8, CI 3.5-6.8), and cataracts (HR=31.8, CI 16.7–60.5). Survivors were less likely to earn a bachelor's degree (RR=0.49, CI 0.39-0.60), to marry (RR=0.35, CI 0.29–0.42), to live independently (RR=0.58, CI 0.52-0.66) and to have a pregnancy or a partner become pregnant (RR=0.23, CI 0.17–0.3). **Conclusions:** Among adult survivors of childhood medulloblastoma/PNET, significant neurologic morbidity and lower levels of educational attainment and social independence exist. Given the high survival rates for these children, interventions to reduce these sequelae and support the survivors should be a high priority.

**9516 Poster Highlights Session (Board #2), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Quality of life and cognitive dysfunction in breast cancer survivors on a feasibility study of donepezil versus placebo.** *Presenting Author: Julia Lawrence, Comprehensive Cancer Center of Wake Forest University, Winston-Salem, NC*

**Background:** Breast cancer survivors report long term cognitive and quality of life effects due to cancer and chemotherapy. Cognitive enhancers (donepezil) could be a treatment option. We conducted a randomized, placebo-controlled phase II study to determine the feasibility of a larger phase III trial to improve cognitive function in breast cancer survivors with self-reported cognitive problems 1 to 5 years following chemotherapy. **Methods:** 62 patients were randomized to receive donepezil (5mg x 6 weeks + 10 mg x 18 weeks) or placebo. Participants completed a comprehensive battery of neurocognitive tests and questionnaires measuring cognitive symptoms, mood, fatigue, sleep disturbance and quality of life at baseline, 24, and 36 weeks post randomization. Women were screened for cognitive impairment with the FACT-Cog Perceived Cognitive Impairment subscale and were eligible if they scored <63. **Results:** The study opened at 16 sites and enrolled 62 women over 6 months (accrual rate of 10.2subjects/month). Ages ranged from 39 to 79 years (median of 56 years). 90% of the women were Caucasian, 87% were overweight or obese, and 65% had completed chemotherapy 1 and 3 years ago. Baseline FACT-PCI scores ranged from 5 to 61; 34 (55%) had scores < 30. Retention was 84% at 12 weeks and 76% at 24 weeks. Adherence to donepezil while on study ranged from 88% to 100%. Scores on the quality of life measures (SF-36, FACIT-Fatigue, PROMIS-7, Epworth Sleepiness Scale, Beck Depression Index and the Beck Anxiety Index) improved over the 24 weeks of treatment in both groups. In addition, scores for most of the neurocognitive tests improved over time in both arms. The study was not powered to detect differences in QOL or neurocognitive performance between arms, but positive trends in favor of Donepezil were noted for total recall and discrimination on the HVLT (Hopkins Verbal Learning Test) (p=0.08 and 0.02, respectively). **Conclusions:** In this cohort of breast cancer survivors reporting cognitive problems 1-5 years following chemotherapy, we had excellent accrual, retention and adherence. QOL and HVLT improved over 24 weeks. These data support a phase III trial of donepezil for the treatment of cognitive dysfunction in this population. Clinical trial information: NCT01466270.

**9517 Poster Highlights Session (Board #3), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Cause-specific mortality among patients with Hodgkin lymphoma (HL) up to 40 years after treatment.** *Presenting Author: Michael Schaapveld, Department of Psychosocial Oncology and Epidemiology,The Netherlands Cancer Institute, Amsterdam, Netherlands*

**Background:** HL treatment is associated with high risk of treatment-related morbidity, including second cancers and cardiovascular diseases. However, only few studies examined excess mortality after prolonged follow-up up to 40 years. **Methods:** We studied cause-specific mortality in a multicenter cohort comprising 3,575 5-year HL-survivors, diagnosed before age 51 and treated between 1965 and 1995. Follow-up was complete until at least January 2010 for 96% of the patients. For 93% of deaths, the cause was known. Mortality after HL was compared with mortality in the general population by calculating standardized mortality ratios (SMRs) and absolute excess mortality (AEM), expressed per 10,000 person-years. Treatment-specific SMRs were compared by Poisson regression. **Results:** After a median follow-up of 21.6 years since HL treatment 1,328 patients had died (19.5% from HL, 32.5% from solid tumors (ST), 15.5% from cardiac diseases (CD), 7.0% from NHL/leukemia). The SMR for causes other than HL was 8.2-fold that of the general population. The cohort experienced 149.2 excess deaths per 10,000 patients per year. The SMR and AEM for causes other than HL increased throughout follow-up: after ≥35 years the SMR was 19.2, translating into 505.9 excess deaths per 10,000 patients per year. ST accounted for the largest part of the excess mortality (overall SMR 5.6, AEM 56.1). While the SMR for ST remained stable, the SMR for CD (overall SMR 9.8, AEM 29.4) increased during follow-up (SMR at ≥35 years 28.8, $p_{trend}<0.001$)). Adjusted for sex, age and follow-up time, risk of death from CD was increased for patients treated with supradiaphragmatic radiotherapy (RT) (Relative Risk (RR) 4.8, p<0.001) or anthracyclines (RR 1.5, p=0.044), independently. The SMR for infectious causes (2.9% of all deaths, including deaths due to influenza/pneumonia) was 6.5-fold increased. Both splenectomy (2.1, p=0.041) and spleen RT (RR 3.2, p=0.001) were associated with increased risk of death due to infectious causes compared to patients not receiving such treatment. **Conclusions:** Even after ≥35 years since treatment, HL patients experienced elevated SMRs and AEMs from ST and CD. Both splenectomy and spleen RT increased mortality due to infections.

**9518 Poster Highlights Session (Board #4), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Comparison of primary and secondary breast cancer in adolescents and young adults (AYA).** *Presenting Author: Melanie Goldfarb, University of Southern California, Keck School of Medicine, Los Angeles, CA*

**Background:** Breast cancer is one of the top malignancies in AYA females (ages 15-39) and may develop de novo or in patients previously treated for cancer. This study compares the tumor characteristics, treatment, and overall survival (OS) of primary and secondary (SMN) breast cancers in the female AYA population. **Methods:** All cases of invasive AYA breast cancer contained in the 1998-2010 American College of Surgeons National Cancer Database were divided into two cohorts according to primary or secondary occurrence. Comparisons using appropriate statistical methods were performed. **Results:** Of 107,373 cases of invasive breast cancer, 6,241 (6.2%) had experienced a prior malignancy. Compared with cases of primary breast cancer, patients with SMNs were more often non-Hispanics (OR:1.21, CI:1.05-1.40), insured (OR:1.58, CI:1.17-2.14), and aged 35-39 (OR:1.34, CI:1.22-1.46). SMNs were more often ER- (OR:1.23, CI:1.09-1.41), PR- (OR: 1.16, CI:1.02-1.32), microcarcinomas <1cm (OR:2.08, CI:1.89-2.30) with lobular histology (OR:1.35, CI:1.15-1.57) that presented without positive lymph nodes (OR:1.38, CI:1.27-1.51) but with distant metastases (OR: 1.60, CI:1.33-1.93). Matched by stage, SMN patients underwent more total mastectomies but received less chemotherapy, radiation, or hormonal therapy. However, SMN patients received definitive surgical treatment almost twice as fast compared to primary cancers (36.12 vs. 67.26 days, p<0.001). Patients with SMNs had a significantly decreased 3-year OS (79% vs 88.5%, p<0.001) with SMN status as an independent risk factor for decreased OS (HR: 1.69, CI: 1.483-1.93). **Conclusions:** AYAs with non-primary breast cancer have smaller, more ER-/PR- tumors but undergo more radical surgery with less adjuvant therapy than AYA's with primary malignancies. SMN status alone is an independent risk factor for decreased OS; AYAs with a breast SMN have almost a 10% lower 3-year OS. Whether the outcome disparity results from previous cancer treatment or differences in biology, environment, or access to care are areas needing further investigation.

**9519 Poster Highlights Session (Board #5), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Long-term survivorship in adult primary glioblastoma: Clinical and neurological outcomes of a large, single-center study.** *Presenting Author: Katherine B. Peters, Duke University Medical Center, Durham, NC*

**Background:** Primary brain tumors represent 1% of all diagnosed cancers, but the survival rates of patients (pts) with the most malignant form of these tumors, glioblastoma (GBM), continues to be poor with <3% of pts surviving at 5 yrs and median OS ranging from 12-14 months. A trend to tailor care to survivorship in oncology has included survivors of other cancers such as breast and prostate, but little has been done to define long-term survivorship in primary GBM and the particular concerns of this population. We sought to identify adult long-term survivors (LTS) in primary GBM and define the clinical and neurological outcomes in this population. **Methods:** In a single-center retrospective study, we evaluated over 9,000 records from January 1, 1998 to February 8, 2010 to identify adult primary GBM pts that survived ≥5 yrs and these were defined as LTS. **Results:** We identified 155 LTS of primary GBM with a median OS of 11.0 yrs (95% CI 9.0, 13.1) and a median follow-up of 9.6 yrs (95% CI 8.7, 10.7). LTS were younger with a mean age of 44.9 yrs (sd=12.1) at diagnosis and had good functional status with KPS≥ 90 for 77.3% (N=120). Most patients had gross total resection (87.7%) and all patients received radiotherapy and chemotherapy (100%). For these LTS, continued oncologic care was required as 52.2% (N=81) had 1-7 recurrences and 52.2% (N=81) had treatment with ≥ 5 chemotherapy regimens. At time of identification of pts for this analysis, there was a reduction in KPS with only 87 pts (56.2%) having a KPS≥ 90. Neurologically, a majority of LTS were on anti-epileptic medications (N=107 (69.1%)) at time of identification. Neurocognitive testing was available for 43 LTS (27.7%) and 39 pts (90.7%) had measurable impairment on testing. Other neurological sequelae included radiation necrosis (N=25), cerebrovascular accident (N=10), hydrocephalus requiring VP shunting (N=6), and dementia (N=3). **Conclusions:** To date, this is the largest single-center retrospective analysis of primary GBM LTS and clinical and neurological outcomes in this population. LTS of primary GBM continue to require specialized oncologic and neurological care and considerations to provide specialized survivorship care for this group are warranted.

**9520 Poster Highlights Session (Board #6), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Treatment summaries and care plans for post-treatment cancer survivors: Association of quality of life with empowerment.** *Presenting Author: Ellen Ingalls Beckjord, University of Pittsburgh, Pittsburgh, PA*

**Background:** We developed a conceptual framework based on Self-Determination Theory that suggests providing treatment summaries (TSs) or care plans (CPs) will positively impact quality of life (QOL) via positive impact on empowerment. We tested this framework with data from the 2012 LIVESTRONG Survey. **Methods:** 5,274 post-treatment cancer survivors (average age = 51; average 7.3 years post-diagnosis) responded to an online survey (fielded June-December 2012) that asked about receipt of a TS, follow-up instructions (FUI), and a CP. QOL was operationalized as a score (1-10) on the Distress Thermometer. Empowerment was measured with three items on confidence in getting support; ability to discuss concerns openly with a doctor; and ability to improve mood. Multivariate logistic and linear regressions modeled the odds of receiving a TS, FUI, or CP and the relationships between TS, FUI, or CP and QOL and empowerment adjusting for sociodemographic and medical characteristics. **Results:** 92% received FUI; 52% received a TS; and 17% received a CP. Women, those further from diagnosis, and those without insurance had lower odds of receiving a TS, FUI, or CP. White survivors were less likely than non-Whites to receive a TS or CP but were more likely to get FUI. Survivors who received more treatment were less likely to get a TS but more likely to get FUI or a CP. TS, FUI, and CP were all positively associated with survivors' empowerment; TS and FUI were associated with better QOL. Sequential regressions showed that the relationships between TS or FUI and QOL were mediated by a positive association between TS or FUI and empowerment. **Conclusions:** These analyses supported our framework linking post-treatment information interventions (TS, FUI) to better QOL via positive associations with empowerment. Some survivors are more likely to report receipt of a TS, FUI, or CP than others; the association between receipt and shorter times since diagnosis may reflect practice changes. As TSs and CPs become more common, research should examine cost- and time-effective methods TS and CP development and delivery and their impact on empowerment, QOL, and health behaviors over time.

**9521 Poster Highlights Session (Board #7), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**The role of the physician in the prognostic accuracy of advanced cancer patients and their caregivers.** *Presenting Author: Rachel Jimenez, Harvard Radiation Oncology Program, Boston, MA*

**Background:** Accurate understanding of prognosis among terminally ill patients and their informal caregivers is necessary for informed medical decision-making. We report on the relationship between physician prognostic discussions and prognostic accuracy of advanced cancer patients and their caregivers. **Methods:** Coping with Cancer is an NCI/NIMH-funded prospective, longitudinal study of advanced cancer patients and their informal caregivers. Baseline interviews conducted at seven outpatient oncology centers throughout the United States between September 2002 and August 2008, asked patients and caregivers if they had discussed prognosis with a physician and to estimate the patient's life expectancy. **Results:** 240 patient-caregiver dyads were identified. Median survival was 3 months. 39% (94/240) of dyads offered a numeric estimate of prognosis; the remainder answered: "I don't know." 12% of patient and 29% of caregiver estimates were accurate (+/- 3 months of survival); 34% of patients and 31% of caregivers overestimated prognosis (+/- >3-12 months of survival); 52% of patients and 36% of caregivers grossly overestimated prognosis (>12 months from death). Only 2% of patients and 4% of caregivers underestimated prognosis. Caregivers reported more prognostic discussions with the patient's physician (58.3% caregivers; 33.3% patients; $\chi^2 = 7.6$; df=1; p=0.006) and were significantly more accurate in their life-expectancy estimates when reporting a conversation had taken place (OR 5.3, 95% CI 1.7-16.9; p = 0.002), but patients were not. Accurate life expectancy estimates were significantly associated with patient with completion of a DNR Order (OR 11.7; 95% CI 3.6-38.0; p < 0.001). **Conclusions:** Patients and caregivers overestimate life expectancy, but caregivers recall more prognostic discussions with physicians and are more accurate about the patient's prognosis following such discussions than patients. However, patients with greater prognostic accuracy are more likely to complete a DNR order. Therefore, physicians should involve family caregivers in prognostic discussions whenever possible to promote a more accurate understanding of the patient's life-expectancy and advance care planning.

**9522 Poster Highlights Session (Board #8), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Web-based stepped collaborative care intervention in the context of advanced cancer.** *Presenting Author: Jennifer Lynne Steel, University of Pittsburgh, School of Medicine, Pittsburgh, PA*

**Background:** According to the NIH consensus statement, the three most common and debilitating symptoms for cancer patients are depression, pain and fatigue. The aims of this study were to test the efficacy of a web-based collaborative care intervention to reduce cancer-related symptoms and improve quality of life in advanced cancer patients. **Methods**: Patients with advanced cancer were randomized to a web-based stepped collaborative care intervention or usual care arm. The primary outcomes of the intervention included the Center for Epidemiological Studies-Depression (CES-D), Brief Pain Inventory, the Functional Assessment of Cancer Therapy (FACT)-Fatigue, and the FACT-Hepatobiliary. Secondary outcomes included Interleukin (IL)-1b, IL-6 and Natural Killer cells and the Caregiver Quality of Life Index and Caregiver CES-D. An intent to treat analyses was performed and effect sizes were reported using the Cohen's d (Small<0.20; Medium=0.30-0.70; Large>0.80) or Phi (Small=0.10; Medium=0.30; Large=0.50). **Results:** A total of 261 patients and 179 caregivers were enrolled in the study. Patients with clinical levels of symptoms, who were randomized to the intervention arm, reported reductions in depression (Cohen's d=0.32), pain (Cohen's d=0.74), fatigue (Cohen's d=0.48) and improvements in quality of life (Cohen's d =0.38) when compared to patients randomized to the usual care arm at 6-months. Patients randomized to the intervention arm also had reductions in IL-6 (Phi=0.34), IL-1b (Phi=0.38) and increases in NK cell numbers (Phi=0.49). The family caregivers of patients randomized to the intervention arm also had lower levels of stress (Cohen's d=0.75) and depressive symptoms (Cohen's d=0.37) when compared to the usual care arm at 6-months. **Conclusions:** The web-based collaborative care intervention was found to be effective in reducing cancer-related symptoms, immune system dysregulation, and improving quality of life in both the patients and family caregivers. Clinical trial information: NCT01640522.

**9523 Poster Highlights Session (Board #9), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Palliative radiotherapy for bone metastases: Population-based utilization near end of life in a Canadian province.** *Presenting Author: Manpreet Singh Tiwana, BC Cancer Agency, Prince George, BC, Canada*

**Background:** Palliative radiotherapy (RT) plays an important role in the care of patients dying with bone metastases (BM) and is guided by life expectancy . We sought to determine the patterns of RT fractionation in patients with BM towards their end of life in a population-based, publicly funded health care system. **Methods:** Consecutive patients with BM treated with RT between 2007 through 2011 were identified in a provincial Canadian cancer registry database. Associations between choice of RT fractionation, patient and provider characteristics were analyzed. **Results:** A total of 16,898 courses of palliative RT were delivered to 8,601 patients from 2007 through 2011. Of these RT courses 1,734 (10%) and 709 (4%) were prescribed to patients in the last 2-4 weeks and <2 weeks of their life, respectively. Multiple fraction RT was prescribed 52%, 46%, and 36% for patients who died >4, 2-4, and <2 weeks of receiving palliative RT, respectively (p<0.001). Fifteen percent of courses were planned for ≥5 RT fractions in patients who died within 2 weeks of receiving palliative RT. The proportion of patients who died within 4 weeks of RT varied by primary tumour site; lung 25%, gastrointestinal 23%, genitourinary 11%, lymphoma 9%, breast 6%, and other 19.4% (p < 0.001). The proportion of patients who died within 4 weeks of RT varied by treatment site; spine 17%, extremity 14%, pelvis 12%, other 13% (p < 0.001). After controlling for gender, age, tumour type, and treatment site, patients were less likely to receive multiple fraction RT in the last 4 weeks of life (OR 0.54; 95% CI 0.49 – 0.59; p <0.0001). **Conclusions:** This population-based analysis found that 14% of patients with bone metastases received radiotherapy during the last 4 weeks of their life. There was significant variability by primary tumour type, with approximately ¼ of lung and gastrointestinal patients receiving RT with the last 4 weeks of life, suggesting physicians treating these sites should consider benefits of RT versus the short prognosis in these tumour sites. Appropriately, patients who received RT with the last 2 or 2-4 weeks of life were less likely to receive a multiple fraction RT course compared to patients alive >4 weeks since RT.

**9524 Poster Highlights Session (Board #10), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Utilization of antineoplastic chemotherapy near the end of life in patients with solid tumors.** *Presenting Author: Shilpa Paul, Huntsman Cancer Institute, Salt Lake City, UT*

**Background:** The American Society of Clinical Oncology considers cessation of cancer-directed therapy for patients with solid tumors who lack clinical benefit from further treatment as a key opportunity to improve care and reduce costs. This study evaluated the use of chemotherapy (chemo) in solid tumors near the end of life at the Huntsman Cancer Institute (HCI). **Methods:** Patients with breast (BC), non-small cell lung (NSCLC), melanoma (MEL), and ovarian (OC) cancer who received chemo within the last 365 days of life at HCI from 1995-2012 were evaluated. Comparison of chemo use in the last 30 days of life (EOLChemo) was compared across cancer types, stage at diagnosis and change in use over time (2007-2012). Kaplan-Meier analysis was used to assess overall survival (OS) from diagnosis in stage IV patients by EOLChemo utilization. **Results:** The study included a total of 856 patients with BC (n=271, 31.7%), NSCLC (n=237, 27.7%), MEL (n=263, 30.7%), and OC (n=85, 9.9%) who received chemo at HCI within the last year of life. Median age at diagnosis of cancer was 59 years (IQR 29-95) and the average age at death was 63 years (IQR 54-73). The median time from diagnosis of cancer to death was 19.9 months and median time from last chemo to death was 1.9 months (95% CI 57-68, IQR 0.8 – 4.0). Of all patients identified, 253 (29.6%) received EOLChemo. Utilization of EOLChemo was similar (p=0.2452) across cancer types: 72 (27%) BC, 73 (28%) MEL, 78 (33%) NSCLC, and 30 (35%) OC patients. Across all cancer types there was no significant increase in EOLChemo over the past 6 years (p=0.1634). More patients diagnosed with stage IV cancer (n=97, 46.4%) received EOLChemo than those diagnosed with stage I disease (n=21,10%), p=0.0115. Stage IV patients who received EOLChemo had reduced OS compared to those who received chemo greater than 30 days from death (6.8 vs 10.2 months, HR 1.49, CI 1.16-1.90, p=0.0018). **Conclusions:** Of all patients who received chemo in the last year of life, a high percentage (~30%) occurred in the last 30 days of life, irrespective of cancer type. Chemotherapy use in the last 30 days of life was associated with reduced OS. Increased efforts for cessation of chemo near the end of life are warranted.

**9525 Poster Highlights Session (Board #11), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Results from an interdisciplinary palliative rehabiliation program for patients living with advanced cancer.** *Presenting Author: Martin Robert Chasen, Ottawa Hospital Cancer Centre, Ottawa, ON, Canada*

**Background:** After treatment, patients with active cancer face a considerable burden from the effects of both the disease and its treatment. Symptom burden has been found to remain consistent until a few weeks before death, when it worsens. The Palliative Rehabilitation Program (PRP) is an interdisciplinary program designed to ameliorate disease effects and to improve the patient's functioning. A particular concern in Palliative Care is depression, which is known to impair functioning and recovery. Depression is also one of the top-two reasons for referral to the PRP, each year. The present study evaluated changes in functioning, symptoms, and well-being after the program. As well, a pilot longitudinal study of symptoms of depression was conducted, three months following PRP completion. **Methods:** There were 171 referred patients with advanced cancer who enrolled in the 8-week PRP; 108 completed the program. Measures of physical, nutritional, social, and psychological functioning were evaluated at entry to the program and at completion. At 3-month follow-up, 20 patients returned self-report measures of depression by mail. **Results:** Participants experienced significant improvements in performance status ($p < 0.000$), nutrition ($p = 0.003$), symptom severity ($p = 0.021$ to 0.000), symptom interference with functioning ($p = 0.001$ to 0.000), fatigue ($p = 0.008$ to 0.000), and physiological measures ($p = 0.002$ to 0.000). Symptoms of depression continued to decrease following PRP completion (linear trend: $p$=0.002). Updated results will be presented. **Conclusions:** Patients living with advanced cancers who underwent the PRP experienced significant improvement in functioning across several domains. Improvements in depression scores continued to improve after completion.

**9526 Poster Highlights Session (Board #12), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Outpatient management of cancer-related pulmonary embolism: Analysis of 562 consecutive patients from the EPIPHANY study.** *Presenting Author: Paula Jiménez-Fonseca, Hospital Universitario Central de Asturias, Oviedo, Spain*

**Background:** Cancer is as a predictor of adverse outcomes in symptomatic pulmonary embolism (PE). Nowadays, the increasing diagnosis of incidental thrombosis in scheduled CT scans implies a change in PE presentation. Clinical guidelines suggest that home treatment is an appropriate alternative for selected low-risk PE-patients although specific data regarding this approach in cancer population remain scarce. The aim of the present report is to describe clinical characteristics, outcomes and feasibility of outpatient management of patients with cancer-related PEs. **Methods:** EPIPHANY is an ongoing multicenter observational study of consecutive cancer-related PEs (acute symptomatic and incidentally-found in scheduled CT scans) recruited from daily clinical practice with a minimum 3-month follow-up after PE. Outpatient management was considered on discharge from hospital less than 24 hours after PE diagnosis. **Results:** From January 2006 to September 2013 we enrolled 562 cancer patients with PE, 385 of whom (68%) were treated in hospital and 177 (32%) were managed as outpatients. Most patients treated at home (93%) had advanced cancer (TNM stages III-IV), most (77%) were being treated with chemotherapy or biological/targeted therapies and 6% underwent major surgery within 1 month. Patients treated at home more likely had an incidentally-detected PE (91% vs. 35%; p<0.001) and were 'truly asymptomatic' cases (86% vs. 30.5%; p<0.001) compared to patients treated with conventional hospitalization. The rate of major complications within 15 days of PE in patients treated at home was 3.4% (95% CI, 1.9-4.9%). Overall mortality rates were lower in outpatients at 30 days (2.3% vs. 21%; p<0.001) and 90 days (9.6% vs. 33%; p<0.001) of follow-up compared to patients treated in hospital. The most frequent cause of death was cancer progression in both groups. The rates of venous thromboembolic recurrences and major bleeding events at 30 and 90 days were comparable in both groups. **Conclusions:** Cancer-related PE can be managed at home in a high proportion of patients, especially those incidentally diagnosed. Further studies addressed to better define low risk patients in this setting should be developed.

**9527 Poster Highlights Session (Board #13), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Cancer worry, anxiety, and behaviors in girls at familial or genetic risk for breast cancer.** *Presenting Author: Angela R. Bradbury, University of Pennsylvania, Philadelphia, PA*

**Background:** Most girls in families at high risk (HR; familial or genetic) for breast cancer learn of that risk at a young age. Additionally, new guidelines support disclosure of incidental findings in cancer predisposition genes regardless of age. The association of this information with psychosocial well-being and health behaviors is unknown. **Methods:** 238 HR and control girls (11-19 YO) and mothers (48 *BRCA1/2*+) completed surveys to evaluate adjustment and behaviors. We used linear and logistic regressions with variable selection. **Results:** Daughter general anxiety (D-Anx), intrusive BC worry (IBCW), and avoidant BC worry (ABCW) were significantly higher in HR girls (Table 1). D-Anx did not differ by mother BC history. In adjusted models, only mother ABCW was associated with D-Anx (Coef 1.4, p<0.01). Mother IBCW (coef 0.3, p<0.01), mother depression (coef -0.2, p=0.01) and higher daughter perceived risk of BC (PRBC, coef 0.7, p=0.01) were associated with D-IBCW. Mother IBCW (coef 0.3, p<0.01) and daughter PRBC (coef 0.5, p=0.02) were associated with D-ABCW. There were no significant differences in risk (e.g. alcohol or tobacco use) or general preventive behaviors (e.g. exercise or diet). HR girls were more likely to perform self-breast exam (SBE) and less likely to have ever had a clinical breast exam (CBE). **Conclusions:** Adolescent girls at familial /genetic BC risk have higher general and BC specific worry, even when mom does not have a history of BC. Daughter BC worry is associated with mother BC worry, regardless of risk group. Interventions to promote adaptive responses to BC risk in mothers and daughters could be beneficial. Also, research evaluating outcomes of disclosure of genetic risk and incidental findings for adult cancer in adolescents is needed.

| | HR (n=173) Mean (SD) | Control (n=65) Mean (SD) |
|---|---|---|
| **Daughter** | | |
| **Anxiety** | 66.1 (27.7)** | 57.5 (29.5)** |
| **IBCW** | 3.0 (4.6) ** | 1.3 (2.6)** |
| **ABCW** | 2.5 (5.0)** | 0.8 (2.0)** |
| **Depression** | 44.7 (29.3) | 41.6 (26.2) |
| **Behaviors** | N (%) | N (%) |
| **Tried alcohol** | 68 (41) | 22 (36) |
| **Tried cigarettes** | 20 (12) | 4 (6) |
| **Exercise (days/week, SD)** | 3.2 (1.7) | 3.5 (1.7) |
| **SBE** | 84 (50)* | 22 (36)* |
| **CBE** | 38 (22)** | 23 (37)** |
| **Knowledge and perceptions** | | |
| **Perceived higher-risk BC** | 125 (74)** | 19 (32)** |
| **Awareness of BC genes** | 47 (28)** | 4 ( 6)** |

*P= 0.07; **P<0.05.

**9528 Poster Highlights Session (Board #14), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Psychosocial outcomes of siblings of pediatric stem cell transplant survivors.** *Presenting Author: David Kyle Buchbinder, CHOC Children's Hospital, Orange, CA*

**Background:** In addition to associated morbidity and mortality of hematopoietic stem cell transplantation (HSCT) for the recipient, one of the consequences is the impact of the HSCT experience on the family. Our aim was to describe the psychosocial health of siblings of HSCT survivors and to identify factors with adverse psychosocial health. **Methods:** A multi-institutional cross-sectional study design was utilized to assess parent-reported sibling psychosocial health, as measured by the Short Form (SF)-10 Health Survey for Children and the Pediatric Symptom Checklist 17 (PSC-17). Parent physical / emotional health was assessed using the SF-12. Family impact was assessed using the Impact on Family Scale. HSCT and demographic data were collected. Summary statistics were calculated and compared to norms. Associations between sibling psychosocial health and parent physical / emotional health as well as family impact were assessed using correlations and regression. **Results:** Eighty-nine siblings (53% males) with a mean age of 11.2 years (range 4-14) representing HSCT survivors post-HSCT (mean 5.2 years, range 1-14), with malignant (73%) and non-malignant (27%) disorders were assessed. SF-10 psychosocial (mean 49.88, sd 10.90, $p=0.92$) and physical (mean 51.55, sd 8.59, $p=0.10$) health scores were not different from normative data. Behavioral / emotional problems (PSC-17 total score $> 15$) were noted in 24% of siblings. Parents demonstrated greater physical (mean 52.91, sd 8.29, $p=0.002$) and diminished mental (mean 45.89, sd 10.57, $p<0.001$) health compared to norms. Factors associated with adverse sibling psychosocial health included adverse parent physical / emotional health ($p=0.003$ and $p<0.0001$), and greater family impact ($p<0.05$). Factors associated with greater sibling behavioral / emotional problems included adverse parental emotional health ($p=0.006$). **Conclusions:** Siblings of HSCT survivors demonstrate positive outcomes overall; however, behavioral / emotional problems are evident. These concerns are associated with parental emotional health. The impact of HSCT on siblings and parents remains beyond the initial HSCT period. Psychosocial care for HSCT families should be extended for selected siblings and parents.

**9529 Poster Highlights Session (Board #15), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Distress and psychiatric morbidity in cancer patients: Prevalence and association with mortality in a two-year longitudinal study.** *Presenting Author: Caryn Mei-Hsien Chan, University of Malaya, Kuala Lumpur, Malaysia*

**Background:** Distress and psychiatric morbidity in cancer patients are associated with poorer outcomes including mortality. In the present study, we aimed to prospectively examine the prevalence of distress and psychiatric morbidity in a consecutive series of cancer patients in follow-ups of up to 24 months from diagnosis and its association with mortality. **Methods:** Participants were 467 consecutively recruited adult cancer patients attending oncology follow-ups at a single academic medical centre. Assessment consisted of the Hospital Anxiety and Depression Scale (HADS) at baseline (T1) and 4- to 6-weeks (T2), and structured clinical interviews at 6-months (T3) and 12- to 18-months (T4). All patients were followed up to 24-month survival with comparison between co-morbid psychiatric cases and non-cases made. Overall survival was calculated using the Kaplan-Meier method. The research protocol was reviewed and approved by the institutional ethics committee. **Results:** Of 467 patients, 217 patients with elevated total HADS scores ($\geq 16$) at baseline (T1) and 4- to 6-weeks (T2) met criteria for a DSM-IV-TR Axis I disorder (major mental disorders) at 6-months follow-up (T3). At 12- to 18-months follow-up (T4), 115 patients were re-interviewed, with 102 patients assigned a diagnosis. Overall prevalence of psychiatric comorbidity was approximately 46%. Seventy four deaths occurred during the 24-month study period (27 in the non-case group, 47 in the case group). The main cause of death was disease progression. Cancer patients without psychiatric morbidity had a survival benefit of 2.24 months, or 67 days. Mean survival at 24 months was 20.87 months (95% CI 20.06-21.69) for cancer patients with psychiatric morbidity versus 23.11 months (95% CI 22.78-23.43) for those without ($p < 0.001$). **Conclusions:** Findings demonstrated a survival benefit of 2.24 months for cancer patients without psychiatric comorbidity. The high rate of psychiatric morbidity makes it essential for clinicians to identify patients most at risk and offer appropriate intervention, as there is good evidence to support the efficacy of monitoring and active treatment.

**9530 Poster Highlights Session (Board #16), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Efficacy of a video-based psychological intervention for cancer-related insomnia: Results of a randomized controlled trial.** *Presenting Author: Josée Savard, Université Laval, Québec, QC, Canada*

**Background:** Cognitive-behavioral therapy (CBT) is considered the treatment of choice for insomnia but is only rarely offered to cancer patients. It is therefore important to develop treatment formats that would maximize its accessibility in routine care. This study aimed at comparing the short- and long-term efficacy of two different formats of CBT for insomnia, a professionally-administered format (PCBT-I) and a video-based format (VCBT-I), to that of a no-treatment control condition (CTL). **Methods:** A sample of 242 women with breast cancer was randomized to: 1) video-based CBT-I (VCBT-I; $n=80$), composed of a 60-min animated video + 6 booklets; 2) professionally-administered CBT-I (PCBT-I; $n=81$), composed of 6 weekly sessions of 50 min; and 3) no treatment ($n=81$). The main study variables, collected at pre- and post-treatment, as well as at 3-, 6-, and 12-month follow-ups, were the Insomnia Severity Index (ISI) total score and sleep parameters derived from a daily sleep diary: sleep onset latency (SOL), wake after sleep onset (WASO), early morning awakenings (EMA), total wake time (TWT), and sleep efficiency (SE). **Results:** Mixed models analyses revealed that both PCBT-I and VCBT-I were associated with significantly greater sleep improvements, assessed subjectively, as compared to CTL at post-treatment. However, compared to VCBT-I, PCBT-I was associated with significantly greater improvements of ISI scores and EMA, depression, fatigue and dysfunctional beliefs about sleep. The remission rate of insomnia was significantly greater in PCBT-I as compared to VCBT-I (71.3% vs. 44.3%, $p<.005$).Except for WASO, no significant differences were found between the post-treatment and follow-up assessments in PCBT-I and VCBT-I groups (time effects). Between group differences at 3-, 6-, and 12-month follow-ups revealed larger treatment effects in PCBT-I when compared to CTL alone (ISI, WASO, EMA, SE) or both VCBT-I and CTL (SOL, TWT). **Conclusions:** Both short-term and long-term findings show that our video-based CBT-I is a most valuable alternative but that face-to-face sessions remain the optimal format for administering efficaciously CBT for insomnia in cancer patients. Clinical trial information: NCT00674830.

**9531 Poster Highlights Session (Board #17), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Effect of cognitive behavioral therapy for insomnia (CBT-I) and/or armodafinil on insomnia in cancer survivors.** *Presenting Author: Anita Roselyn Peoples, Department of Surgery, University of Rochester Medical Center, Rochester, NY*

**Background:** Insomnia is an underreported distressing side effect of cancer and its treatment, which can persist for months after treatment affecting the course of cancer survival. It exacerbates fatigue and results in reduced quality of life (QOL), allowing for the possibility that treatment of insomnia may improve associated symptoms and QOL. Although CBT-I is considered the nonpharmacologic treatment of choice for insomnia in the general population, it often results in short-term daytime sleepiness. The present study examines whether CBT-I in combination with a wakefulness promoting agent, armodafinil (A), results in greater overall reduction in insomnia in cancer survivors. **Methods:** Primary analyses examine if one or more of the intervention conditions (i.e., CBT-I, A, or both), when compared to placebo (P) group, reduce insomnia in cancer patients following completion of chemotherapy and/or radiotherapy. We report on 88 cancer survivors (mean age 56, 88% female, breast cancer 68%) randomized to one of four 7-week long intervention conditions: 1) CBT-I+A, 2) CBT-I+P, 3) A only, and 4) P only. Insomnia severity was assessed by the validated Insomnia Severity Index (ISI) questionnaire at consent, following the intervention (post), and again three months later (follow-up), with higher scores indicating greater insomnia. **Results:** Mean post ISI scores in groups 1-4 were 4.12, 5.61, 11.32, and 10.28, respectively. ANCOVA with multiple imputation and controlling for scores at time of consent showed that both CBT-I+A ($p=0.001$) and CBT-I+P ($p=0.01$) groups had significantly less insomnia than those in the placebo group, with effect sizes of 1.31 and 1.02, respectively. Armodafinil and placebo groups were not significantly different ($p=0.584$); nor was the CBT-I+A group significantly different from the CBT-I+P group ($p=0.421$). Follow-up ISI scores were essentially the same as post scores. **Conclusions:** These findings show that CBT-I results in clinically significant improvement in insomnia, with effects that persist long term. Armodafinil had no significant effect on insomnia nor on the efficacy of CBT-I. Supported by NCI grant 5 R01 CA126968. Study medication was provided by Teva Pharmaceutical USA. Clinical trial information: NCT01091974.

**9532 Poster Highlights Session (Board #18), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Omega-3 fatty acids for aromatase inhibitor–induced musculoskeletal symptoms in women with early-stage breast cancer (SWOG S0927).** *Presenting Author: Dawn L. Hershman, Columbia University Medical Center, New York, NY*

**Background:** Musculoskeletal symptoms are the most common side effect of aromatase inhibitors (AIs) and can result in decreased quality of life and discontinuation of therapy. Omega-3-fatty acids (O3-FAs) have anti-inflammatory effects and can be effective in decreasing arthralgias from rheumatologic conditions. Omega-3 fatty acids are used by 25% of breast cancer survivors. **Methods:** Women with early-stage breast cancer, taking an AI for ≥90 days and who had a worst pain/stiffness score of ≥5 of 10 using the Brief Pain Inventory (BPI-WP) were randomized to receive either 3.3 grams of O3-FAs or placebo (soybean/corn oil) daily for 12 weeks. Subjects completed quality of life (FACT-ES) and pain assessment (WOMAC, M-SACRAH) at baseline, weeks 6, 12 and 24. Multiple linear regression was used to examine the difference in BPI-WP (primary outcome) between the two groups. Clinically significant change was defined as ≥2-point drop from baseline. **Results:** Among 262 patients registered, 249 were considered evaluable with 122 women in the O3-FA arm and 127 in the placebo arm. No notable imbalances by arm were observed. Baseline BPI-WP was 6.98 and 7.09 in the O3-FA and placebo groups respectively. The mean observed BPI-WP score decreased by 1.74 points at 12 weeks compared to baseline with omega-3, decreased by1.50 points with placebo and decreased further by 24 weeks (2.22 & 1.81 points, respectively) despite discontinuation at 12 weeks. In a linear regression adjusting for the baseline score, osteoarthritis and taxane use, adjusted 12-week BPI-WP scores were similar in both arms (p=0.58). The proportion of patients with a ≥ 2-point drop in 12 week BPI -WP was 61% on Omega-3 and 57% on Placebo, p=.44. O3-FAs resulted in increased grade ≥1 diarrhea (15 vs 6 patients). Serial fasting blood is being analyzed for cholesterol and inflammatory markers. **Conclusions:** We found a substantial (60%) and sustained improvement of AI arthralgias with both the omega-3 and placebo, but found no meaningful difference between the groups. These results suggest either the placebo (soybean/corn oil) had beneficial effects or that a large placebo effect should be expected when conducting trials for AI arthralgias. Clinical trial information: NCT01385137.

**9533 Poster Highlights Session (Board #19), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Effectiveness trial of a community-based supervised exercise program in cancer survivors.** *Presenting Author: Prue Cormie, Edith Cowan University, Perth, Australia*

**Background:** The majority of cancer survivors (50-90%) do not participate in sufficient exercise and there is a paucity of research investigating the effectiveness of 'real life' exercise interventions. The aim of this trial was to determine if a supervised exercise program administered as it would be in a standard survivorship care setting improves patient outcomes. **Methods:** 430 survivors (301 female, 129 male; 61 ± 12 years; BMI: 27 ± 5) within 2 years of a cancer diagnosis participated in this investigation. Participants had been diagnosed with one of 40 different types of cancer, predominately breast – 41%, prostate – 13%, bowel – 10% & lymphomas – 8%. Between 2011-2013 participants self-enrolled in a 3-month community-based exercise program involving aerobic and resistance exercise supervised by accredited exercise physiologists across 12 fitness centres in Western Australia. Assessments were conducted at baseline, post-intervention and 6-months follow-up. **Results:** 306 participants (71%) completed the program attending an average 18 ± 5 out of a possible 24 sessions. No adverse events occurred during the exercise sessions. Significant ($p \leq 0.05$) improvements were observed post-intervention in diastolic blood pressure (3%, -2.1 ± 9.9 mmHg), waist circumference (1%, -0.8 ± 4.6 cm), physical function (400m walk 6%, -15 ± 40 s; repeated chair rise 18%, -2.2 ± 2.5 s; strength 23%, 18 ± 19 kg [n=135]; balance 6%, 4 ± 8 [n=140]), quality of life (all domains of the SF-36 3-10%, 1.4-4.3 ± 5.5-8.7 NBS), fatigue (18%, -2.6 ± 8.1 FACIT-F) and psychological distress (13%, -1.1 ± 5.2 BSI-18). 57% of eligible participants completed the 6-month follow-up (questionnaires only). Significant improvements in all domains of quality of life (4-12%, 1.5-5.1 ± 6.4-10.4 NBS) and fatigue (30%, -4.7 ± 8.9) remained with a borderline improvement in psychological distress (11%, -1.0 ± 6.6 p = 0.053). The estimated monthly medical expenditure (SF-6D utility index) for participants was reduced significantly at post (12%, -$44 ± 114) and follow-up (14%, -$54 ± 139). **Conclusions:** A community-based exercise program of just 3 months in duration resulted in significant and sustained improvements in the physical, mental and social wellbeing of cancer survivors.

**9534 Poster Highlights Session (Board #20), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Effects of resistance training on fatigue and quality of life in breast cancer patients undergoing radiotherapy.** *Presenting Author: Karen Steindorf, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg, Germany*

**Background:** Breast cancer patients during and after radiotherapy often suffer from cancer-related fatigue which frequently impairs quality of life (QoL). Exercise may decrease fatigue and improve emotional well-being. However, studies on resistance training for patients during radiotherapy are scarce. Thus, we assessed the effects of a 12-week supervised resistance training intervention on fatigue and QoL in breast cancer patients during adjuvant radiotherapy within a randomized controlled trial. **Methods**: 160 patients (80/arm) with breast cancer stage 0-III undergoing adjuvant radiotherapy were randomly assigned to 12-weeks of progressive resistance training (2x/week) or group-based relaxation training (2x/week). The primary endpoint fatigue was assessed with the 20-item FAQ (0-10 scale), quality of life with the EORTC-QLQ-C30 and BR23 (0-100 scale). Statistical analyses were based on analysis of covariance models for the individual changes from pre- to post-intervention. **Results**: In intention-to-treat analyses, significant between-group mean differences (MD) favoring the intervention group were found for general fatigue (MD=-0.51, 95% confidence interval (CI): -1.01, -0.01, p=.044, effect size (ES)=0.33) and the subscale physical fatigue (MD=-0.83 (-1.48, -0.18), p=.013, ES=0.40), but not for affective (p=.91) or cognitive fatigue (p=.65). For QoL, significantly larger improvements regarding role function (MD=8.5 (0.6, 16.3), p=.035, ES=0.35) and pain (MD=-7.4 (-14.4, -0.3), p=.040, ES=0.34) were seen among exercisers compared to controls. Future perspective improved significantly stronger in the relaxation group than in exercise group (MD=-8.4 (-16.6, -0.1), p=.047, ES=0.34). **Conclusions**: This large randomized exercise intervention trial indicates that a 12-week resistance training program is an effective strategy to improve fatigue and important components of QoL in breast cancer patients during adjuvant radiotherapy. Further, as group-based relaxation training was chosen as control group and not usual care, our results indicate that resistance training provides beneficial effects that may go beyond psychosocial effects induced by group-based programs. Clinical trial information: NCT01468766.

**9535 Poster Highlights Session (Board #21), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Physical activity during cancer treatment (PACT) study: Short- and long-term effects on fatigue of an 18-week exercise intervention during adjuvant chemotherapy in patients with breast or colon cancer.** *Presenting Author: Anne M May, University Medical Center Utrecht, Utrecht, Netherlands*

**Background:** Fatigue is a major problem of cancer patients. Thirty percent of cancer survivors still report serious fatigue three years post- treatment. Physical exercise during cancer treatment might reduce symptoms of fatigue. The primary aim of the present multicenter randomized controlled trial was to compare the short- and long-term effects on fatigue of an 18-week exercise intervention during adjuvant chemotherapy for breast or colon cancer patients. **Methods:** 237 patients (204 breast and 33 colon cancer) were randomly assigned to supervised aerobic and resistance exercise (n=119) or usual care (n=118). In addition to the supervised exercise, the intervention group was asked to be physical active for 30 minutes a day on 3 other days. Fatigue was assessed with the validated Multidimensional Fatigue Inventory at baseline (i.e. within 6 or 10 weeks after diagnosis for breast and colon cancer patients, respectively), after 18 weeks and after 9 months. **Results:** Intention to treat analyses using linear mixed-effects models showed a significant effect over time in favor of the intervention group for general and physical fatigue (p=0.001 and 0.02, respectively). Changes of general and physical fatigue were -0.90 (95% confidence interval: -1.77 to -0.04) and -1.24 (2.17 to -0.32) from baseline to 18 weeks and -1.12 (-2.01 to -0.22) and -0.66 (-1.62 to 0.30) from baseline to 9 months, respectively. Effects for mental fatigue, reduced activity and motivation were not significantly different. **Conclusions:** The 18-week exercise program during adjuvant treatment for breast or colon cancer showed positive results on general and physical fatigue directly after the intervention and also 4 ½ months later. Hence, exercise might be a beneficial addition to routine cancer care during adjuvant cancer treatment. Clinical trial information: ISRCTN43801571.

**9536 Poster Highlights Session (Board #22), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Effect of exercise on weight, body fat, and serum inflammatory biomarkers in breast cancer survivors with aromatase inhibitor arthralgias: The hormones and physical exercise (HOPE) study.** *Presenting Author: Melinda Irwin, Yale University, New Haven, CT*

**Background**: We recently reported that exercise reduced AI-associated arthralgias. This analysis examined potential mechanisms mediating the effect on exercise on arthralgia, specifically weight, body fat and serum C-reactive protein (CRP), IL-6, and TNF-$\alpha$. **Methods**: Women taking an AI for breast cancer and experiencing arthralgia were randomized to exercise (150 min/wk of moderate-intensity aerobic exercise and twice-weekly supervised resistance exercise) or control. Weight, dual energy X-ray absorptiometry scans, and a fasting blood sample were collected at baseline and 12-months. We used analysis of covariance, adjusted for baseline values, to evaluate mean weight, fat and inflammatory changes across groups, and used Baron and Kenny approach for mediation analysis. We evaluated moderation effects by including an interaction in the analysis. **Results**: We randomized 61 to exercise and 60 to control. Exercisers participated in, an average, 70% of resistance training sessions and 119 min/wk of aerobic exercise. Weight, body fat and CRP decreased at 12 months among exercisers (Table 1). Changes in these variables were not correlated with changes in arthralgia, and the interactions were not significant. After adjusting for weight, body fat and CRP, exercise decreased arthralgia by 35% vs. no change among control, p = .0059. **Conclusions**: Exercise decreased weight, body fat and CRP in breast cancer survivors experiencing AI-associated arthralgia. However, these changes did not mediate the effect of exercise on arthralgia. Exercise exerts beneficial effects on arthralgia via mechanisms not related to weight or systemic inflammation.

**Changes in weight, body fat, and inflammatory biomarkers (mean (SE)).**

| | Baseline | | | 12 M change | | |
|---|---|---|---|---|---|---|
| | Exercisers | Control | p-value | Exercisers | Control | p-value |
| **Weight (kg)** | 78.4 (2.1) | 75.9 (2.1) | 0.40 | -2.5 (0.8) | 0.1 (0.7) | 0.018 |
| **Body fat (%)** | 40.8 (0.8) | 40.7 (0.8) | 0.90 | -1.4 (0.6) | 0.3 (0.7) | 0.056 |
| **CRP (mg/L)** | 3.36 (0.51) | 3.27 (0.51) | 0.89 | -0.21 (0.37) | 0.52 (0.41) | 0.09 |
| **IL-6 (pg/mL)** | 1.77 (0.14) | 1.60 (0.15) | 0.39 | -0.009 (0.12) | 0.16 (0.12) | 0.34 |
| **TNF-$\alpha$ (pg/mg)** | 1.81 (0.09) | 1.72 (0.09) | 0.47 | 0.12 (0.24) | 0.25 (0.26) | 0.71 |

**9537 Poster Highlights Session (Board #23), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Genetic associations of fatigue and other symptom domains after breast cancer treatment: Results from a prospective cohort study.** *Presenting Author: Kate Webber, University of New South Wales, Sydney, Australia*

**Background:** We have previously reported on the natural history of cancer related fatigue and other symptoms after adjuvant breast cancer therapy in a prospective cohort study. This paper reports genetic associations with symptom phenotypes in this cohort. **Methods:** Women with early stage breast cancer from six metropolitan teaching hospitals in Sydney were enrolled post-surgery but before adjuvant therapy and followed for up to 5 years, with optional participation in a genetic association substudy. Self-report questionnaires recorded physical and psychological health and disability. Symptom scales for pain, fatigue, depression, anxiety, neurocognitive disturbance and neurotoxicity were derived by prinicipal components analysis from self-report questionnaires at completion of treatment. Genetic associations were sought with functional single nucleotide polymorphisms (SNPs) in cytokine genes tumour necrosis factor (TNF)-$\alpha$, interferon (IFN)-$\gamma$, Interleukin (IL)-10, neuropeptide Y(NPY) and the purinogenic transporter gene P2RX7. **Results:** 151 of the 218 participants provided samples for genetic analyses, of whom 109 were unambiguously Caucasian with corresponding self-report questionnaire data at completion of adjuvant therapy. Depression and anxiety were associated with both the IL-10 -1082 A/A genotype (both p=0.001), as well as the P2RX7 rs208294 A/A genotype (p=0.019 and 0.031). The IL-10 -1082 A/A genotype was also associated with higher levels of fatigue (p=0.032). Associations were found between high levels of neurocognitive dysfunction and homozygosity for the high expression G/G variant of TNF-$\alpha$ -308 (p=0.049). No significant associations between symptoms and NPY or IFN-$\gamma$ were seen in this cohort. **Conclusions:** These findings support for the notion that susceptibility to mood disturbance, fatigue and neurocognitive dysfunction after cancer therapy has a genetic basis. Furthermore, as these associations have also been reported in non-cancer settings, the observed findings may represent inherent susceptibility to these symptoms rather than a response unique to cancer or its treatment.

**9538 Poster Highlights Session (Board #24), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Exercise-induced changes in gene expression, muscular strength, and cancer-related fatigue in older prostate cancer patients.** *Presenting Author: Karen Michelle Mustian, University of Rochester Medical Center, Rochester, NY*

**Background:** Radiation therapy (RT) and androgen deprivation therapy (ADT) impair muscular, mitochondrial and immune function, and result in muscle weakness and cancer-related fatigue (CRF) among prostate cancer patients. We investigated the influence of an exercise intervention (EXCAP), including resistance and aerobic training, on expression of 4825 mitochondrial and nuclear genes, muscular strength and CRF. **Methods:** In this phase II randomized clinical trial, older prostate cancer patients (N=58; mean age=67), receiving RT (47%) or ADT (53%), were randomized to 6 wks of EXCAP (7 days/wk) or standard care (RT or ADT with no exercise). RNA was isolated from muscle biopsies for microarray analyses of 4825 mitochondrial and nuclear genes (N=11). Muscular strength was assessed using multiple repetition maximum testing (chest press and leg extension). CRF was assessed via valid self-report questionnaires (BFI, MFSI). Assessments were pre- and post-intervention. Analyses included robust multi-array average normalization, analyses of covariance (ANCOVA), correlations and partial least squares (PLS) with cross-validation. **Results:** MYH8, MYL5, ACTN3, XIRP1, MTTM, and HLA-DQB1 were significantly correlated with muscular strength and CRF (all p<0.05). Analyses revealed >2-fold down regulation in MYH8 and XIRP1 in the exercise group, no >2-fold changes in expression in the control group, and a >2-fold difference between groups on MTTM where MTTM was down-regulated >1.5-fold in controls with no change in exercisers (all p<0.05). ANCOVAs revealed a trend for group differences in muscular strength (all p<0.10) with significant group differences in CRF on the BFI (p<0.05) and a trend on the MFSI (p<0.10): exercisers improved while controls worsened. PLS suggested down-regulation of MYL5, ACTN3, and HLA-DQB1 may optimally predict increases in CRF. **Conclusions:** Results suggest exercise improves muscular strength and CRF and these improvements may be mediated via exercise-induced expression changes in genes involved in muscle generation and contraction (MYH8, MYL5, ACTN3, XIRP1), mitochondrial function (MT-TM) and immune function (HLA-DQB1). Funding DOD W81XWH-07-1-0341. Clinical trial information: NCT00815672.

**9539 Poster Highlights Session (Board #25), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Randomized trial of Tibetan yoga in breast cancer patients undergoing chemotherapy.** *Presenting Author: Lorenzo Cohen, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Mind-body practices improve quality of life (QOL), yet prior trials have not included *active* control groups. Our prior work found a Tibetan Yoga Program (TYP) resulted in fewer sleep disturbances. This study assessed the effects of TYP versus Stretching Program (STP) and Usual Care (UC) on sleep, fatigue and QOL of breast cancer patients undergoing chemotherapy. **Methods:** Patients with stage I-III breast cancer undergoing chemotherapy were eligible. Participants were randomized to TYP, STP or UC. TYP and STP consisted of four 90-minute sessions. TYP consisted of controlled breathing, visualization, meditation and postures. STP included common stretches for recovery and mirrored TYP postures. Sleep disturbances (PSQI), fatigue (BFI) and breast cancer-specific QOL (FACT-B) were assessed at baseline, 1 week and 1 and 6 months after the last session. **Results:** Participants were 283 women (mean age=48.8 years). We analyzed participants who completed baseline and at least one follow-up with GLM, controlling for corresponding baseline measures and age, menopausal status, stage, time since diagnosis, surgical procedure and chemotherapy regimen. Analyses revealed a significant group main effect at 6-months post-intervention for sleep duration (means: TYP=0.85; STP=1.33; UC=1.21; p=0.02), with TYP reporting greater sleep duration than STP (p=0.008) and UC (p=0.02). Similar results were found for sleep efficiency (means: TYP=1.57; STP=2.17; UC=2.29; p=0.06), with TYP being significantly different from UC (p=002). There were no significant group differences for BFI. For FACT-B, there was a significant group effect at 1-week post-intervention (means: TYP=12.5; STP=14.3; UC=13.9; p=0.05), with TYP reporting fewer symptoms than STP (p=0.02) and UC (marginal at p=0.06). At 3-months post-intervention, there was a significant group effect for FACT-B (means: TYP=7.9; SG=10.5; UC=8.7; p=0.04), with group differences between TYP and STP (p=0.01). **Conclusions:** Participating in a Tibetan yoga program resulted in better long-term sleep quality and QOL than an active control intervention or usual care. Tibetan yoga should be considered to help improve these symptoms for breast cancer patients undergoing chemotherapy. Clinical trial information: NCT00507923.

**9540 General Poster Session (Board #190), Sun, 8:00 AM-11:45 AM**

**Fentanyl exposure after subcutaneous and transdermal administration: Results from a population pharmacokinetic study in cancer patients.** *Presenting Author: Astrid W. Oosten, Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands*

**Background:** Transdermal (td) fentanyl is widely used for the treatment of cancer-related pain but is unsuitable for fast titration for severe pain. Titration with subcutaneous (sc) fentanyl is safe and effective. Nonetheless, little is known about the pharmacokinetics (PK) of sc fentanyl compared to the td route and the optimal scheme for rotation from sc to td fentanyl is unknown. Therefore, we performed a population pharmacokinetic study to unravel sc and td fentanyl PK and rotations in cancer patients (pts). **Methods:** Plasma samples for PK analysis were collected from hospitalized pts treated with td or sc fentanyl for moderate-severe cancer-related pain. Pts who were titrated with sc fentanyl were rotated to td fentanyl 1:1 in case of adequate pain control with stable doses. After patch application, sc administration was continued in unchanged dose for 6 hours and in a 50% dose for another 6 hours (Kornick et al, 2001). Baseline and outcome parameters of treatment were registered. PK data were analyzed employing NONMEM, utilizing the model as described for td use (Kokubun et al, 2012) as a starting point. Expected fentanyl levels during and after rotation were calculated using the final model. **Results:** A median of 13 (range 1-86) samples were available for 47 pts, during td administration for 5, sc for 10 and both for 32 pts. The CL/F was estimated to 33.5 L/h following td fentanyl and 54.5 L/h following sc fentanyl. In 7 out of 10 pts with plasma samples available during rotation from sc to td fentanyl, a rise in fentanyl plasma concentrations occurred with clinical signs of fentanyl-related toxicity in 4 pts. Also, calculated fentanyl levels showed a rise during rotation when using the two-step taper in 12 hours. **Conclusions:** This is the first study describing the pharmacokinetics of sc and td fentanyl in a single pt cohort. CL/F was lower for td fentanyl, suggesting that the dose of fentanyl assumed to be delivered using the td route is underestimated. When converting from sc to td fentanyl, the 12 hour method using a 2 step taper can lead to a rise in plasma fentanyl levels and carries a high risk of toxicity. Our new insights champion a shorter time period to rotate fentanyl from sc to td. Clinical trial information: EudraCT Number: 2009-013022-16.

**9541 General Poster Session (Board #191), Sun, 8:00 AM-11:45 AM**

**Intensity of end-of-life care among adolescents and young adults with cancer.** *Presenting Author: Jennifer W. Mack, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Cancer is the leading disease-related cause of death among adolescents and young adults (AYAs), but little is known about the care that AYA patients with cancer receive at the end of life (EOL). Previous work suggests that younger adults may be at risk for receiving aggressive EOL care. However, prior work has focused on the over-65 population in Medicare, with younger adults defined as those closer to 65. Thus much remains unknown about the care that AYA patients receive at the EOL. **Methods:** We evaluated existing measures of EOL care intensity among 381 AYA patients with stage IV/disseminated cancer who received care in Kaiser Permanente Southern California (KSPC), an integrated health care delivery system, and died in the years 2001 to 2010. Patients were eligible for study if they were aged 15-39 at death. Patient characteristics and measures of EOL care intensity were evaluated using KPSC's SEER-affiliated cancer registry and electronic medical records. Intense EOL care measures included chemotherapy use in the last 14 days of life, intensive care unit (ICU) care in the last 30 days of life, more than one emergency room (ER) visit in the last 30 days of life, and hospitalization in the last 30 days of life. We also evaluated a composite measure of medically intensive EOL care comprising any of the aforementioned measures. **Results:** Patients were aged 15-24 (23%), 25-34 (34%), and 35-39 (43%) at death; 50% were male and 48% were white (12% black, 12% Hispanic, 29% Asian, 1% other). Primary cancers included leukemia (25%), lymphoma (12%), colorectal (9%), lung/bronchus (8%), breast (7%), and bone/soft tissue (6%). 11% of patients received chemotherapy within 14 days of death. In the last 30 days of life, 17% of patients were admitted to the ICU; 48% had >1 ER visit; and 66% were hospitalized. Overall, 76% of subjects received at least one aspect of medically intensive EOL care. **Conclusions:** AYA patients frequently receive medically intensive EOL care, with more than three-quarters of patients receiving at least one aspect of aggressive EOL care. These findings suggest the need to better understand EOL needs and access to palliative care in this young population.

**9542 General Poster Session (Board #192), Sun, 8:00 AM-11:45 AM**

**Multimorbidity and racial disparities in use of hospice by older patients dying from cancer.** *Presenting Author: Siran M. Koroukian, Department of Epidemiology & Biostatistics, Case Western Reserve University, Cleveland, OH*

**Background:** While previous studies have documented lower use of hospice by Non-Hispanic Blacks (NHBs) than by Non-Hispanic Whites (NHWs), racial variations have not been examined in the context of multimorbidity (MM), which affects minority patients disproportionately. We sought to determine the impact of MM severity on NHBs' use of hospice in a U.S. representative sample of older adults. **Methods:** We used data from the linked 1991-2008 Health and Retirement Study (HRS), Medicare data, and the National Death Index (NDI). From the NDI, we identified fee-for-service patients ≥65 years of age who died from cancer (n=812), and retrieved their demographic data, presence of comorbidities (COM), functional limitations (FL), and geriatric syndromes (GS) from their last HRS interview. We characterized severity of MM by 3 levels: none or only one of COM, FL, or GS (MM0/1); presence of two of COM, FL, or GS (MM2); or presence of all three of COM, FL, and GS (MM3). Hospice use was identified from Medicare claims data. We developed multivariable logistic regression models to analyze the association between race and hospice use, adjusting for MM and other patient covariates. **Results:** Nearly 12% of the study population was NHB; 61.3% of NHBs and 53.0% of NHWs were identified in MM3 (p=0.057). Overall, 61% of the patients received hospice care (63.7% in NHWs, and 43.0% in NHBs, $p < 0.001$). The distribution NHBs and NHWs by MM was similar across hospice users and non-users. Adjusting for MM and other confounders, NHBs were significantly less likely than NHWs to utilize hospice (Adjusted odds ratio: 0.42, 95% Confidence Interval: 0.27-0.66, $p < 0.001$). **Conclusions:** Despite the greater representation of NHBs in the highest severity of MM category, NHBs remain significantly less likely than NHWs to use hospice, even after adjusting for MM. The findings carry important implications with regard to disparities in providing optimal, and cost effective quality of end-of-life care.

**9543 General Poster Session (Board #193), Sun, 8:00 AM-11:45 AM**

**Cancer care near the end of life (EOL) in the era of molecular-targeted agents: Changes of trend during 10 years at single institution.** *Presenting Author: Younak Choi, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea*

**Background:** In the era of molecular targeted agents, EOL care and use of chemotherapy at the EOL seems to be changed over time. The purpose of this study was to investigate and compare the cancer care near the EOL during 10 years. **Methods:** Advanced solid cancer patients who received palliative chemotherapy and had died at Seoul University Hospital were enrolled. We categorized the consecutive patients into two groups; died in 2002 (n=57), and died in 2012 (n=206). Medical records of the patients were reviewed. Aggressiveness of cancer care near the EOL was evaluated and compared in terms of following aspects; intensive care unit (ICU) care within the last one month, ER visit within the last one month, period between last chemotherapy and death, number of regimens, cycles of chemotherapy, and consultation for hospice. **Results:** The median patient age was 62 years, and 65.4% of patients (n=172) were male (primary tumor: 91 lung cancer, 27 colorectal cancer, 18 breast cancer, and 127 other). ICU care within the last month increased from 2.7 % in 2002 to 19.9% in 2012 ($P < 0.001$), and ER visit within the last month also increased from 33.6 % to 74.8% ($P < 0.001$). Median time between last chemotherapy and death has been significantly shortened from 66.0 days in 2002 to 34.0 days in 2012 ($P < 0.001$). Mean number of regimen and cycles of chemotherapy also significantly increased (1.8 to 2.5, $P < 0.001$, 5.5 cycles to 11.6 cycles, $P < 0.001$, respectively). Of note, 17.0% patients received molecular targeted agents as the last chemotherapy regimen in 2012, while none of patients received molecular targeted agents in 2002 ($P < 0.001$). Although consultation for hospice care increased from 9.1% to 37.4% ($P < 0.001$), timing of consultation was delayed from median 53 days before death to 8 days before death ($P = 0.004$). **Conclusions:** Cancer care near the EOL becomes aggressive in the era of molecular targeted agents. ICU care before death and chemotherapy use near the EOL, including molecular targeted agents, has increased and becomes aggressive during 10 years, while hospice referral has been delayed. Further nation-wide investigations are warranted.

**9544 General Poster Session (Board #194), Sun, 8:00 AM-11:45 AM**

**Patterns of chemotherapy near the end of life for patients receiving palliative bone radiotherapy.** *Presenting Author: Powell Perng, The Johns Hopkins University School of Medicine, Baltimore, MD*

**Background:** Appropriate timing of chemotherapy (CT) cessation is important for optimizing quality of life, with consensus guidelines recommending termination of CT within the last 2-4 weeks of life. Yet CT near the end of life is used in 10-30% of patients, often with little realistic chance of benefit (Kelly R, Smith TJ. Lancet Oncology 2014). We review patterns of CT at the end of life among patients receiving palliative bone radiation (RT) at a high-volume academic institution. **Methods:** Electronic medical records were used to identify patients treated with palliative bone RT at 2 centers from 9/1/2007-7/15/2012. Patient demographics and last recorded systemic (hormonal, non-hormonal oral, and non-hormonal IV) therapy characteristics were collected, and rates of CT in the last 2 and 4 weeks of life were calculated. Factors were compared using $\chi^2$and ANOVA analyses. **Results:** Complete records were found for 210 patients, and 92% were deceased at the time of analysis. Among decedents, median age at death was 64 years (22-94), and primary was 36% lung, 15% breast, 13% prostate, 5% hematologic, and 31% other sites. 12% never received CT, and 30% and 13% received CT $<4$ weeks and $<2$ weeks from death. Primary site of disease for patients receiving CT $<4$ weeks from death were 25% lung, 17 % breast, 19% prostate, 8% hematological, and 31% other cancers; there was no significant difference in site between patients receiving CT $<4$ vs. $\geq 4$ weeks or $<2$ or $\geq 2$ weeks from death. Type of CT did not significantly vary relative to time until death; CT $<4$ and $<2$ weeks from death was 53% and 52% IV, 31% and 36% oral, and 17% and 12% hormonal, respectively. 16% and 7% of all patients received IV CT $<4$ weeks and $<2$ weeks from death, respectively. Patients referred to hospice were less likely to receive CT $<4$ and $<2$ weeks from death ($\chi^2$ $p=0.003$ and $p=0.001$, respectively). There was no difference in time-to-death from date of last CT based on cancer primary or CT type. **Conclusions:** Of patients receiving palliative bone RT, rates of CT at the end of life are relatively low, using the Quality Oncology Practice Initiative benchmarks. Chemotherapy use at the end of life is lowest among patients referred to hospice, supporting engagement of hospice in terminally ill patients.

**9545 General Poster Session (Board #195), Sun, 8:00 AM-11:45 AM**

**Evaluation of falls in older adults in a comprehensive cancer center: How are we doing?** *Presenting Author: Emily Jean Guerard, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

**Background:** Falls are a major cause of morbidity and mortality in older adults ($>$ 65 years old) with as many as one in three reporting a fall in the previous year. Twenty percent of falls lead to serious injuries resulting in declines in function and increased likelihood of institutionalized care. Screening for falls is quick and simple and should be included in the clinical evaluation of an older adult by all clinicians since proven interventions to decrease falls can lead to improvements in function, treatment tolerability, and overall quality of life. The aim of this study is to evaluate medical oncologists' ability to recognize and intervene on falls in older cancer patients. **Methods:** As of October 2013, the Carolina Senior Registry had a total of 528 cancer patients greater than 65 years old seen at UNC who were queried about falls as part of a brief geriatric assessment (GA) [Hurria et. al. J. Clin Oncol 2011]. The history and physical and/or clinic notes completed by a medical oncologist within six months after completion of the GA were retrospectively reviewed for the following: documentation of falls, gait assessment, referral to either geriatrics or physical and/or occupational therapy, and measurement of a 25-hydroxy vitamin D level. **Results:** 125 (24%) of the 528 UNC cancer patients in the registry had at least one fall in the previous 6 months. Of these 125 patients, 54% had one fall and 47% had two or more falls. Seventy of these charts were reviewed and the results are shown in the Table. **Conclusions:** In an academic comprehensive cancer center, older adults who fall were not adequately evaluated by medical oncologists. Our estimates indicate that no more than 10% of patients who experience falls have appropriate medical record documentation or referrals. Practical time-sensitive methods for identification and management of falls are needed. We plan to test a point of service tool to improve medical oncologists' awareness of falls and expedite referrals for effective interventions. Supported in part by the Breast Cancer Research Foundation, New York, NY.

| Outcomes | N=70 (100%) | 95% CI |
|---|---|---|
| **Falls documented** | 2 (3%) | 0-10% |
| **Gait assessment** | 13 (19%) | 10-30% |
| **Referrals** | 2 (3%) | 0-10% |
| **Vitamin D level** | 13 (19%) | 10-30% |

**9546 General Poster Session (Board #196), Sun, 8:00 AM-11:45 AM**

**A prospective study to evaluate the Vulnerable Elders Survey-13 (VES-13) as a tool to identify frail older cancer patients (pts).** *Presenting Author: Laura Biganzoli, Sandro Pitigliani Medical Oncology Department, Hospital of Prato, Istituto Toscano Tumori, Prato, Italy*

**Background:** A major challenge in the care of older cancer pts is identification of who might benefit from adjuvant chemotherapy (CT). Frail pts (FP) typically tolerate CT poorly and/or die from causes other than cancer. It is crucial to identify FP to spare them toxicities of potentially non beneficial and non cost-effective therapy. Fried Frailty Criteria (FFC), based on the Cardiovascular Health Study (CHS) tool, and Balducci Frailty Criteria (BFC), based on several components of a comprehensive geriatric assessment (CGA), are the two most commonly used measures to identify FP. Recently a VES-13 score of $\geq 7$ has been suggested as a means to identify FP. **Methods:** Early-stage cancer pts aged $\geq$ 70 years who were candidates for adjuvant therapy were classified as frail/ not frail at baseline based on CHS assessment, CGA and VES-13 score. As FP are at risk of disability and death, pts were seen 6-monthly to assess for functional decline (FD), defined as either a change from no impaired activities of daily living (ADL) or instrumental ADL (IADL) to any IADL or ADL impairment, or a decrease of $\geq 2$ or $\geq 1$ in IADL or ADL score, respectively, confirmed at two consecutive reviews. Date and cause of death were also captured. To avoid cancer itself confounding the ability of the evaluated tools to identify FP, the main analysis included only tumor-independent events; that is, events occurring in pts without cancer recurrence. A baseline blood sample was taken to assess if analysis of serum metabolomic spectra could identify a metabolic "frailty" signature. **Results:** 185 pts, median age 77 years (range 70-91), were enrolled. Most pts had breast (65%) or colorectal cancer (30%). Median follow-up was 36 months. The incidence of tumor-independent events in relation to frailty according to VES-13, BFC and FFC and accuracy of each tool are reported in the table. **Conclusions:** VES-13 score $\geq 7$ may more accurately identify older patients at risk of health deterioration than FFC or BFC. Data comparing metabolomics with other tools to identify FP will be presented.

| Tool | Criteria used to define FP | FP | | Events | | Overall accuracy (95% CI) |
|---|---|---|---|---|---|---|
| | | n | % | n | % | |
| **CHS** | FFC | 31 | 17 | 15 | 48 | 65% (58% - 72%) |
| **CGA** | BFC | 47 | 25 | 18 | 38 | 70% (63% - 77%) |
| **VES-13** | Score $\geq 7$ | 47 | 25 | 27 | 57 | 75% (68% - 81%) |

**9547 General Poster Session (Board #197), Sun, 8:00 AM-11:45 AM**

**Changes in items of a comprehensive geriatric assessment (CGA) during follow-up: Results from the IN-GHO registry.** *Presenting Author: Friedemann Honecker, Tumor and Breast Center ZeTuP, St. Gallen, Switzerland*

**Background:** Elderly cancer patients (pts) are a heterogenous population. A CGA helps to describe the heterogeneity in a structured way, and can help to detect changes occurring during cancer therapy. The internet based IN-GHO registry prospectively collected data of elderly cancer pts from $>$100 centres in Germany and Austria, both at baseline, and during follow-up within 6 months. **Methods:** Demographic data, data on activities of daily living (ADL), instrumental activities of daily living (IADL), Karnofsky-Performance-Statuts (KPS), comorbidity (Charlson score), number of co-medication, mobility (Timed-Up&Go), cognition (Mini-Mental State Examination), and depression (2-question screening SCID) were collected at baseline. ADL, IADL, and KPS were documented again within 8-12 weeks after baseline. Differences of 5 or more points in ADL, 1 or more points in IADL, and 10% or more in KPS were classified as changes. Data from 3,168 pts aged 70+ years were documented, and changes in items of CGA were analyzed by McNemar test to compare the number of pts with increased and decreased scores. **Results:** Mean age was 76 years, 23.9% were $>$ 80 years. 52.7% were female, 77.9% were treated as outpatients, 73.5% had a solid tumor, and 26.5% had a hematological neoplasia. At baseline, ADL was $<$100 in 37.6% (data from 3,113 pts), IADL was $<$8 in 46.6% (data from 3,133 pts), and KPS was $<$80% in 23.5% (data from 2,771 pts). During follow-up, the following changes were observed: ADL score decreased in 23.0% and increased in 13.4% ($p<0.001$; data from 2,261pts), IADL score decreased in 29.8% and increased in 11.8% ($p<0.001$; data from 2,266 pts), and KPS score decreased in 35.5% and increased in 17.7% ($p<0.001$; data from 1,999 pts). Most frequently observed changes affected the items climbing stairs in ADL, and housekeeping in IADL, respectively. **Conclusions:** In ADL, IADL, and KPS, significant changes were observed in elderly cancer pts during follow-up. Highest frequency of changes was observed in KPS. While the majority of changes signified deterioration, a minority of pts showed improvement, indicating a beneficial effect of therapy.

**9548 General Poster Session (Board #198), Sun, 8:00 AM-11:45 AM**

**The underutilization of occupational and physical therapy for older adults with cancer.** *Presenting Author: Mackenzi Pergolotti, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

**Background:** Older adults are at risk of suffering adverse consequences of cancer and its associated treatments. Occupational and physical therapy (OT/PT) services seek to reduce morbidity, mortality and improve the quality of life of individuals, however little is known about the needs and use of OT/PT for this population. **Methods:** This study analyzed data from an institution-based registry of older adults 65 + with cancer and linked billing-claims data. Patients completed a geriatric assessment for registry and their clinicians were blind to results. Variables include cancer type and status, functional status (defined by Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL), cognition, falls, timed up and go (TUG), and social limitations), social support, demographics linked to billing claims for inpatient and outpatient OT/PT. Logistic regression was used to model predictors of need. **Results:** 524 patients with cancer, median age of 71, 87% Caucasian, 57 % married, 53% post-secondary education, 81% retired, 63% with breast cancer were included. 65% have at least one functional deficit and 42% have at least two functional deficits potentially requiring OT/PT. Deficits included 40% ADL, 35% IADL and 25% falls. In a multivariable model, less education and older age were significantly associated with the number of deficits (p = 0.05, 0.0001). Odds of having any deficits were higher for patients with no post-secondary education compared to adults with advanced degrees [OR= 1.8] and increased with age [5 year OR= 1.4]. Of patients with functional deficits, 6% (20/339) received OT/PT within the last year and 1.6% (5/319) received OT/PT within 3 months of noted deficit. **Conclusions:** There is severe underutilization of OT/PT for older adults with cancer. This project is significant because it is the first to outline and define predictors of functional needs and usage of OT/PT in an older population with cancer. These results outline the great need for intervention and referrals to OT/PT in this population. Future policy should be directed towards identifying and breaking down barriers to receipt of rehabilitation services by older cancer patients to decrease morbidity, and improve quality of life.

**9549 General Poster Session (Board #199), Sun, 8:00 AM-11:45 AM**

**Geriatric oncology: Comprehensive geriatric assessment tools (CGA) implementation and interdisciplinary clinical approach for elderly patients (pts) in AC Camargo Cancer Center (ACCCC), Sao Paulo, Brazil.** *Presenting Author: Aldo A. Dettino, A. C. Camargo Cancer Center, Clinica David Erlich, Sao Paulo, Brazil*

**Background:** Ageing is a global phenomenon, also in Brazil. That shift in demographics has huge impact in healthcare. Although still emerging in developing nations, there is no major national innitiative focusing on oncologic geriatric pts. The study describes a program to improve care in >70y cancer pts in A C Camargo Cancer Center, Sao Paulo. We hypothesized that incorporating CGA into daily practice can improve individualized care. **Methods:** aims of the study were to evaluate if: 1) CGA could be feasible in daily practice, 2) it could be useful as a tool in treatment/tx decision making, 3) analyse the impact of CGA in the selection of tx, with its ability to predict complications (such as dose reduction, hospitalization, or tx discontinuation) in a recently implemented Oncogeriatric Unit. Pts >70y, candidates to receive systemic tx, underwent CGA assessments, which included scales of: ADL (Katz, Lawton), mini-nutritional assessment, depression (GDS), comorbidities and polypharmacy. Patients were classified as fit (around 50%), borderline or frail. Fit pts received mainly full treatment; frail/borderline pts, mainly modified tx and/or specific supportive care. **Results:** From Mar/12-Jan/13, 620 pts were evaluated by CGA - female 56%; cancers (%): breast 30, prostate 14, colorectal 13, hematologic 12. Katz A=75%, Lawton 27=50%; polipharmacy (>=5): 49%; depression 10%, undernutrition: 28%. There was association between the choice of oncologic treatment (original vs modified: 89 vs 11%; with additional dose reduction 11%) with Katz (p=0.011, likelihood ratio[lr]=6), Lawton (p<0.001, lr=26), depression (p=0.035, lr=9) and nutrition scales (p=0.004, lr=14). The ability to complete the individualized proposed treatment (96%) was correlated with Lawton (p=0.04, lr=9) scale. Hospitalization during chemotherapy was associated with comorbidities (p=0.038), altered Katz (p=0.004, lr=4.5), Lawton (p=0.012, lr=6.5) and depression scales (p=0.032, lr=10). **Conclusions:** In this cohort, the incorporation of CGA in daily practice was feasible and useful to predict complications of systemic cancer tx.

**9550 General Poster Session (Board #200), Sun, 8:00 AM-11:45 AM**

**Age as an independent predictor of chemotherapy treatment decisions in 20 common cancers.** *Presenting Author: Peter Hall, Leeds Institute of Health Sciences, Leeds, United Kingdom*

**Background:** There have been recent concerns regarding ageism in oncological management. A debate is on-going as to what extent age alone influences the decision to offer a patient adjuvant or palliative chemotherapy, or whether apparent ageism is simply a reflection of correlation between age and other prognostic or predictive factors. This study aims to measure the independent effect of age on the decision to use chemotherapy in 20 common cancers. **Methods:** Patients with an ICD-10 coded diagnosis of cancer were identified within a regional cancer registry between 2000 and 2011. The data was linked to UK national diagnostic data (Hospital Episode Statistics) to provide information on comorbidity. The odds ratio for receiving chemotherapy dependent on age was estimated using logistic regression to adjust for stage, morphology, grade, socioeconomic status, surgery, radiotherapy, other treatments and 15 different comorbidities. Cox regression analysis on 10 year overall survival was used test for a predictive effect of age on benefit from chemotherapy, adjusted for these factors. **Results:** 96,165 patients were included in the study. The odds ratio for older patients receiving chemotherapy (age 70 or greater) was 0.03 (95% CI 0.03 - 0.04, p=<0.001) for early breast cancer; 0.10 (95% CI 0.05 – 0.20, p = <0.001) for metastatic breast cancer; 0.43 (95% CI 0.25-0.74, p=0.003) for ovarian cancer; 0.18 (95% CI 0.15 – 0.22, p=<0.001) for Dukes B and C colorectal cancer; 0.21 (95% CI 0.17 – 0.27, p<0.001) for metastatic colorectal cancer and significant for all other cancer types. For overall survival, the interaction between age and chemotherapy was significant (p<0.01) for many tumour types including early breast cancer, colorectal cancer, bladder cancer and pancreatic cancer. **Conclusions:** Age exerts an independent effect on the decision to treat with chemotherapy in all types of cancer studied. There is evidence that the size of this effect and the age cut-off for a likely decision to treat varies between cancer types. Age may be predictive of benefit from chemotherapy in many cancer types. Further research is needed to clarify to contribution of subjective attributes such as performance status, frailty and patient or clinician attitudes on treatment decisions.

**9551 General Poster Session (Board #201), Sun, 8:00 AM-11:45 AM**

**Multidisciplinary risk assessment to reveal cancer treatments in unfit cancer patients.** *Presenting Author: Pascaline Boudou-Rouquette, Cochin Hospital, AP-HP, Paris Descartes University, Sorbonne Paris Cité, Paris, France*

**Background:** Older age is a cause of disparity in cancer treatment decision. Treatment guidelines for patients with comorbidities, polypharmacy, denutrition or psycho-social frailty are needed. A pre-therapeutic multidimensional assessment might improve the unfit patient management. We developed an experimental program of integrated medicine called ARIANE. We report 18 months activity of this outpatient setting evaluation, its feasibility and impact on treatment decision-making. **Methods:** Unfit patients with predefined cancer treatment strategy entered into the program. A one-day evaluation combined consultations of cardiologist, geriatrician, diabetologist, anesthetist, pharmacist, pain specialist, dietician, psychologist and social worker. Evaluation of performance status, ECG, ejection fraction, ASA score, diabetes, social vulnerability and malnutrition was performed including a geriatric assessment, which focused on items like comorbidity (CIRS-G), dependence (ADL, IADL), fails (Up and Go Test), cognitive impairment (MMSE, Clock Drawing Test) and depression (GDS scale). A pharmacist assessed the risk of drug-drug interactions. **Results:** Eighty-seven pts, median age 81 years (range 25-94), 76% male, 51% PS 0-1, 77% grade 3 or 4 comorbidity were included. Genito-urinary, lung cancers and sarcoma represented 77% of pts. Eighty-two percent of pts were assessed by at least ≥ 7 participants. Identified factors of vulnerability were polypharmacy (n=65; 75%; >3 drugs), social distress or severe malnutrition (both n=21; 24%), depression (n=17; 19.5%) and cognitive impairment (n=13; 15%). We identified drug interactions in 18 pts (27%). The risk assessment resulted in anticancer treatment changes in 47/87 patients (54%): protocol adaptation (n=19/87; 22%), less aggressive treatment (n=15/87; 17.2%), or more intensive therapy (n=13/87; 15%). **Conclusions:** A one-day multidisciplinary risk assessment is an answer to the complexity of unfit cancer patients and improves the safety of anticancer treatments.

**9552 General Poster Session (Board #202), Sun, 8:00 AM-11:45 AM**

**Association of frailty markers with treatment decision in patients seen in oncogeriatric clinic: Results from the ASRO pilot study.** *Presenting Author: Anais Farcet, Centre Gerontologique Departemental, Marseille, France*

**Background:** Comprehensive geriatric assessment (CGA) is the gold standard to help oncologist in choosing the best cancer treatment in their older patients. Some authors recently suggest that the concept of frailty, developed by L Fried, could be a more useful approach in this population. We investigated if frailty markers (FM) are associated with treatment recommendations in an oncogeriatric clinic. **Methods:** This prospective multicenter study included patients 65 years and older, with solid tumors, referred to the oncogeriatric consultation after a cancer treatment plan. A CGA includes 9 domains (autonomy, comorbidities, medication, cognition, nutrition, mood, neurosensory deficits, falls and social status) was performed. Five FM were assessed (nutrition, physical activity, energy, mobility, strength). Patients were classified as Frail (3 or more FM), pre frail (1 or 2 FM) or not frail (0 FM). Treatment recommendations were classified in 3 categories: Standard treatment, Standard treatment with adaptation, supportive/palliative care. A polytomus logistic regression models were used to analyze factors associated with treatment recommendations. **Results:** 217 patients, mean age 83 years (± SD 5,3) were included. The most prevalent of the FM were mobility (77%), physical activity (65%), and nutrition (61 %). 42% had at least 3 markers. In univariate analysis, grip strength, physical activity, mobility, nutrition, ADL, IADL, social status, depression, ECOG-PS and sexe were significantly associated with treatment recommendations. In the multivariate analysis, only the number of FM and ADL were significantly associated with treatment recommendations (respectively p=0.001 and p=0.015). Treatment recommendations were significantly different into the 3 FM groups (p=0,001). In the non frail group, standard treatment or standard treatment with adaptation was maintained for more than 90% of patients. In the frail group, a support/palliative care was proposed for 60% of patient. **Conclusions:** Frailty markers are associated with treatment recommendations in older cancer patients. Longitudinal studies are warranted to better precise their use in geriatric oncology setting.

**9553 General Poster Session (Board #203), Sun, 8:00 AM-11:45 AM**

**Frailty markers for prediction of mortality in first-line chemotherapy for colon cancer patients: Results of MOST/ASRO 101 study.** *Presenting Author: Frederique Retornaz, Centre Gerontologique Departemental, Marseille, France*

**Background:** The concept of frailty may help in to detect vulnerability in patients with digestive cancer in surgery setting. We investigated whether frailty markers predict grade 3-4 toxicity or 6 months death in older colon cancer patients receiving a first line chemotherapy. **Methods:** This prospective multicenter study included patients aged ≥75 years, with colon cancer, receiving first line of chemotherapy for adjuvant or metastatic situation. Five frailty markers were examined (nutrition, physical activity, energy, mobility, strength). Logistic regression was used to examine the association between frailty markers and grade 3-4 toxicity at 3 and 6 months, and cox regression to examine deaths at 6 months. **Results:** 99 participated, and 98 were eligible for analysis. Median age was 79 years. At baseline, 26 patients (26.5%) had 3 or more frailty markers. Twenty six (26.5%) had grade 3-4 toxicity after 3 months, and 18 (18.4%) after 6 months. Twelve patients died during the 6 months follow-up. In multivariate analysis, at 3 months and 6 months, none of the studied frailty marker predicted grade 3-4 toxicity. At six months, significant predictive factors for death were the frailty marker "energy" (Hazard Ratio [HR]; 13.92 (95% CI [3.22-60.15] p=0.0004) and presence of 3 or more frailty markers at baseline (HR, 4.50 (95% CI [1.30-15.64] p=0.02). **Conclusions:** Frailty markers are predictive of death at 6 months but are not predictive of severe toxicity. These results suggest that frailty markers, in particular "energy" should be taken into account when treating an elderly cancer population. Further researcher investigating the usefulness of frailty markers is needed.

**9554 General Poster Session (Board #204), Sun, 8:00 AM-11:45 AM**

**Outcomes of invasive mechanical ventilation in elderly patients with metastatic cancer.** *Presenting Author: Achuta Kumar Guddati, Massachusetts General Hospital, Boston, MA*

**Background:** Aggressive management of elderly patients with metastatic cancer has helped prolong their survival. Respiratory failure in elderly patients with metastatic disease may significantly contribute to a decline in their functional status. However, the outcomes of the use of invasive mechanical ventilation (IMV) in patients with rapidly declining functional status have not been studied in detail. **Methods:** Using the Healthcare Cost and Utilization Project – Nationwide Inpatient Sample database 2000-2009, patients aged 65 and above undergoing IMV were identified using appropriate ICD-9-CM codes. The rates of prolonged IMV (≥96 hours) and use of tracheostomy were examined. Chi square test and Wilcoxon rank test were used to compare discrete and continuous variables respectively. Significance was defined as p value set at <0.05. Bonferroni's correction as applied for multiple comparisons. **Results:** 4,256,372 patients aged 65 and above underwent IMV during the years 2000 to 2009. Of these, 192,852 (4.5%) had metastatic cancer. After adjusting for age, the odds of mortality were 1.86 times higher (95% CI 1.8-1.9) when compared to those without any cancer. The outcomes of patients undergoing IMV are shown below (see Table). **Conclusions:** The hospital LOS and hospital charges in patients undergoing IMV were higher in patients with cancer and in those with metastatic disease. The mortality was however significantly higher in patients with metastasis. Of the survivors, almost twice the number of patients are discharged to hospice facilities when compared to cancer patients with no metastatic disease. The use of prolonged IMV portends a higher mortality and worser outcomes in elderly patients with metastatic disease.

| | No cancer | Solid organ cancer | Metastatic solid organ cancer |
|---|---|---|---|
| **Mortality (%)** | 39.4 | 42.4* | 53* |
| **Prolonged IMV (> 96 hrs)** | 39.8 | 37.8 | 37.6 |
| **Tracheostomy (%)** | 8.8 | 10.3* | 8.4 |
| **Disposition of survivors** | | | |
| **Home** | 21.6 | 25.2* | 20.4 |
| **Home healthcare** | 14.1 | 19.7* | 22.6* |
| **Skilled Nursing Facility** | 50.6 | 41.2* | 37.3* |
| **Hospice** | 4.5 | 6.6 | 13.5* |
| **Others** | 9.2 | 7.3 | 8.2 |
| **Median LOS in survivors, days(IQR)** | 12 (7-20) | 13(8-21)* | 14(8-22)* |
| **Median time to death** | 6(2-14) | 8(3-16)* | 8(3-16)* |
| **Median hospital charges, USD** | 61,035 | 68,378* | 67,181* |

* p<0.025 when compared with no cancer.

**9555 General Poster Session (Board #205), Sun, 8:00 AM-11:45 AM**

**Phase angle for prognostication of survival in patients with advanced cancer.** *Presenting Author: David Hui, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Accurate survival prediction is essential for decision making in cancer therapies and care planning. Objective physiologic measures may improve the accuracy of prognostication. In this prospective study, we determined the association of phase angle, hand grip strength, and maximal inspiratory pressure with overall survival in patients with advanced cancer. **Methods:** We enrolled hospitalized patients with advanced cancer who were seen by palliative care for consultation. We assessed the phase angle, hand grip strength, maximal inspiratory pressure and known prognostic factors including Palliative Prognostic Score (PaP), Palliative Prognostic Index (PPI), serum albumin and body composition. We conducted univariate and multivariate survival analysis, and examined the correlation between phase angle and other prognostic variables. **Results:** 222 patients were enrolled: average age 55 (range 22-79), female 59%, gastrointestinal cancers 33%, mean Karnofsky performance status (KPS) 55%, and median overall survival 106 days (95% confidence interval [CI] 71-128 days). The median survival for patients with phase angle 2-2.9°, 3-3.9°, 4-4.9°, 5-5.9° and ≥6° was 35, 54, 112, 134 and 220 days, respectively (P=0.001). We found that PaP (P<0.001), PPI (P=0.003), KPS (P<0.001), fat free mass (P=0.02) and hypoalbuminemia (P<0.001) were significantly associated with survival, but not cancer diagnosis (P=0.10), hand grip strength (P=0.08) and maximal inspiratory pressure (P=0.08). In multivariate Cox regression analysis, phase angle, PaP, albumin, and fat free mass were independently significant (Table). Phase angle was only weakly ($\gamma$<0.4) associated with other prognostic variables. **Conclusions:** Phase angle was a novel predictor of poor survival, independent of established prognostic factors in the advanced cancer setting. This objective and noninvasive tool may be useful for bedside prognostication.

**Multivariate survival analysis.**

| Variables | Hazard ratio (95% CI) | P value |
|---|---|---|
| **Phase angle (per degree increase)** | 0.86 (0.74-0.99) | 0.04 |
| **Palliative Prognostic Score (per point increase)** | 1.07 (1.02-1.13) | 0.008 |
| **Albumin (per g/dL increase)** | 0.67 (0.50-0.91) | 0.009 |
| **Fat free mass (per kg increase)** | 0.98 (0.96-0.99) | 0.02 |

**9556 General Poster Session (Board #206), Sun, 8:00 AM-11:45 AM**

**Availability of single-fraction palliative radiotherapy for cancer patients receiving end-of-life care within the Veterans Healthcare Administration.** *Presenting Author: Drew Moghanaki, Hunter Holmes McGuire Veterans Affairs Medical Center, Richmond, VA*

**Background**: Multiple randomized phase III trials have established a single fraction of palliative radiotherapy is equally effective at relieving pain when compared to longer treatment courses. However, recent surveys demonstrate <20% of radiation oncologists in the US offer this shorter treatment option. As 500,000 Veterans currently receive cancer care within the Veterans Healthcare Administration (VHA), a study was conducted to determine whether this finding held true in this healthcare system. **Methods**: A web-based survey was emailed to all radiation oncologists currently practicing at VHA medical centers. Associations of responses were evaluated by Fisher's exact test. **Results**: The response rate was 90% (70/78). Half of respondents were full-time employees of the VHA, and the majority (70%) had thoroughly read guidelines on palliative radiotherapy for bone metastases recently published by either the American College of Radiology (ACR, 2009) or American Society of Radiation Oncology (ASTRO, 2011). Single-fraction palliative radiotherapy for bone metastases had been prescribed by 76% of respondents, and 93% had prescribed a short course of ≤6 fractions. Respondents were less likely to have prescribed a single fraction for patients who had survival estimates of either >6 months or >12 months, (66% vs 37%, $p < 0.0001$).Those not offering single-fraction palliative radiotherapy (24%) were more likely to be >10 years out of training (37% vs 10%, $p = 0.01$), and more likely to have worked in private practice at some point in their career (36% vs 12%, $p = 0.03$). There were no associations with employment status, history of an academic appointment, or having previously read the recently published ACR or ASTRO guidelines. **Conclusions**: Single fraction palliative radiotherapy is widely available in the VHA. Its use is preferred by radiation oncologists for patients with a limited life expectancy of less than 6 months. These data demonstrate rapid adoption of recently published guidelines that are designed to ensure access to care is not limited by a preference for prolonged treatment courses that may discourage patients and clinicians from seeking this care.

**9557 General Poster Session (Board #207), Sun, 8:00 AM-11:45 AM**

**Phase II clinical trial of *uncaria tomentosa* (cat´s claw) in patients with advanced solid tumors.** *Presenting Author: Larissa Carvalho Lopes De Paula, ABC Foundation School of Medicine, Santo André, Brazil*

**Background:** Cat's claw (*Uncaria tomentosa*) is a native amazonic plant that exhibits anti-inflammatory and antitumor properties. **Methods:** This prospective phase II study assessed the effects of a 100-mg dose of a dry extract of *U. tomentosa*three times per day on individuals with advanced solid tumors, with no further therapeutic options and with at least 2 months life expectancy. We used the EORTC QLQ C30 and FACIT-F questionnaires to assess the participants´ quality of life, the HADS questionnaire to assess their anxiety and depression and the Pittsburgh index (PSQI) to assess their sleep quality. In addition, several biochemical and inflammatory parameters were analyzed. **Results:** We recruited 51 volunteers; their median age was 64 (33-85) years old, and 47% were females. Their scores on the Karnofsky scale were equal to or less than 80% for more than 65% of the volunteers. Treatment caused an improvement in the patients' overall quality of life ($p= 0.0411$) and social functioning ($p= 0.0341$), as assessed by EORTC QLQ C-30, and a reduction of fatigue ($p= 0.0496$) by the Chalder Fatigue Questionnaire. None of the biochemical or inflammatory parameters assessed (interleukins 1 and 6, C-reactive protein, tumor necrosis factor alpha, erythrocyte sedimentation rate and alpha-1-acid glycoprotein) exhibited significant changes. No tumor response was detected according to the RECIST criteria; however, the disease stabilized for more than eight months in four participants. The medication was well tolerated by most patients. **Conclusions:** We conclude that use of cat´s claw might be beneficial for patients with advanced cancer because it could improve their quality of life and reduce fatigue. The mechanism of this action does not seem to be related to the anti-inflammatory properties of this plant. Clinical trial information: NCT02045719.

**9558 General Poster Session (Board #208), Sun, 8:00 AM-11:45 AM**

**Assessing 2-month clinical prognosis in patients with solid tumors: Final results of PRONOPALL study.** *Presenting Author: Hugues Pierre Bourgeois, Clinique Victor Hugo, Le Mans, France*

**Background:** In 2008, results about a prognostic score defined by 4 factors (Karnofsky index PS, number of metastatic sites, serum albumin and LDH levels) in a population of 177 hospitalized patients in two hospitals were published (Barbot et al, 2008). Albumin threshold is 33 g/L and LDH one is 600 IU/L. The scoring allowed to define 3 different patient populations: A : low score (0 to 3), B: intermediate score (4 to 7) and C : high score (8 to 10). The survival rates at 2 months were 92.2% ± 3.8 (population A), 42.7% ± 5.2 (population B) and 8.3% ± 4.6 (population C). **Methods:** in order to validate this score, we decided to start a multicentric trial with a high proportion of out-patients. **Results:** between October 2009 and October 2010, 302 patients were included from 16 institutions. Inclusion criteria: adult patients with a solid tumor in a palliative setting with one or more of the three following criteria: life expectancy of less than 6 months, PS ≥ 2, evidence of disease progression during palliative chemotherapy. All patients signed an informed consent form. 265 (88%) patients were evaluable for the first analysis. 37 patients were not eligible. Median age: 66 years [37-88], women 59%, men 41%. PS 0-1 (45%), PS 2 (37%), PS 3-4 (18%). The most frequent primary sites: breast (29%), colon/rectum (28%), lung (13%), ovary (11%), pancreas (11%), other (8%). One metastatic site (32%), two (35%), more than two (31%). Median LDH level was 397 IU/L [118-4314]. Median level of serum albumin was 35 g/L [13-54]. According to the prognostic score, the 2-month survival rate was 92% and the median survival rate was 301 days [209-348] (population A, 131 patients), 64% and 78 days respectively [71-113] (population B, 113 patients) and 24% and 35 days respectively [14-56] (population C, 21 patients). These three populations are statistically different ($p<0.0001$). Among the 4 factors, only PS, LDH and serum albumin were statistically connected to survival rate ($p<0.0001$). 63 patients, aged 75 years and older, allowed to validate the prognostic score for oncogeriartric patients too ($p=0.0002$). **Conclusions:** PRONOPALL confirms the three prognostic profiles defined by the combination of these four factors and is useful in daily practice. Clinical trial information: 2009-A00936-51.

**9559 General Poster Session (Board #209), Sun, 8:00 AM-11:45 AM**

**Spirituality and quality of life among caregivers of advanced cancer patients.** *Presenting Author: Tai Chung Lam, Dana-Farber Cancer Institute/ Brigham and Women's Cancer Center, Boston, MA*

**Background:** Religion and/or spirituality (R/S) is important to most advanced cancer patients, and often upholds patient quality of life (QoL) within illness. However, the role of R/S within the caregiving experience has not been adequately studied. **Methods:** Data from 570 caregiver-patient dyads participating in the Coping with Cancer study were included. Caregivers completed R/S measures on R/S importance, positive and negative religious coping, and degree of spiritual support from medical teams and religious communities. The correlations of caregiver R/S variables to patient R/S were assessed. Multivariable models (MVA) were employed to assess relationships of caregiver R/S measures with their QoL (SF-36 questionnaire) and perceptions of care-giving experience, controlling for confounding factors (e.g., sociodemographic factors, self efficacy). **Results:** Caregivers (median age 53 years, 51% spouses) largely reported religion to be important (85%). Most (85%) endorsed at least some positive religious coping, and 31% endorsed at least some negative religious coping. Thirty-nine percent and 17% of caregivers reported being highly supported by R/S communities and medical system, respectively. Caregivers' R/S variables were correlated with patient R/S, including religiosity ($r=.24$, $p<.001$), positive religious coping ($r=.41$, $p<.001$) and negative religious coping ($r=.21$, $p<.001$). In MVA assessing relationship of R/S variables to caregiver QOL, negative religious coping was significantly related to lower caregiver QoL (SF-36 mental component summary, $\beta=-2.2$, $p<.001$). In MVAs of the relationship of R/S to perceptions of care-giving experience, greater positive religious coping (OR 1.95, $p=.04$) and greater medical team spiritual support (OR 2.02, $p=.01$), were related to more positive perceptions of the caregiving experience. **Conclusions:** R/S is important to most caregivers and is correlated with patient R/S. Caregiver negative religious coping is associated with poorer QoL. Caregiver positive religious coping and spiritual support from medical teams are related to caregivers' positive perceptions of caregiving experience. Results suggest approaches to improve caregiver QoL should involve intervention on R/S.

**9560 General Poster Session (Board #210), Sun, 8:00 AM-11:45 AM**

**Differences between patient and caregiver ratings of advanced cancer patients' quality of life and correlates of their disagreement.** *Presenting Author: Tai Chung Lam, Dana-Farber Cancer Institute/Brigham and Women's Cancer Center, Boston, MA*

**Background:** Assessment of patient quality of life (QoL) by surrogates, particularly informal caregivers (e.g. spouse), is important to the care of advanced cancer patients. However, accuracy of such surrogate QoL assessments has been questioned. This study sought to assess differences between patients' QoL self-assessments compared to assessments by their informal caregivers, and to determine characteristics associated with the disagreement. **Methods:** Data from 570 advanced cancer patient-caregiver dyads participating in the multi-site, Coping with Cancer study were included. Patients assessed their QoL with the McGill QoL questionnaire. Caregivers estimated patients' QoL using the same questionnaire. Paired t-tests were used to compare the dyadic estimates of QoL scores. Multiple linear regression (MVA) was performed to examine factors potentially associated with the difference in dyadic QoL estimates. **Results:** Caregivers' mean age was 53 years, 71% were female, and 51% were spouses. The overall mean patient QoL score, as assessed by caregivers, was lower than the overall mean QoL by patient assessment [6.4 (SD=1.8) vs. 7.1 (SD=1.6), p<.0001]. In MVA assessing factors contributing to patient-caregiver differences in QOL assessment, sociodemographic factors, overall coping, positive religious coping, and interpersonal support were not associated with any significant disagreement. Higher level of caregiver negative religious coping ($\beta$=.31, p=.0002) and burden ($\beta$=.77, p<.001), lower caregiver self-efficacy ($\beta$=-.54, p=.005), higher stressful caregiving adult reactions to experiences of dying scale (SCARED) ($\beta$=1.28, p<.0001) and higher patient self-estimated QoL ($\beta$=2.92, p<.0001) were significantly associated with greater disagreement between patient and caregiver estimates of patient QoL. **Conclusions:** Caregiver assessments of patient QoL are underestimated as compared to patient self-assessment. Caregiver factors, including negative religious coping, self-efficacy, burden and SCARED, are associated with patient-caregiver disagreement in estimates of patient QoL, suggesting ways to improve accuracy of caregivers' evaluation of patient QoL.

**9561 General Poster Session (Board #211), Sun, 8:00 AM-11:45 AM**

**Change in palliative performance scale score as prediction of survival in patients with advanced cancer.** *Presenting Author: Yong Joo Lee, Department of Palliative Medicine, Seoul St. Mary Hospital, The Catholic University of Korea, Seoul, South Korea*

**Background:** The Palliative Performance Scale (PPS) is a widely-used prognostic tool in patients with advanced cancer. While single PPS measures are predictive of survival, the utility of serial PPS measurements warrants further study. We hypothesized that changes in PPS are associated with survival, and thus may be useful in forecasting health services utilization in Korea, where late referral to palliative care services is common. This study examines associations between change in PPS score and survival in patients with advanced cancer. **Methods:** We identified a cohort of 606 inpatients who died at a Korean university hospital's hospice/palliative care center, and abstracted relevant chart data. PPS scores were measured twice as part of standard care: (1) on admission, and (2) after three days in the hospital (D3). 'Change at D3' was defined as the difference between initial PPS and PPS at D3, divided by initial PPS. We used a Cox regression modeling approach to explore the association between this change score and survival, adjusting for the influence of age, sex and primary cancer type. **Results:** Patients' median survival was nine days (range 1-65). Change scores were statistically significantly associated with survival. A change score of >30% yielded a hazard ratio for death of 2.66 (95% CI 2.19-3.22), compared to a change score of ≤ 30%. PPS of ≤ 30 on D3 also independently predicted survival, with a hazard ratio of 1.67 (95% CI 1.38-2.02) compared to PPS of >30. PPS at admission was not independently associated with survival. **Conclusions:** A change of over 30% in PPS appears to predict survival in patients with advanced cancer at our center, even after adjustment for confounders. PPS at admission did not predict survival. Change in PPS may be a more sensitive indicator of impending death than a single PPS measurement at admission in cancer patients near the end of life. Further prospective study is needed to test this important finding in other populations.

**9562 General Poster Session (Board #212), Sun, 8:00 AM-11:45 AM**

**Intensive care unit admissions and in-hospital mortality in patients admitted through the emergency department of a comprehensive cancer center.** *Presenting Author: Ahmed F. Elsayem, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** The National Cancer Policy Forum advocated for improving quality of end life care, and reducing cost for cancer patients. Identifying those at high risk for Intensive Care Unit (ICU) admission, and hospital death may allow earlier palliative care and avoid futile interventions. The purpose of this study is to examine risk factors for ICU admission, and hospital death among cancer patients admitted through the Emergency Department (ED). **Methods:** We queried MD Anderson Cancer Center databases for all patients who visited our ED in 2010. ICU admission and hospital deaths of these patients were reviewed, and individual patients' data were analyzed. **Results:** In 2010, 16,038 ED visits were made by 9,246 unique cancer patients. Of these patients, 5,362 (58%) were admitted to the hospital at least once (range 1-13 admits). Of all patients admitted through the ED, 697 (13%) were admitted at least once to ICU. Of all patients admitted, 11% died during hospitalization; of those, 29% died in ICU. Among patients who died in ICU, 73/233 (31.3%) had hematologic malignancies and 96/354(27.1%) had solid tumors (P<.001). Patients admitted to ICU had median lengths of hospital stay (MLOS) of 13 days for hematologic and 8 days for solid tumors (P<.001; using means); patients without ICU admission had MLOS of 6 and 5 days, respectively (P<.001). In a multivariate logistic regression model for predicting in-hospital mortality, we found that ED presenting symptoms of respiratory distress or altered mental status (fever and pain non-significant); primary tumor of lung cancer, leukemia, unknown primary, or lymphoma; and non-white race were independent predictors of death, while controlling for age, gender and residence. **Conclusions:** Cancer patients admitted through the ED experience high ICU admission rates, and hospital mortality. Lung and certain other cancers; race; and symptoms of respiratory distress and altered mental status were associated with increased risk of in-hospital death. Patients with these risk factors may benefit from efforts to improve palliative care and prevent unnecessary interventions.

**9563 General Poster Session (Board #213), Sun, 8:00 AM-11:45 AM**

**Pre and postradiation lymphopenia predicts survival in management of bone metastases.** *Presenting Author: Sara R. Alcorn, Department of Radiation Oncology and Molecular Radiation Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD*

**Background:** Radiation-induced lymphopenia (RIL) has recently been identified as an adverse prognostic factor in select solid tumors, yet its prognostic value is unknown in the management of metastatic lesions. We examine the relationship between RIL and survival in patients receiving palliative radiation (RT) for bone metastases. **Methods:** Palliative bone RT plans were identified through medical records at a high-volume institution from 9/1/2007-7/15/2012. Patient and treatment characteristics were recorded, including lymphocyte count (LC) ≤6 weeks before RT and within 1-3 months after RT. Comparative statistics were performed using t-tests, ANOVA, and Kaplan-Meier analyses. **Results:** Of 573 palliative bone RT plans, 405 plans from 251 patients with complete baseline data were analyzed; 227 plans had complete post-RT data. At a median follow-up of 4.3 months, 9% of patients were living. Median age and KPS were 64 years (range 22-94) and 70 (range 30-100), respectively. RT sites were 51% spine, 20% pelvis, 19% extremity, and 10% other. Median RT dose was 30 Gy (range 2-48 Gy). Prior to RT, 13% and 46% of patients had LC<500 and LC<1000, respectively; on survival analyses, baseline LC <500 was associated with lower median survival as compared to LC≥500 (1.4 vs 5.6 mo.; p<0.001), as was baseline LC<1000 vs LC≥1000 (3.1 vs 6.7 mo.; p<0.001). Mean LC was significantly higher before RT (1270, SD=1247) than after RT (903, SD=867; paired samples t-test p<0.001.) Excluding baseline LC<500, median survival was lower for patients with LC<500 vs LC≥500 after RT (4 vs 11.1 mo.; p<0.001); post-RT LC<1000 did not predict survival. Whereas daily pre-RT steroid use was associated with higher percent change in LC after RT (t-test p=0.001), steroids at the time of post-RT labs and peri-RT chemotherapy did not significantly affect LC. Histology, RT site, RT to >4 vertebral bodies, and RT dose >30 Gy were also not associated with post-RT LC. **Conclusions:** Lymphopenia prior to and after RT appears to be a prognostic factor in the treatment of bone metastases, and significant RIL can occur irrespective of RT characteristics such as field and dose. These data suggest for careful consideration of hematologic status during patient selection for palliative RT.

**9564 General Poster Session (Board #214), Sun, 8:00 AM-11:45 AM**

**Previous cancer of spouse as a predictor for mortality after personal diagnosis of cancer.** *Presenting Author: Tamar Peretz, Sharett Institute of Oncology, Hadassah Hebrew University Medical Center, Jerusalem, Israel*

**Background:** Previous experience may affect further coping with illness. The aim of the current study was to evaluate the association between prior cancer of spouse with mortality following a personal diagnosis of cancer. **Methods:** A historical prospective study, with cohort inception and baseline measurement of people participating in the Central Bureau of Statistics 1995 census, was designed. Cancer incidence was ascertained through the Israel Cancer Registry and followed up until 2011. Multivariate Cox proportional hazards models were used to assess hazard ratios for mortality among study subjects following cancer of their spouse, while controlling for age, sex, marital status and ethnicity. In order to exclude lead time bias and smoking effect, further analyses which restricted to stage IV cancers and models which excluded smoking associated cancers (lung, head and neck, renal, and bladder cancers) were carried. **Results:** A total of 133,550 cases of cancer and 61,048 deaths were reported during the study period. The effect on mortality was mediated by spouse's survival at the time of self-diagnosis; mortality of spouse, at the time of personal diagnosis of cancer was associated with increased risk for death (HR=1.07, 95%CI: 1.02-1.12) compared with reduced risk of personal mortality following a diagnosis of cancer in spouse whose was alive at time of diagnosis (HR=0.90, 95%CI: 0.87-0.94). The gender effect was more prominent in stage IV patients; only males were susceptible to the negative effect after spouse mortality (HR=1.20, 95%CI: 1.06-1.36) while the protective effect of a spouse who was alive at time of self-diagnosis was significant only among females (HR=0.79, 95%CI: 0.71-0.89). These results were similar in the models which included only non-smoking associated cancers. **Conclusions:** Mortality followed cancer diagnosis is affected by prior diagnosis of cancer among the spouse. This effect is influenced by the survival of the spouse at the time of cancer diagnosis and gender.

**9565 General Poster Session (Board #215), Sun, 8:00 AM-11:45 AM**

**Biopsychosocial predictors of pain among women recovering from surgery for gynecologic cancer.** *Presenting Author: Kelsey R. Honerlaw, University of Wisconsin, School of Medicine and Public Health, Madison, WI*

**Background:** Pain is a common and sometimes debilitating symptom for women recovering from surgery for gynecologic cancer, but little is known about psychological and biological risk factors that account for individual differences in pain. We investigated the extent to which psychological distress and inflammation were associated with pain post-surgery. **Methods:** Women (N=90) who underwent surgery for ovarian or endometrial cancer participated in this prospective, longitudinal study. They completed well-validated self-report measures of pain (intensity and interference with daily activities) and distress (depression and anxiety) at 1 week, 1 month, and 4 months post-surgery. Inflammatory cytokines were measured in peripheral blood at the same time points using an electrochemiluminescence platform. Mixed-effects and subject-level fixed-effects linear regression models were used to examine the extent to which distress measures and cytokines predicted pain intensity and interference. **Results:** Pain intensity and interference improved greatly over the four months post-surgery (p values$<$0.001).Participants who reported greater depression and anxiety experienced greater pain intensity ($z=8.00$, $p<0.001$; $z=3.32$, $p=0.001$). The same pattern was seen for pain interference. Those with higher IL-6 and IL-10 also experienced greater pain intensity ($z=2.44$, $p=0.015$; $z=2.03$, $p=0.042$), but not interference. All models controlled for time since surgery, surgical method (laparoscopy or laparotomy), disease stage, age, and BMI. Within-subjects analyses revealed that among individual patients, changes in distress and cytokine levels across the assessments were associated with corresponding changes in pain, with patients reporting greater pain intensity when depression ($t=4.92$, $p<0.001$), IL-6 ($t=2.72$, $p=0.008$), and IL-10 ($t=2.40$, $p=0.019$) were most elevated. Pain interference was greatest when depression ($t=6.61$, $p<0.001$) and anxiety ($t= 2.58$, $p=0.011$) were highest. **Conclusions:** Results suggest that depression, anxiety, and inflammation may exacerbate pain following surgery for gynecologic cancer. These risk factors can be targeted to improve post-surgical recovery and enhance quality of life.

**9566 General Poster Session (Board #216), Sun, 8:00 AM-11:45 AM**

**Effect of contralateral prophylactic mastectomy on quality of life in women undergoing surgery for breast cancer: A prospective study.** *Presenting Author: Chang Xia, Hematology, Oncology, and Blood & Marrow Transplantation, UIHC, Iowa City, IA*

**Background:** There has been a marked increase in the use of contralateral prophylactic mastectomy (CPM) for women with unilateral breast cancer. Previous studies on quality of life (QoL) measures for women who have undergone CPM are mixed. Most surveys were conducted only post-operatively. This analysis reports QoL changes within the same patient before and after surgery, using a validated tool. **Methods:** This study includes women who were prospectively enrolled in the University of Iowa Breast Molecular Epidemiologic Resource. We included all women who had mastectomy on the affected side. Patients completed a validated QoL survey (FACT-B) which covered: overall QoL and additional cancer-specific concerns. Responses followed a five-point scale. Surveys must have been completed any time before surgery and 6-18 months after surgery. A Fixed Effects linear regression model was used to discern within-person changes in QoL measures before and after surgery. Analysis was stratified by unilateral mastectomy (UM) or CPM. **Results:** The study cohort included 34 women, 17 received CPM and 17 received UM. Mean age was 61.5 for women who chose UM and 50.6 for women who chose CPM ($p<0.001$). There were no differences in baseline QoL measures between the two groups. After surgery, both groups felt less nervous, though the change in the CPM group was greater ($p<0.001$). There were no other differences for the UM group in pre-post QoL measures. Women undergoing CPM did have QoL decrements (Table). **Conclusions:** Women who chose CPM feel less nervous after surgery. However, these women lose some sense of femininity and are more likely to experience physical post-operative sequelae. This adds to knowledge that can be used to counsel women about physical and emotional costs associated with CPM that manifest 6-18 months after surgery.

| | UM | | CPM | |
|---|---|---|---|---|
| QoL: Pre to postoperative change | Pre-post change | p | Pre-post Change | p |
| I feel nervous | -1.18 | <0.001 | -1.46 | <0.001 |
| I am able to feel like a woman | 0 | 1.0 | -1.18 | 0.01 |
| I have certain parts of my body where I experience pain | 0.73 | 0.21 | 1.18 | 0.03 |
| Movement of my arm is painful | 0.57 | 0.14 | 0.88 | 0.03 |
| I have stiffness of my arm | 0.43 | 0.27 | 0.63 | 0.04 |
| My arm feels numb | 0.43 | 0.60 | 1.13 | 0.07 |

**9567 General Poster Session (Board #217), Sun, 8:00 AM-11:45 AM**

**Default of cancer treatment association with psychological distress and desire for psychological support.** *Presenting Author: Caryn Mei-Hsien Chan, University of Malaya, Kuala Lumpur, Malaysia*

**Background:** Default of treatment is highly prevalent among cancer patients, with delayed or incomplete treatment shown to result in worse clinical outcomes such as treatment resistance, disease progression as well as poorer survival. Our objective was to identify psychosocial variables and characteristics associated with cancer default. We hypothesized that cancer patients who are psychologically distressed are more likely to: (a) refuse, delay or discontinue cancer treatment and routine patient follow up, and (b) decline offers for psychological support. **Methods:** This study is part of a larger prospective study assessing the psychosocial needs of patients with cancer. A total of 467 consecutive adult cancer patients attending scheduled oncology follow-ups at a single academic medical centre completed the Hospital Anxiety and Depression Scale and reported their preference for psychological support at baseline, 4-6 weeks and 12-18 months follow-up. Default was defined as refusal, delay or discontinuation of treatment or visit, despite the ability to do so. **Results:** A total of 159 of 467 (34.0%) cancer patients were defaulters. Of these 159 defaulters, 89 (55.9%) desired psychological support, compared to only 13 (4.22%) of 308 non-defaulters. Although not associated with each other, desire for psychological support and psychological distress were the only variables found to be significantly associated with default of appointment or cancer treatment using a chi-square and a repeated-measures ANCOVA at $p = 0.001$ and $p = 0.015$ respectively. No other remarkable differences between defaulters and non-defaulters were discerned. **Conclusions:** To date there are few published studies on rates of default among adult oncology patients. Our results show that defaulters had higher psychological distress but greater desire for support compared to non-defaulters. Patients who refuse cancer treatment initially should be offered psychological support, with their desire for treatment re-evaluated later on. Patients may be more willing to accept cancer treatment if desirous of and given psychological support. This in turn could potentially increase treatment acceptance rates and improve survival.

**9568 General Poster Session (Board #218), Sun, 8:00 AM-11:45 AM**

**Mental mood of gynecologic cancer patients assessed by distress and impact thermometer (DIT; a two-item, self-report questionnaire) and hospital anxiety and depression scale (HADS; a 14-item, self-report questionnaire) during the initial treatment in the first 6 months: KCOG-G1103 study.** *Presenting Author: Yoshio Itani, Nara Prefectural Nara Hospital, Nara, Japan*

**Background:** Thirty percent of cancer patients are reported to suffer from psychological distress which detracts from treatment adherence, but that is often underestimated in clinical settings. HADS is one of the validated scales for screening emotional distress in cancer patients. However, it is not used widely because it is cumbersome to score. DIT is a 2-item (the Distress and the Impact) self-report questionnaire, but is not well verified. **Methods:** One hundred and seventeen patients were enrolled between 2011.5.1 and 2012.3.31 and 95 were eligible. Median age was 54 years (range 31–77). The numbers of completed questionnaires (HADS & DIT) at (a) pretreatment, (b) 3 months, and (c) 6 months were 95, 80, and 70, respectively. No patients relapsed during the investigated period. **Results:** 1) Areas under the curve of receiver operating characteristic curves for Distress and Impact with respect to HADS positivity were 0.855 and 0.875 respectively. At Distress $\geq$4 and Impact $\geq$2, sensitivity, specificity, positive predictive value, and negative predictive value were 0.818 (95% confidence interval (CI): 0.707–0.898), 0.875 (95%CI: 0.739–0.945), 0.9 (95%CI: 0.786–0.957), and 0.778 (95%CI: 0.637–0.875), respectively. 2) In each patient, the mean scales of (b) were significantly reduced in HADS (mean 3.2; $p<0.0002$) and in Distress (mean 1.7; $p<0.0001$), but not in Impact (mean 0.66; $p=0.072$) compared with (a). Those of (c) were significantly reduced in HADS (mean 4.5; $p<0.0001$), in Distress (mean 2.3; $p<0.0001$), and in Impact (mean 1.09; $p=0.031$) compared with (a) (Student's paired t-test). **Conclusions:** 1) DIT is a reliable tool for ruling out clinical psychiatric distress. 2) For the first 6 months of treatment, mental mood would have a tendency to be improved, but not completely. Therefore, gynecologic oncologists should screen psychiatrically distressed patients by DIT and introduce them to psychiatric treatment early in the initial treatment. Clinical trial information: 000005727.

**9569 General Poster Session (Board #219), Sun, 8:00 AM-11:45 AM**

**The subjective quality of life of young patients with breast cancer and their partners.** *Presenting Author: Laurence Vanlemmens, Centre Oscar Lambret, Lille, France*

**Background:** The subjective experience of young breast cancer (BC) women has some specifics related to the impact of illness and treatments on the issues specific to their age. The partner is most often the primary caregiver and is himself affected by the disease. A better understanding of couples facing cancer at every stage of treatment program appears crucial to improve the overall care. This study aims to better understand the quality of life of these young couples (women <45 at diagnosis), by comparing the subjective experience of patients and partners from chemotherapy (CT) to the end of treatments period. **Methods:** 491 couples in which the woman has non-metastatic BC (28.7% under CT, 10.2% under Trastuzumab, 33% under hormone therapy, 28.1% under supervision) completed a self-administered questionnaire assessing their subjective experience. **Results:** Patients report more difficulties than partners in terms of management of children and of everyday life, body image and sexuality, career management and financial difficulties. The 2 groups were comparable with regard to the feeling of couple cohesion and the deterioration of relations with relatives. In addition, patients reported more support from relatives than partners, but this support decreases along the treatment program. While overall, patients undergoing CT and Trastuzumab and their partners reported more difficulties than those under hormone therapy or under surveillance, the negative affectivity / apprehension for the futureremains stable and relatively high from CT to the end of treatment, for the patient as well as for her partner. **Conclusions:** The difficulties of patients appear to be particularly strong in the early course of care and decrease over time, indicating a gradual adjustment to the disease. It is the same for partners, who also have concerns. However, there are differences between the experience of patients and partners. A longitudinal follow-up assessing the couple experience in a dyadic design would allow us to support these findings, and ultimately to better assess the couples' needs in order to better respond to it by an optimal care management, including the establishment of follow-up consultations for couples.

**9570 General Poster Session (Board #220), Sun, 8:00 AM-11:45 AM**

**Has health-related quality-of-life assessment in EORTC clinical trials helped to obtain regulatory approvals and change clinical practice? A review of the EORTC experience in cancer clinical trials.** *Presenting Author: Efstathios Zikos, European Organisation for Research and Treatment of Cancer Headquarters, Brussels, Belgium*

**Background:** Health-related quality of life (HRQOL) has been an important part of the randomised controlled trials (RCTs) conducted by EORTC since 1980. This review aims to provide an update on a previous descriptive evaluation of EORTC RCTs from 2002 and select those whose HRQOL results changed clinical practice and helped to obtain regulatory approvals. **Methods:** The EORTC database was reviewed, restricting the search to the period 2002–2013. The published review from 1980–2001, involving over 65,000 patients, was also taken into consideration. We investigated the number of EORTC RCTs including HRQOL and identified those that altered clinical practice and influenced label claims. **Results:** 52 RCTs with HRQOL assessment were identified, involving 37,417 patients. The majority of phase II and III RCTs (n=45) have HRQOL as secondary endpoint. EORTC also conducted supportive care and translational research trials with an HRQOL component. The EORTC clinical groups with the most RCTs containing HRQOL were Radiation Oncology (17%, n=9) and Brain Tumour (13%, n=7). As examples of practice-changing RCTs, EORTC 22952-26001 found whole-brain radiotherapy not to improve OS while affecting HRQOL adversely (global health status (GHS), physical/cognitive functioning, and fatigue). EORTC 62072 in patients with advanced soft-tissue sarcoma, following chemotherapy treatment, found that pazopanib toxicity did not translate into significantly worse HRQOL (GHS: P=0.291; average difference=2.6 points) and nearly tripled PFS (HR 0.31; $p<0.0001$). RCTs whose HRQOL component helped to obtain regulatory approvals were EORTC 18991, 26981, and 62072. **Conclusions:** Our review shows how patient perspective in palliative and curative trials has been considered of major importance in oncology and demonstrates how recent findings in EORTC RCTs have altered clinical practice, providing recommendations for future improvements and helping label claims. The inclusion of patient perspective in drug development shows that a more comprehensive HRQOL assessment has taken place over time as better instruments have become available.

**9571 General Poster Session (Board #221), Sun, 8:00 AM-11:45 AM**

**Mobile cognitive assessment battery (MCAB) for assessment of cancer-related cognitive changes.** *Presenting Author: Shelli Kesler, Stanford University, Stanford, CA*

**Background:** A majority of patients with cancer report cognitive decline associated with cancer treatments. Traditional cognitive measures may lack adequate sensitivity to these cognitive difficulties, are weakly associated with patient self-report and have limited feasibility. We aimed to evaluate cognitive change in patients with breast cancer (BC) using our novel Mobile Cognitive Assessment Battery (MCAB) and compare MCAB with traditional neuropsychological measures. **Methods:** We have enrolled 39 women newly diagnosed with primary BC (mean age = 50 +/- 9 years) and 35 matched healthy women. Patients were assessed prior to any surgery requiring general anesthesia (T1) and again within one month of completing chemotherapy but prior to any radiation or hormonal therapy (T2). Controls were assessed at yoked intervals. We administered the Comprehensive Trail Making, Controlled Oral Word Association and Rey Auditory Verbal Learning tests, the Behavioral Rating Inventory of Executive Function (BRIEF) and our in-house MCAB. MCAB is administered via mobile tablet with tests including n-back, multi-tasking, and task switching. We compared cognitive function between the groups at baseline using analysis of variance, change in cognitive function over time using linear mixed modeling and correspondence between subjective and objective measures using Pearson correlations. **Results:** There were no differences between groups in cognitive function at T1. Compared to controls, the BC group showed no change in cognitive function from T1 to T2 as measured by traditional tests. Patients' self-rated cognitive problems (BRIEF) increased significantly over time ($p = 0.031$). MCAB (requiring 15 minutes to administer), detected significantly lower cognitive function over time in the BC group compared with controls in task switching ($p < 0.001$) and multi-tasking ($p = 0.019$). Traditional tests (40 minutes) were not significantly correlated with patients' self-ratings although MCAB tests were ($p < 0.039$). **Conclusions:** Our MCAB may be more convenient, more sensitive to changes in cognitive function and subjective patient report associated with BC treatment compared to traditional measures.

**9572 General Poster Session (Board #222), Sun, 8:00 AM-11:45 AM**

**Feasibility of neurocognitove and psychological assessments in allogeneic stem cell transplantation: A pilot study.** *Presenting Author: Tara K. Gregory, Colorado Blood Cancer Institute, Denver, CO*

**Background:** Neurocognitive and psychological measures may provide insightful and even prognostic information, yet are not routinely incorporated into pre-allogeneic hematopoietic stem cell transplant (HSCT) assessments. We conducted a longitudinal pilot study to assess the feasibility of using neurocognitive and psychological tools in the HSCT setting. **Methods:** Patients age 27-72 with diagnoses of hematologic malignancies underwent neurocognitive/psychological assessments within 4 weeks prior to HSCT, at day +100 and day +180. The Montreal Cognitive Assessment (MOCA) Version 7 assessed neurocognitive impairment. Center for Epidemiological Studies Depression Scale (CES-D), State-Trait Anxiety Inventory (STAI), and Neuropsychiatric Inventory(NPI), evaluated depression, anxiety, and caregiver interpretation of patient distress, respectively. Evaluations were performed by a clinical psychologist. **Results:** 21 successive patients scheduled for HSCT were evaluated for feasibility of conducting the above evaluations. One patient declined to participate in the full initial evaluation. The evaluation was scheduled during a pre-existing psychosocial intake and required an additional 30 minutes of clinician and patient time. The MOCA required 10 minutes. The CES-D, STAI, and EORTC QLQ–C30 required 5 minutes each. Scoring required 10 minutes. Neurocognitive impairment was frequent at baseline and worsened post-HCST. Pre-HSCT anxiety/depression was very severe (expected incidence <10%), and persisted in 6-month survivers. Most patients had sub-clinical levels of anxiety/depression which may impact function. **Conclusions:** Longitudinal neurocognitive/psychological inventories in the HSCT setting are feasible and informative. An expanded, prospective study will be performed to correlate the measures with post transplant outcomes and QoL.

| Measure | Pre-HSCT n=20 | Day 100 n=12 | 6 month n=8 |
|---|---|---|---|
| **MOCA** | 30% | 16% | 0 |
| **Normal** | 50% | 25% | 38% |
| **Low normal** | 20% | 59% | 62% |
| **Below normal** | | | |
| **Depression severe** | 25% | 8% | 33% |
| **Anxiety severe** | 20% | 8% | 50% |
| **Global QoL** | 30% | 17% | 25% |
| **80+** | 40% | 50% | 38% |
| **60-79** | 30% | 33% | 38% |
| **<60** | | | |
| **Overall survival** | 100% | 75% | 50% |

**9573 General Poster Session (Board #223), Sun, 8:00 AM-11:45 AM**

**Evaluation of an online, skill-building, group intervention for cancer patients and caregivers: Pillars4Life.** *Presenting Author: Jonathan David O'Donnell, Duke University School of Medicine, Durham, NC*

**Background:** Psychosocial distress is common for those with cancer; new interventions are needed. Pillars4Life is an online educational program that teaches coping skills in a group format. What is the relationship between participation in the LiveStrong-funded Pillars4Life program and personal psychosocial outcomes? **Methods:** This was a longitudinal observational cohort study. Cancer patients and caregivers participating in the Pillars4Life program were recruited from the 20 hospitals that received the LiveStrong Community Impact Award. Consenting participants participated in 10 weekly sessions and completed electronic surveys at baseline and 3 months. Patient reported measures included: distress [Distress Thermometer (DT), Patient Care Monitor (PCM)], depression [Patient Health Questionnaire 9 (PHQ9)], anxiety [Generalized Anxiety Disorder 7 (GAD7)], posttraumatic stress [PTSD Checklist-Civilian (PCLC)], quality of life and despair (PCM), fatigue [Functional Assessment of Chronic Illness Therapy (FACIT)], and cancer-related wellbeing [Functional Assessment of Cancer Therapy-General (FACTG)] outcomes. **Results:** Participants (n=80) were: mean age 55.5±11.1 years; 90% female; 87% white; 58% married; 46% employed; and 91% cancer patients, of which 54% had breast cancer and 72% were receiving treatment. Mean scores significantly improved from baseline to month 3 on all patient-reported outcome measures: DT (-0.8, $p$=.01); PCM Distress (-2.9, $p$=.01); PHQ9 (-2.7, $p$<.001); GAD7 (-2.2, $p$<.001); PCLC (-4.9, $p$<.001); PCM Quality of Life (3.8, $p$<.001) and Despair (-3.6, $p$<.001); FACIT-Fatigue (3.7, $p$=.004); and FACT-G (5.7, $p$=.002). Patient participants who reported distress at baseline (DT≥4; n=43) had clinically significant improvements (moderate to strong effect sizes ranged from 0.5 to 1.0 standard deviation units) in DT; PCM Distress, Quality of Life, and Despair; PHQ9; GAD7; PCLC; FACTG, among others. **Conclusions:** Participation in Pillars4Life was associated with statistically and clinically significant improvements on key psychosocial and quality of life patient-reported outcomes measures. Importantly, distressed patients experienced meaningful improvement.

**9574 General Poster Session (Board #224), Sun, 8:00 AM-11:45 AM**

**Quality of life of young mothers with breast cancer in Germany.** *Presenting Author: Dorothea Fischer, University of Schleswig-Holstein, Campus Luebeck, Luebeck, Germany*

**Background:** Aim of the study is to analyze the health-related quality of life (QoL) in young breast cancer patients and to compare it to that of an age-heterogeneous breast cancer cohort and of an age-adjusted general population sample. Further, predictors for a reduced QoL should be identified. **Methods:** A retrospective study analyzed quality of life of 517 young mothers (at least 1 child <12 years) first diagnosed between 2006 and 2011 with primary breast cancer. The patients participated in a resident mother-child program. The standardized questionnaire focused on medical, clinical and social data and especially on QoL (EORTC QLQ-C30, -BR23). The data were compared with those of an age-heterogeneous cohort with breast cancer and an age-adjusted general population sample from the state of Schleswig-Holstein, Germany. **Results**: The median age of the young cohort was 39 years. Inability to work, being unemployed and a higher body mass index were predictors for a reduced global QoL /health status. Unanticipated treatment and clinical issues did not affect quality of life. Young breast cancer patients – as compared to the older breast cancer cohort – showed a reduced social, emotional and cognitive functioning. In contrast, physical and sexual functions were significantly higher and stress by hair loss was significant better tolerated by the younger patients. Compared to the general population the patients showed a seriously reduced QoL. **Conclusions:** Because of their high risk of reduced QoL, young breast cancer patients with children under the age of 12 should be carefully observed with a focus on emotional and social functions and their ability to work. Our results imply the need to develop interventional procedures to enhance QoL in the vulnerable group of young breast cancer patients.

**9575 General Poster Session (Board #225), Sun, 8:00 AM-11:45 AM**

**Social and perceptual influences on alcohol consumption in cancer survivors.** *Presenting Author: Lawson Eng, Princess Margaret Hospital, Ontario Cancer Institute, Toronto, ON, Canada*

**Background:** We previously demonstrated that second-hand smoke (SHS) is inversely associated with smoking cessation in lung and other cancers (PMID: 24419133, 23765604, Eng *et al*, ASCO 2013; abst 9536) with adjusted odds ratio of 6-9. We now evaluated the effects of social alcohol exposure (i.e., having spouse, friends, or peers drink alcohol) on alcohol consumption. **Methods:** 707 cancer survivors across multiple disease sites at a single cancer centre were surveyed on their smoking and alcohol consumption prior to and after diagnosis. Home, spousal and peer exposure to smoking and alcohol and the perceived impact of these behaviours on prognosis, fatigue and quality of life were documented. Multivariate logistic regression models evaluated their association with change in each habit after diagnosis adjusted for significant socio-demographic and clinico-pathological covariates. **Results:** 116 patients smoked at diagnosis; 60% quit afterwards, none of the 218 ex-smokers or 367 never smokers started smoking after diagnosis. Among 354 current drinkers, 192 reduced consumption while 20 of the 129 ex-drinkers restarted. Negative perceptions of alcohol consumption were associated with cessation of alcohol use ($aOR_{quality\ of\ life}$ = 1.8, 95% CI [1.1-2.9]; $aOR_{prognosis}$ = 2.8 [1.6-4.8]; $aOR_{fatigue}$ = 2.2 [1.4-3.6]), and with negative perceptions on smoking (r = 0.31 to 0.35, p = 5.0E-17 to 5.6E-13). Neither smoking nor alcohol perceptions were associated with smoking cessation (p > 0.05). Exposure to SHS was associated with exposure to social alcohol use (ORs = 1.9 to 4.1, p = 5.0E-3 to 0.05). Social exposure to others drinking alcohol was associated with cancer survivors restarting to drink alcohol after diagnosis ($aOR_{home\ exposure}$ = 2.7 [0.9-8.2]; $aOR_{peer\ exposure}$ = 2.9 [1.1-7.9]; $aOR_{spousal\ exposure}$= 6.0 [1.2-29.1]). **Conclusions:** Spouse, peer, and home exposure to alcohol use by others was associated with cancer survivors restarting alcohol use, and with SHS exposure. The social environment can have an important impact on the health habits of cancer survivors.

**9576 General Poster Session (Board #226), Sun, 8:00 AM-11:45 AM**

**Factors influencing advanced cancer patients' preferences for quality or length of life.** *Presenting Author: Eva C. Winkler, National Center for Tumor Diseases, Heidelberg, Germany*

**Background:** The integration of individual patients' preferences is paramount for patient-oriented care in oncology at the End of Life (EOL). The aim of this study was to explore patients' preferences for Quality (QL) or Length of Life (LL) and the factors influencing them. In addition, communication preferences of patients about limiting treatment were explored. **Methods:** We surveyed 194 cancer patients at the National Center for Tumour diseases and the Thorax Clinic at Heidelberg University using a set of questionnaires. Socio-demographic, clinical data, preferences regarding QL and LL, communication preferences cancer-related distress and family role in the decision-making were assessed. **Results:** Patients' attitudes toward treatment could be categorized into striving for QL, striving for LL, and no clear preference. Patients' preferences were slightly higher for QL (mean=3.5; SD=0.7) than for LL (mean=3.15; SD=0.9). Patients who indicated that their next of kin play an important role in therapeutic decisions were more likely to strive for LL (p=.01). Patients who preferred LL tended to avoid communications with their physicians about limiting treatment (p=.03) whereas patients who strived for QL preferred their physicians initiating this discussion early on (p=.00). Patients were predominantly men (68%); mean age was 63 years (SD=10.3). Age, gender, prognosis and cancer-related distress had no impact on preferences for QL or LL. **Conclusions:** Family involvement in treatment decisions had considerable impact on patients' preferences and was associated with patients striving for LL. Those patients did not want their oncologists to discuss treatment limitation with them. Hence, in orchestrating decision making about cancer specific treatment near the EOL it is important for oncologists to involve the family and enable the communication about realistic treatment goals early on.

**9577 General Poster Session (Board #227), Sun, 8:00 AM-11:45 AM**

**Traumatic stress symptoms in patients with acute leukemia (AL).** *Presenting Author: Gary Rodin, Princess Margaret Hospital, University Health Network, Toronto, ON, Canada*

**Background:** AL is associated with an immediate threat to life, an intensive treatment regimen, and substantial suffering relating to the disease and its prognostic uncertainty. This longitudinal study was undertaken to assess psychological and physical distress in the first 3 months following diagnosis or relapse of AL. We report here the findings at 3 months. **Methods:** Patients with newly diagnosed or recently relapsed acute myeloid, lymphoblastic and promyelocytic leukemia were recruited at Princess Margaret Cancer Centre within one month of diagnosis or relapse. Patients completed a baseline assessment and monthly follow-ups for 3 months. The frequency of traumatic stress symptoms that met criteria for acute stress disorder (ASD; symptoms above threshold <1 month) was determined. Multivariate regression analysis was used to identify predictors of traumatic stress symptoms. Self-report measures included: Stanford Acute Stress Reaction Questionnaire (SASRQ), Memorial Symptom Assessment Scale, CARES Medical Interaction Subscale, Experiences in Close Relationships-SF and FACIT SP-12. **Results:** 178 participants completed >3 time-points; mean age was 49+16 years, 58% male, 91.6% newly diagnosed, and 96.6% receiving chemotherapy with curative intent. Mean SASRQ score at baseline was 27.2+21.8 (range 0-97) and 27% reported symptoms >threshold for ASD at baseline. Of those who provided at least 3 assessments, 10% scored above cut-off 3 or more times; 12.4% twice; 20.8% only once; and 56.7% at no time. Regression analyses indicated that female gender, psychological symptoms, worse communication with health care providers, lower spiritual well-being and attachment anxiety were significant predictors of traumatic stress. **Conclusions:** Significant traumatic stress symptoms occurred in more than 40% of patients with AL within 3 months of diagnosis, which persisted in almost 25% of the sample across 3 or more time-points. Traumatic stress symptoms in this population are linked to a number of potentially treatable factors. Further research is needed to demonstrate the benefit of early psychological and palliative interventions.

**9578 General Poster Session (Board #228), Sun, 8:00 AM-11:45 AM**

**Marital distress (MD), quality of life, and psychological morbidity among advanced cancer patients (ACP) in phase I trials and their spousal caregivers (SC).** *Presenting Author: Fay J. Hlubocky, The University of Chicago Medicine, Chicago, IL*

**Background:** Prior research identifies marriage as a protective resource for couples during the cancer trajectory. However, the prevalence of potential MD and its effect on the quality of life (QOL) and psychological morbidity of ACP in Phase I trials has not been described. **Methods:** A prospective cohort of ACP enrolling in phase I trials was assessed at baseline (T1) and one month (T2) using the following measures: depression (CES-D), state-trait anxiety (STAI-S/T), quality of life/qol (FACIT-Pal), global health (SF-36), and marital satisfaction (DAS). Semi-structured interviews evaluated ACP-SC experiences re MD including: fulfillment, contentment, intimacy, conflict. **Results:** To date, a total of 54 married phase I ACP-SC couple dyads (n=108 subjects) were separately interviewed at T1 and T2. For the total population: median age 60y (28-78y); 50% male; 88% Ca; 68%> HS educ; 57% GI dx; 52% income <$65,000 yr. Couples were married on average for 37y (15-50y) and 18% ACPs reported this was a second marriage. At T1, 45% of ACP reported marital fulfillment; 37% reported marital contentment; 67% reported intimacy concerns; 65% reported marital conflict. For SC at T1, 31% reported marital fulfillment; 50% reported marital contentment; 74% SC reported intimacy concerns; and 79% reported marital conflict. Rates remained stable for both ACP and SC with the exception of increased self-reported marital conflict at 68% and 83% respectively at T2. At T2, ACP who reported marital conflict had higher STAI-S (33 ± 10 v 28 ±12, p=0.01) and CES-D (13 ± 12 v 11 ± 9, p=0.03). SC with self-reported marital conflict had higher STAI-S anxiety (39 ± 17 v 35 ± 13, p=0.03) at T2. In regression analyses, ACP with intimacy concerns had poorer FACIT-Pal QOL over time. Also, SC with intimacy concerns at T2 was negatively associated with SF-36 and DAS scores over time. ACP and SC qualitative inquiry re MD exposed various themes: conflicts re EOL tx/advanced directives/estate planning; lack of physical/emotional intimacy; non-existent sex life; lack of communication. **Conclusions:** MD is negatively associated with QOL among clinical trial subjects and SC in phase I trials.

**9579 General Poster Session (Board #229), Sun, 8:00 AM-11:45 AM**

**Persistent pain following breast cancer surgery: A case-control study.** *Presenting Author: Sara N. Edmond, Duke University Medical Center, Durham, NC*

**Background:** Persistent pain following surgery for breast cancer is increasingly recognized as an important clinical problem. The mechanisms responsible remain to be determined, but psychological factors have been implicated in studies of breast cancer survivors. However, case control studies that provide direct comparisons to matched samples of healthy women are rare in this literature. **Methods:** We recruited breast cancer survivors (n=200) at the time of their first postsurgical mammogram (approx 1 yr) and compared their responses on validated self-report measures of pain, and select psychological factors (symptoms of anxiety and depression) to a matched sample (n=150) of healthy women receiving mammograms on the same day. The majority of women were white, married, and well educated. Only racial representation differed between the groups, so all analyses controlled for that factor. **Results:** Women with a history of cancer were more likely to meet criteria for persistent pain and reported greater levels of pain intensity, pain unpleasantness, pain interference, and pain frequency (all p<0.01). They also reported using medication for pain more frequently (p<0.01). There were no statistical differences in BMI, caffeine consumption, or smoking status. Symptoms of depression, but not anxiety were significantly (p=0.01) higher in women with histories of breast cancer. Persistent pain was related to the severity of the women's depressive symptoms (p=0.002). When persistent pain and symptoms of depression were included in multivariate analyses of case-control differences, there was no longer a significant difference between the groups in persistent pain (p=0.25). **Conclusions:** Women who have undergone breast cancer surgery have higher levels of persistent and current pain, as well as higher levels of depressive symptoms compared to women without histories of breast cancer. Analyses suggest that higher levels of depressive symptoms may make a substantial contribution to the higher levels of persistent pain in these women. Future research should test this causal assumption with randomized trials of behavioral interventions known to reduce the contribution of psychological factors to pain (e.g., targeted pain coping skills training).

**9580 General Poster Session (Board #230), Sun, 8:00 AM-11:45 AM**

**Survival differences by race/ethnicity in adolescents and young adults diagnosed with non-Hodgkin lymphoma.** *Presenting Author: Chun Chao, Kaiser Permanente Southern California, Pasadena, CA*

**Background:** Adolescents and young adults (AYAs) with cancer have not experienced the same degree of survival improvements as in younger children and older adults. Several barriers have been identified in delivering optimal oncology care in AYAs, including lack of knowledge on the biology and factors affecting survival in AYA cancer. Here we evaluated if survival differs by race/ethnicity in AYAs diagnosed with non-Hodgkin lymphoma (NHL). **Methods:** AYAs (ages 15-39) diagnosed with incident NHL in 1990-2010 were identified at Kaiser Permanente Southern California (KPSC), a large managed care organization. KPSC members have relatively equal health care access, which minimizes confounding due to access variations. Information on demographic and cancer characteristics was obtained from KPSC's Surveillance, Epidemiology and End Results-affiliated cancer registry. Mortality data were obtained from California and national death registries. Patients were followed from NHL diagnosis to 5 year after or 12/31/2012, whichever came first. Multivariable Cox model was used to evaluate the association between race/ethnicity and mortality, adjusting for age, sex, cancer stage and year of diagnosis. **Results:** A total of 724 AYAs with NHL were included (mean age at diagnosis: 31), of whom 60% were male, 45% were non-Hispanic white, 10% were African American, 36% were Hispanic, and 8% were Asians. The distribution of stages at diagnosis was 18% stage I, 17% stage II, 16% stage III, and 40% stage IV. Overall 5-year survival was 70% (number of deaths =218). Compared to non-Hispanic whites, all minorities were associated with increased 5-year mortality: hazard ratio for African American = 1.74, 95% confidence interval (1.10-2.74), for Hispanic =1.31 (0.95-1.82), and for Asians =1.84 (1.03-3.28). Male sex, increasing age and advanced cancer stage were all significantly associated with elevated mortality. A significant survival improvement was observed over calendar years. **Conclusions:** A survival disparity for race/ethnicity was observed in AYAs with NHL despite relatively equal access to care. These results call for studies to further understand mechanisms underlying the inferior survival among minority subgroups.

**9581 General Poster Session (Board #231), Sun, 8:00 AM-11:45 AM**

**The potential role of pNF-H, a biomarker of white matter damage in central nervous system, as a predictive marker of chemotherapy-induced cognitive impairments.** *Presenting Author: Akina Natori, Division of Medical Oncology, Department of Internal Medicine, St. Luke's International Hospital, Tokyo, Japan*

**Background:** Chemotherapy-induced cognitive impairments (CICI) have been recognized as a clinically-significant issue for cancer survivors, it is urgently required to elucidate the mechanism of CICI and develop diagnostic and therapeutic measures. Previous studies using magnetic resonance imaging showed more decreased white matter integrity in CICI patients than healthy controls. Increased level of the circulating phosphorylated form of the high-molecular-weight neurofilament subunit NF-H (pNF-H), which is one of the major structural proteins in axon, has been reported to be elevated in central nervous system (CNS) disorders. We hypothesize CICI is caused by demyelination in CNS. We examined neuropsychological tests and serum pNF-H level in breast cancer patients receiving adjuvant chemotherapy in a cross-sectional manner. **Methods:** Early breast cancer patients in various phase of treatment (5 were naïve to chemotherapy, 20 were after 1 cycle of chemotherapy, 20 were after 3 cycles of chemotherapy, 20 were after 7 cycles of chemotherapy, 12 were past chemotherapy patients) were assessed by neuropsycological tests (EuroQOL-5 Dimension, Hospital Anxiety and Depression Scale, State Trait Anxiety Inventory, PainDetect, Epworth Sleepiness Scale, Colored Progressive Matrices, and Cognition Fail Question) and pNF-H at one point. Patients with pNF-H >70.5 $\mu$g/ml were considered pNF-H positive. The Chi-square test and the Mann-Whitney test were used to compare data. **Results:** Increased level of pNF-H was observed in 28.8% of patients who underwent chemotherapy. The rate of pNF-H positive patients of each group significantly increased in proportion to the number of chemotherapy (1 cycle:9.1%, 3 cycle:27.8%, 7 cycle: 61.1%; p<0.05), but none of past chemotherapy patients and chemotherapy-naive patients were pNF-H positive. No differences were observed in neuropsycological tests between each group. **Conclusions:** Serum pNF-H level in breast cancer patients on chemotherapy was increased in cumulative dose-dependent manner, suggesting its potential application as a biomarker to survey neural damage after chemotherapy.

**9582 General Poster Session (Board #232), Sun, 8:00 AM-11:45 AM**

**Follow-up of 1,001 adults and children after fertility preservation for oncologic conditions within a publicly financed health care program.** *Presenting Author: Kenny A Rodriguez-Wallberg, Karolinska Institutet and Karolinska University Hospital, Reproductive Medicine, Stockholm, Sweden*

**Background:** Options for fertility preservation (FP) among adults and children are currently available for female and male individuals of all ages. In Sweden, publicly financed health care covers assisted reproduction and freezing of gametes and tissues for medical reasons. **Methods:** We reviewed clinical data of 1001 cancer patients enrolled in the FP programme at Karolinska University Hospital, Sweden, between 1998 and 2013. **Results:** This cohort included 945 adults and 56 children. By the time of this report, 95% of women, 90% of men and 77% of children are in the survival cohort. Most common cancer diagnoses were breast cancer, testicular cancer and lymphoma in adults, and leukemia in children.Women and children were counseled by gynecologists and pediatricians. Adult males were counseled by oncologists. All patients had access to FP options within a few days. Female patients (N=478) were offered cryopreservation of embryos, non-fertilized oocytes or pieces of ovarian cortical tissue. Males (N=523) were offered sperm freezing and cryopreservation of adult or pre-pubertal testicular tissue. Nearly one-third of survivors have returned for fertility counseling and treatment. Transfer of frozen-thawed embryos and use of frozen sperm in fertility treatments had resulted in births in over 50% of cases; in vitro fertilization of frozen-thawed oocytes resulted in transfer of embryos, but not in pregnancies. Ovarian function resumed in three women after transplantation of thawed ovarian tissue, with one pregnancy achieved. No signs of cancer recurrence related to the transplantation of ovarian tissue were observed. Five girls, prepubertal at the time of cancer treatment, underwent additionally ovarian stimulation after puberty, and mature eggs were frozen for the future. **Conclusions:** The utilization rates of cryo-stored gametes and embryos in this cohort are higher than those reported earlier. Although our results are encouraging, the efficacy of FP procedures can only be estimated in the group of cancer survivors who came back for fertility treatment. We have offered counseling and FP within the publicly financed health care. This may not be possible in all countries.

**9583 General Poster Session (Board #233), Sun, 8:00 AM-11:45 AM**

**Effect of exercise on cancer-associated cognitive dysfunction: A proof-of-concept randomized controlled trial.** *Presenting Author: Kristin Campbell, University of British Columbia, Vancouver, BC, Canada*

**Background:** Changes in cognitive function are reported in 15-75% of individuals during or following cancer treatment. Currently, there is little available evidence of effective intervention strategies to address this issue. However, exercise presents a potentially effective intervention, as improvements in cognitive function with exercise have been demonstrated in other populations. However, to date there have been no published randomized controlled trials examining the effect of exercise on cognitive function in cancer survivors. **Methods:** A proof-of-concept randomized controlled trial (RCT) in women, treated for breast cancer within the past 3 years, who self-report persistent cognitive dysfunction following chemotherapy treatment (n=20). Participants were randomized to a 24-week aerobic exercise intervention or delayed exercise control. The primary outcome was self-reported cognitive function and impact on quality of life (QoL), using the FACT-CoG. The secondary outcome was performance on a standard neuropsychological test battery. **Results:** Compared to the control group, the exercise group had improvements in the Impact on QoL subscale (+2.9, 95% CI -0.3 to 6.0, p=0.07) and Comments of Others subscale (+1.4, 95% CI -0.9 to 3.6, p=.20) of the FACT-Cog. The exercise group also had improvements in verbal fluency, using the animal naming (5.7, 95% CI 1.8 to 9.6, p=<0.01) and motor processing speed, using Trail Making A (-12.2 seconds, 95% CI -51.1 to 26.7, p<0.01), while a reduction in time to complete Trail Making B did not reach statistical significance (-12.2 seconds, 95% CI -51.1 to 26.7, p=0.51). **Conclusions:** The results from this proof of concept RCT demonstrate the potential of exercise to improve self-reported symptoms cancer associated cognitive dysfunction and neuropsychological test performance in areas of verbal fluency and motor processing speed. The point estimates and variance provided by this proof-of-concept trial will serve to inform the development of a future, definitive, multi-site RCT.

**9584 General Poster Session (Board #234), Sun, 8:00 AM-11:45 AM**

**Patients' expectations of oncologists and primary care providers (PCPs) in addressing reproductive and sexual health.** *Presenting Author: Ying Wang, University of British Columbia, Vancouver, BC, Canada*

**Background**: The risk of infertility and sexual dysfunction from cancer therapy is inadequately discussed at the time of cancer diagnosis (Wang et al, ASCO 2013) even though these issues can cause significant distress. Our aims were to survey young cancer patients to 1) ascertain their expectations of physicians in addressing these concerns and 2) characterize how patients' expectations modify the likelihood of having discussions about reproductive and sexual health. **Methods**: Patients aged 20 to 39 diagnosed with solid tumors from 2006 - 2008, evaluated at any 1 of 5 regional cancer centers in British Columbia and alive at >/= 2 years after diagnosis were surveyed to determine their views about oncologists' and PCPs' responsibilities for reproductive and sexual health. Survey responses were paired with tumor and treatment characteristics from patients' medical records. Using logistic regression, we explored for associations between expectations and whether or not patient-physician conversations had occurred. **Results**: A total of 453 patients (response rate 57%) were included: median age was 35 years, 29% were men, 88% had ECOG 0, and 78% reported being in a relationship. Tumor sites included breast (50%), testicular (27%), gynecological (17%) and colorectal (6%). Patients expected their PCPs to be more involved than their oncologists in addressing fertility and sexual function (82% vs. 76% and 73% vs. 49%, respectively). However, only 55% and 7% of individuals actually engaged in conversations about these issues with their physicians. In multivariate models, higher patient expectations of oncologists' involvement in reproductive and sexual health did not correlate with greater likelihood of having a discussion (OR 1.22 p=0.49 and OR 0.99 p=0.98, respectively). Conversely, increased patient expectations of their PCPs correlated with receipt of a discussion about fertility (OR 2.44 p=0.01) but not about sexual function (OR 0.62 p=0.15). **Conclusions**: Patients prefer to address their reproductive and sexual health concerns with their PCPs. Whereas most discussions appear to be driven by physician factors, fertility conversations with PCPs can be facilitated by increased patient engagement.

**9585 General Poster Session (Board #235), Sun, 8:00 AM-11:45 AM**

**Feasibility of using home-based mobile sensors for remote patient monitoring in cancer care and prevention.** *Presenting Author: Susan K. Peterson, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Remote monitoring of patients outside of the clinic setting during critical periods of care is an emerging paradigm in oncology. CYCORE (CYberinfrastructure for COmparative effectiveness REsearch) is a software-based prototype for a user-friendly cyberinfrastructure that supports collection and analyses of data from multiple domains using home-based mobile sensors. We evaluated CYCORE's feasibility in three studies that represented diverse oncology settings and that assessed: (1) physical functioning in colorectal cancer (CRC) patients; (2) adherence to swallowing exercises in head and neck cancer (HNC) patients during radiation therapy; and (3) tobacco use in cancer survivors who completed an in-house tobacco treatment program (TTP). **Methods:** Eligible participants were ≥ age 18 years, English proficient, and had a history of cancer. Participants used home-based sensors for two non-consecutive 5-day periods. CRC patient sensors provided blood pressure, heart rate, accelerometry and global positioning system (GPS) data; HNC patient sensors captured video of swallowing exercises; and TTP patient sensors captured expired carbon monoxide and adherence videos. Patient-reported outcome measures were completed daily using smartphones. Feasibility outcomes included study completion rate, and perceived ease of use, self-efficacy and overall satisfaction with sensors. **Results:** For the CRC, HNC and TTP studies, respectively, we enrolled 50, 37, and 50 participants over 18, 8.5, and 20 month time periods, with 96%, 84%, 96% completion rates. Participant characteristics for the respective studies included: 50%, 27%, 72% female; 70%, 92%, 70% White; 68%, 97%, 46% married; and 80%, 68%, 58% with at least some college education. Between 91-100% of all participants rated their ease and self-efficacy for each sensor as highly favorable, 72-100% gave equivalent ratings for overall satisfaction, and 72-93% had low or no concerns about data privacy. **Conclusions:** Using home-based mobile sensors for remote monitoring was feasible and highly acceptable for patients. CYCORE serves as a new model for sensor- and home-based monitoring that can inform both research and clinical care.

**9586 General Poster Session (Board #236), Sun, 8:00 AM-11:45 AM**

**Sexual problems of female cancer survivors compared to women without cancer.** *Presenting Author: Ah Reum An, Department of Family Medicine, Seoul National University Hospital, Seoul, South Korea*

**Background:** Sexual dysfunction is one of the distressing problems experienced by female cancer survivors. In this study, we aimed to investigate female sexual dysfunction of cancer survivors compared to women without cancer in South Korea across various cancer types. **Methods:** We performed a case-control study of 5,350 women visited the center for health promotion and optimal aging at Seoul National University Hospital between January 2010 to December 2011. Cases were defined as women who were diagnosed cancer before the health check-up and completed the female sexual function index (FSFI) questionnaires (n = 233), and controls were women without cancer before and after the health check-up and completed the FSFI questionnaires (n = 3,024). The control group was matched on age to survivors at a 1:1 ratio individually. **Results:** The proportion who are sexually active female cancer survivors were not different from that of controls (37.8% vs. 36.9%, P = 0.848). Among sexually active women, the mean total FSFI score were 22.3 ± 5.4 in cancer survivor group and 24.2 ± 4.4 in control group (P = 0.012). Cancer survivors scored lower than controls in domains of desire, lubrication and orgasm. Thyroid cancer survivors tended to have more difficulties having desire and reaching orgasm than their matched controls with marginal significance. Breast cancer survivors reported significantly more troubles in lubrication and more pain. Cancer survivors of other cancer types tended to have more dyspareunia compared to the controls. No difference in any aspects of sexual function was observed between gynecologic cancer survivors and the controls. **Conclusions:** Female cancer survivors have poorer sexual function compared to women without cancer. Sexual problems vulnerable in cancer survivors seemed different according to cancer types.

**9587 General Poster Session (Board #237), Sun, 8:00 AM-11:45 AM**

**Acute changes in endothelial function with cisplatin among germ cell tumor (GCT) patients (Pts).** *Presenting Author: Darren Richard Feldman, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** We hypothesized that the increased risk of cardiovascular disease (CVD) in GCT pts following cisplatin-based chemotherapy (CBCT) may be due to endothelial damage. **Methods:** In this pilot study, men age ≥18 with GCT, no prior chemotherapy (CT) or radiation, and no history of CVD were enrolled to the CT group (CG) if CBCT was planned and to the surgery group (SG) if only surgical management (orchiectomy +/- RPLND) was planned. Endo-PAT2000, a noninvasive method of quantifying endothelial function, was used to measure the peripheral arterial tonometry reactive hyperemia index (PAT-RHI). Lower values correlate with endothelial dysfunction. Circulating endothelial cells (CECs) were quantified by immunomagnetic capture as a secondary endpoint. Covariates included hypertension, smoking status, dyslipidemia, diabetes, and fasting lipids, glucose, HbA1C, and testosterone. Measurements were obtained at time points $T_1$-$T_5$ for CG pts and $T_1$, $T_2$ and $T_5$ for SG pts (Table). Nonparametric tests were used to compare PAT-RHI values at $T_1$ (baseline) vs later time points in each group and at $T_1$, $T_2$, and $T_5$ across the two groups. **Results:** Among 22 CG pts (median age 29, range 21-49), PAT-RHI was non-significantly lower at $T_2$ (after the 1st dose of CT) and $T_5$ (14-34 weeks post $T_1$) vs $T_1$. For SG pts (n=20, median age 35, range 25-45), PAT-RHI was non-significantly higher at $T_2$ and $T_5$ vs $T_1$. However, PAT-RHI was significantly lower in CG men vs SG men at $T_2$ and $T_5$ (Table). There was also a trend toward greater decreases in PAT-RHI values at $T_2$ vs $T_1$ (p=0.08), $T_5$ vs $T_1$ (p=0.07), and $T_5$ vs $T_3$ (p=0.07) for CG pts with ≥1 (n=12) vs. no CVD risk factors (n=8). For CG men, median number of CECs/7.5mL was lower at $T_2$ (18) vs T1 (35; p<0.01) and borderline higher at $T_5$ (33) vs $T_2$ (p=0.05). There were no differences in CECs over time for SG men. **Conclusions:** CBCT may acutely cause endothelial dysfunction. Further study with a larger sample size and longer follow-up is warranted. Clinical trial information: 01453660.

**Median PAT-RHI.**

| | $T_1$ (C1D1 pre-CT) | $T_2$* (C1D1 post-CT)# | T3 (C1D2 pre-CT) | T4 (C1D5 post-CT) | T5* (End of CT)£ |
|---|---|---|---|---|---|
| CG N=20¥ | 2.00 | 1.67 | 2.13 | 1.99 | 1.83 |
| SG N=20 | 1.87 | 2.22 | -- | -- | 2.31 |

Abbreviations: C, cycle; D, day. *p=0.03 for comparison of CG vs SG at both $T_2$ and $T_5$. #2-5 hrs post $T_1$ for SG pts. ¥22 enrolled, 20 evaluable. £14-34 wks post $T_1$.

**9588 General Poster Session (Board #238), Sun, 8:00 AM-11:45 AM**

**Characterizing self-reported memory problems in adult-onset cancer survivors in the United States: Importance of sleep duration and insomnia.** *Presenting Author: Pascal Jean-Pierre, University of Notre Dame, South Bend, IN*

**Background:** Memory dysfunction is a debilitating adverse effect of cancer and its treatments. We examined the relationships between self-reported memory problems (SRMP) and sleep disorders in adult-onset cancer survivors. **Methods:** We used data from 151 adults, 41-64 years old, cancer survivors who completed the 2007-2008 National Health and Nutrition Examination Survey. Population-weighted binary logistic regression analyses examined SRMP as outcome and included age, sex, education, race-ethnicity, income, and overall health as covariates. Sleep duration was categorized as very short (<=4hrs), short (5-6hrs), normal (7-8hrs) or long (>=9hrs). Initial insomnia was assessed as difficulty falling asleep. Middle insomnia was assessed as difficulty maintaining sleep. Late insomnia was assessed as waking too early. These insomnia subgroup were categorized as none, mild (<15 days/month) and severe (>=15 days/month). A combined insomnia variable categorized individuals as insomnia if they had severe insomnia of any type (early, middle, late). **Results:** Overall, presence of insomnia was associated with SRMP ($p<0.0001$). Severe initial insomnia was associated SRMP ($p=0.006$). Mild and severe middle insomnia were associated with SRMP ($p=0.007$ and $p<0.0001$, respectively). Late severe insomnia was associated with SRMP ($p=0.037$). Additionally, long sleep was negatively associated with SRMP ($p=0.019$). Among participants without a history of cancer ($N=2,001$), none of the sleep variables were associated with increased likelihood of memory problems ($p>0.05$). **Conclusions:** The findings seem to indicate that sleep may be a mechanistic pathway through which cancer impact memory.

**9589 General Poster Session (Board #239), Sun, 8:00 AM-11:45 AM**

**Genetic testing referral patterns and clinical outcomes among high-risk breast cancer survivors.** *Presenting Author: Rashmi Krishna Murthy, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Referral patterns for genetic testing in breast cancer survivors are not well understood. We sought to identify a cohort of high-risk breast cancer survivors who had not been referred to understand patterns of referral and assess clinical outcomes. **Methods:** We identified breast cancer survivors (> 5 years) at MD Anderson who met at least one high-risk criteria and identified those who had not been referred for genetic counseling at our institution. Descriptive statistics were used to assess their characteristics and clinical outcomes. **Results:** We identified 5,941 high-risk breast cancer survivors, of whom 74% (N= 4,406) had not been referred for genetic counseling at our institution. The majority were female with a mean age at diagnosis of 43 years, and a median follow-up time of 116 months. Among those who had not been referred, 44% were initially diagnosed and treated at MD Anderson, whereas the rest were initially diagnosed and treated elsewhere. 52% were diagnosed prior to year 2000 and the majority (70%) had stage I or II disease at diagnosis. Of the patients where receptor status was known (N = 2,406), the majority had hormone receptor positive breast cancer (54%), followed by HER2/neu positive (21%), and triple negative (25%). A total of 606 patients experienced local recurrences (median time 436 months) and 838 patients experienced distant recurrences (median time 316 months). Among 59 patients with death events, 50 died with evidence of breast cancer. A total of 126 patients were diagnosed with secondary malignancies, such as bilateral breast cancer (N = 2), ovarian cancer (N = 7), endometrial cancer (N = 18), pancreatic cancer (N = 1), and thyroid cancer (N = 12). **Conclusions:** A significant number of breast cancer survivors who meet current standards for genetic testing referral may not have undergone BRCA mutation testing. Reasons for lack of referral for genetic testing may include unrecognized risk, lack of complete risk assessment, or not meeting established criteria at the time of diagnosis. The identification of untested high-risk breast cancer survivors allows for further studies that may reveal potential barriers to referrals and creates awareness.

**9590 General Poster Session (Board #240), Sun, 8:00 AM-11:45 AM**

**Long-term survivors in phase I clinical trials: Who are they and what predicts their survival?** *Presenting Author: Begona Jimenez Rodriguez, Drug Development Unit at The institute of Cancer Research and The Royal Marsden NHS Fundation Trust, London, United Kingdom*

**Background:** Phase I trials (PhIT) participants are those who have exhausted standard treatment (tx) or for whom no standard tx exists; most patients (pts) are unlikely to benefit from new drugs. Response rate and median overall survival (OS) are ~ 5-10% and 10 months (m), respectively; however, we observe pts with improved outcomes. This study aims to characterize who these long-term survivors are and define factors predicting for this prolonged OS. **Methods:** Retrospective analysis of patients treated at the Drug Development Unit, RMH-ICR, UK, between 01/05-12/12 and who survived ≥12m within ≥1consecutive PhIT. Kaplan-Meier method was used to estimate OS. Cox-regression-model was applied for HR estimation and for MVA of prognostic (px) factors for OS. **Results:** Of 1424 pts, 86 pts (6%, 44M/42F) survived ≥12m. Median (range): age 56 (23-85), PS 0 (0-1) and no. of prior Tx 2 (0-7). Most common tumor types: 34% gynaecological (79% ovarian) & 24% genitourinary (GU) (86% prostate). RMHscore (0-1/2-3) 76/10. Visceral disease (Y/N %) 46/54 (14% only bone metastases). 20% pts $BRCA^{mut}$. 37 pts (43%) were treated in >1PhIT. % pts and drugs administered: 39.5% DNA repair-chromatin remodeling; 16.3% hormone synthesis; 46.5% growth-factor-receptor-pathways; 28.8% cytotoxic+new drug and 34.9% others. 42% pts had CR+PR v SD in 58% pts. Median OS was 46.5 m, with improved median OS for those who achieved CR+PR v SD (59.7m v 41.8m, p=0.02). Survival rate at 18,24 &36m was 95,90 & 68%. Cox-regression univariate analysis showed px significance of: GU-tumors [HR 0.43 (0.22-0.85),p=0.016), no-visceral –disease [HR 0.42 (0.25-0.72),p=0.002], only-bone-metastases [HR 0.28 (0.1-0.78),p=0.015], RMH<2 [HR 0.45 (0.21-0.96); p=0.034] clinical benefit with last anticancer tx[HR 0.56 (0.32-0.96), p=0.034] and response to PhIT [HR 0.55 (0.32-0.94), P=0.028]. MVA showed only the presence of visceral disease to be an independent px factor for OS. **Conclusions:** Despite an overall poor prognosis, a proportion of pts treated on PhIT demonstrate a clinically meaningful OS; moreover, in those who respond this outcome is significantly better. This is primarily dictated by low burden of disease, and may support the earlier referral of appropriate pts.

**9591 General Poster Session (Board #241), Sun, 8:00 AM-11:45 AM**

**Ventricular arterial coupling in early breast cancer patients following treatment with anthracycline-containing adjuvant chemotherapy.** *Presenting Author: Graeme J Koelwyn, University of British Columbia, Kelowna, BC, Canada*

**Background**: Use of anthracyclines is limited by dose-dependent cardiotoxicity. Research has focused on cardiac specific damage, although injury may extend beyond the heart to the vascular network. We sought to explore the utility of ventricular-arterial coupling (VAC), an integrative measure of heart and arterial function, at rest and during exercise, to evaluate cardiovascular function post therapy. **Methods:** Thirty ER+/HER2- breast cancer survivors (6.1 ± 2.4 yrs post anthracyclines) with normal left ventricular ejection fraction (LVEF) (59 ± 6) and 30 age-activity matched healthy controls were studied. Echocardiographic measurements were performed at rest and during exercise at 25%, 50%, and 75% of a predetermined maximal workload ($W_{max}$) to determine arterial elastance (Ea), end systolic elastance (Ees) and VAC (Ea/Ees). Endothelial flow-mediated dilation (FMD), carotid intima-media thickness (CIMT), arterial stiffness and peak oxygen consumption ($VO_{2peak}$) were also measured. **Results:** At rest, Ea, Ees, Ea/Ees and LVEF were not different between survivors and controls. The expected increase in Ees during exercise was attenuated in survivors compared to controls at 25% $W_{max}$ (5.28 ± 2.39 vs. 7.0 ± 2.11 mmHg/mL, $p<0.001$), 50% $W_{max}$ (5.94 ± 1.62 vs. 8.26 ± 2.76 mmHg/mL, $p<0.001$), and 75% $W_{max}$ (6.75 ± 2.29 vs. 10.26 ± 4.22 mmHg/mL, $p<0.001$). Accordingly, the Ea/Ees ratio was significantly higher at all exercise-related workloads in survivors compared to controls (p's<0.05). Ea, diastolic relaxation and filling, endothelial independent and dependent FMD, CIMT, arterial stiffness and $VO_{2peak}$were not different between groups (p's >0.05). **Conclusions:** While not detectable at rest, significant reductions in contractile performance (Ees) of the left ventricle were observed in survivors when the cardiovascular system was challenged by exercise. This subclinical cardiovascular dysfunction appears to be isolated to the heart as no differences in vascular function were observed at rest or during exercise. VAC assessment during exercise is a viable tool to evaluate late-occurring cardiovascular dysfunction in early breast cancer patients.

**9592 General Poster Session (Board #242), Sun, 8:00 AM-11:45 AM**

**Chemotherapy-induced amenorrhea (CIA) risk associated with taxane/platinum-based chemotherapy in young (≤45 years) breast cancer patients.** *Presenting Author: Priyanka Sharma, University of Kansas Medical Center, Westwood, KS*

**Background:** Twenty-five percent of women with breast cancer (BC) are premenopausal and 15% are diagnosed in reproductive age group (≤45 years), thus at risk of CIA. Although CIA rates with alkylating agents/topoisomerase inhibitors (Alk/Topo) are well documented, there is inadequate data addressing the impact of newer Docetaxel/Carboplatin(TP) regimen on menstrual function. The objective of this study was to determine the incidence of long-term (>12 months) CIA related to different chemotherapy regimens in BC patients < 45 years. **Methods:** We identified 283 premenopausal women with BC ≤ 45 years treated with at least 4 cycles of Neo/adjuvant chemotherapy at University of Kansas from 2005 to 2012. Menstrual status information was extracted from medical records. Standard statistical methods were used to assess the association of CIA with variables of interest. **Results:** 165 patients met eligibility criteria and had sufficient follow up. Median age: 39 years(24–45 yrs), 62%:<41 years and 38%:41-45 years. 41%:HR+, 20%:HER2+/HR+, 12%:HER2+/HR-, 27%: TNBC. 79%(130/165) received Alk/Topo regimens (AC+/-T=113, TAC=8, TC=9) and 21%(35/165) received TP regimen. Median ages of patients receiving Alk/Topo and TP regimens was similar. The overall rate of CIA was 34%. BMI, smoking, parity & Tamoxifen use did not impact CIA. Rates of CIA were lower in younger patients and in patients receiving TP chemotherapy. When examined by age at diagnosis CIA rates were 17% (<41yrs) and 63% (>41yrs), respectively (P<0.001). When examined by chemotherapy type the rates of CIA were 42% (Alk/Topo group) and 6% (TP group), respectively (p<0.001) in all patients and 22% (Alk/Topo group) and 0% (TP group) in patients <41 years (p=0.010). **Conclusions:** Risk of long term CIA with TP regimen is much lower (6%) compared with Alk/Topo regimens (42%) in premenopausal women ≤ 45 years. Premature menopause is associated with considerable side effects like menopausal symptoms, loss of fertility, risk of osteoporosis and cardiovascular disease. Information regarding CIA rates of different chemotherapy regimens is of value to young patients and physicians to aid in adjuvant chemotherapy regimen decision making.

**9593 General Poster Session (Board #243), Sun, 8:00 AM-11:45 AM**

**Cardiovascular mortality (CVM) among testicular nonseminoma (TN) survivors after chemotherapy (CHEM) or surgery (SURG).** *Presenting Author: Chunkit Fung, James P. Wilmot Cancer Center, University of Rochester Medical Center, Rochester, NY*

**Background:** Increased long-term risks of cardiovascular (CV) disease after CHEM for testicular cancer are well established whereas few studies have quantified the association of cisplatin-based chemotherapy with arterial thromboembolic events (ATE). We examined CVM in a large population-based cohort of TN survivors managed with modern combination CHEM, which usually includes cisplatin. **Methods:** Standardized mortality ratio (SMR) of CVM stratified by time since TN diagnosis were calculated for 15,006 TN survivors reported to the SEER program (1980-2010) initially managed with CHEM (n=6,909) or SURG (n=8,097) alone without RT, with each cohort accruing 60,065 (median 6.5) and 81,227 (median 7.9) person-years (PY) of follow up, respectively. **Results:** After CHEM, significant excesses of CVM occurred (n=54; SMR 1.4; 95% CI 1.03-1.8; absolute excess risk (AER) 2.4 per 10,000 PY) including deaths from heart disease (n=42; SMR 1.3; 95% CI 0.9-1.7), cerebrovascular disease (CVA) (n=10; SMR 2.4; 95% CI 1.2-4.4) and other arterial diseases (n=2; SMR 6.5; 95% CI 0.8-23.5). Excess CVM was concentrated within 1 yr after diagnosis, with SMRs during the <1, 1-4, 5-9, 10-14, 15-19 and 20+ yr periods 5.3 (95% CI 2.7-9.5), 1.7 (95% CI 0.9-2.9), 1.2 (95% CI 0.6-2.2), 0.9 (95% CI 0.4-1.9), 1.2 (95% CI 0.5-2.3), and 0.8 (95% CI 0.3-1.7), respectively. In particular, significantly elevated 4- to 22-fold risks of mortality due to either heart disease (n=6; SMR 3.5; 95% CI 1.3-7.5) or CVA (n=5; SMR 21.7; 95% CI 7.1-50.7) occurred in the <1 yr period. In contrast, among those managed with SURG only, no excess deaths were observed, either for all CVM taken together (n=50; SMR 0.8; 95% CI 0.6-1.1), heart disease (n=43; SMR 0.8; P>0.05) or CVA (n=7; SMR 1.07; P>0.05). Univariate Cox regression analysis showed excesses of CVM after CHEM vs. SURG (hazard ratio 1.5; 95% CI 1.01-2.2). **Conclusions:** Early ATE associated with modern CHEM may in part explain the excess deaths due to heart disease and CVA during the <1 yr period. Future analytic studies should not only quantify temporal trends of CV disease incidence and CVM in TN survivors, but include mechanistic investigations to facilitate the development of preventive efforts.

**9594 General Poster Session (Board #244), Sun, 8:00 AM-11:45 AM**

**Long-term quality of life among localized prostate cancer survivors: Qalipro population-based study.** *Presenting Author: Anne-Valérie Guizard, Centre François Baclesse, Caen, France*

**Background:** If treatments can cure localized prostate cancers (LPC) they often induce acute toxicities and definitive sequelae with impact on quality of life (QoL). However, very few studies focused on the long-term QoL of survivors of LPC. The goal of this population based case-control-study was to evaluate QoL 10 years after treatments for LPC in comparison with aged-matched healthy controls. **Methods:** LPC patients diagnosed in 2001 were issued from 11 French Cancer Registries. Controls were recruited among the general population and were matched to patients on age and geographic area. EORTC QLQ-C30, EPIC, HADS and MFI self-reported questionnaires were used to measure QoL, anxiety and fatigue. Patients were identified into 3 groups according to previews treatments: radical prostatectomy (RP), radiotherapy (RT) and radical prostatectomy plus radiotherapy (RP+RT). Patients could receive hormonotherapy (HT). Student's paired t and McNemar $\chi^2$ tests were used for the analysis between patients and controls. Analysis between treatments groups were performed with ANOVA. Only clinically relevant QoL score differences (≥ 5 points) were reported. **Results:** There were 287 patients and 287 controls. The participation rate of patients was of 46. Among LPC patients 143 (50%) were treated with RP, 78 (27%) with RT and 33 (11%) with RP+RT. 60 (21%) and 47 patients (16%) received HT at baseline and at the time of the study respectively. There was no socio-demographic difference between patients and controls. Patients didn't report more anxiety, depression and fatigue than controls, but lower EORTC-QLQ social functioning score (p=0.003). LPC long-term survivors reported more urinary troubles (urinary function and incontinence) (p<0.0001) and more sexual dysfunctions (p<0.0001) than controls, whatever the treatment group. RP and RP+RT groups had worse urinary function and incontinence than RT (p<0.01). LPC survivors treated with HT at the time of study reported more sexual dysfunction (p<0.0001) and hormonal troubles (dysfunction and bother) (p=0.002) than the other survivors. **Conclusions:** 10 years after treatments, long term survivors of LPC reported important urinary and sexual dysfunctions with poor social QoL.

**9595 General Poster Session (Board #245), Sun, 8:00 AM-11:45 AM**

**Chemotherapy-induced ovarian failure in young breast cancer patients: The role of vascular toxicity.** *Presenting Author: Irit Ben-Aharon, Davidoff Cancer Center, Rabin Medical Center, Petach-Tikva, Israel*

**Background:** Chemotherapy-related amenorrhea is a frequent side effect observed in young breast cancer patients (pts). We had formerly described a mechanism of ovarian toxicity manifested by decreased ovarian blood flow and diminished post-treatment AMH levels. We report herein the continuous prospective evaluation of ovarian function in this cohort. **Methods:** Young breast cancer pts (<40 years) undergoing adjuvant/neoadjuvant chemotherapy were evaluated by transvaginal ultrasound prior to initiation of chemotherapy, immediately upon completion of chemotherapy, at 6 and 12 months after cessation of chemotherapy . Doppler-flow velocity indices of the ovarian vasculature and size measurements were visualized. Hormonal profile, AMH and menopausal symptoms were assessed at the same time points. **Results:** Twenty breast cancer pts were enrolled into the study. Median age was 34+5.24 years. Ovarian blood flow was significantly reduced immediately following chemotherapy (p=0.01) after treatment. These parameters were partially recovered at later points of assessment (6 months and 12 months post treatment); patients <35 years exhibited a significant regaining of ovarian blood flow compared with patients >35 years (p<0.05). AMH dropped dramatically in all patients following treatment (P<0.001), and was recovered in only 6 patients (all <35 years). Hormonal profile shortly after chemotherapy depicted a post-menopausal profile for most patients, accompanied by related symptoms. FSH levels were recovered in 14/20 of the patients, and significantly returned to premenopausal range in patients <35 years (p-0.04). The pattern of vascular impairment (reflected by flow velocity) was lessened in patients treated with a trastuzumab-based protocol, though results did not reached statistical significance (p-0.07). **Conclusions:** Continuous prospective evaluation of ovarian vasculature and function in a cohort of young patients with breast cancer following chemotherapy indicate that ovarian toxicity may derive from acute vascular insult. Regaining ovarian function may be affected by age, whereas recovery of blood flow and premenopausal FSH levels at later assessment were notable in patients <35 years.

**9596 General Poster Session (Board #246), Sun, 8:00 AM-11:45 AM**

**Assessing the prevalence of compromised bone health among overweight and obese African-American breast cancer survivors.** *Presenting Author: Patricia M. Sheean, Loyola University Chicago, Maywood, IL*

**Background:** Osteoporosis is considered a late effect of breast cancer treatment. Previous studies included predominantly European-American women and analyzed African-American (AA) survivors in aggregate, despite their known differences in bone mineral density. Our purpose was to examine the prevalence of osteoporosis in a sample of exclusively AA women. **Methods:** This cross-sectional study included 111 overweight or obese AA women, aged 31-80 years, previously diagnosed and treated for stage I-IIIa breast cancer. Women completed questionnaires and underwent dual energy x-ray absorptiometry and phlebotomy prior to their enrollment in a weight loss intervention. Participants were categorized as having normal bone density, low bone mass or osteoporosis using the WHO definition for femoral neck T-scores. **Results:** Despite the frequent use of adjuvant hormone therapies (45%), a decreased ability to absorb ultraviolet light (54% reported dark/very dark skin), suboptimal intake (diet + supplements) of calcium and vitamin D [949 (± 569) mgs and 325 (± 231 IUs), respectively], the infrequent use of bisphosphonates (7%), and a high occurrence of vitamin D insufficiency/deficiency (49% had serum 25(OH)D levels <20 ng/ml), the prevalence of osteoporosis and low bone mass was <1% (n=1) and 16% (n=17), respectively. The 10-year probability of a major osteoporotic fracture was 2.4%. Age (p=0.004) was the only significant predictor of compromised bone health. **Conclusions:** These findings challenge the clinical assumption that osteoporosis is highly prevalent among all breast cancer survivors, providing foundational evidence to support differences by race/ethnicity and reiterating the necessity of regular dialogue concerning nonpharmacologic preventative options (e.g., diet and physical activity).

**9597 General Poster Session (Board #247), Sun, 8:00 AM-11:45 AM**

**Impact of current treatment status on QOL in cancer survivors.** *Presenting Author: Eon Sook Lee, Department of Family Medicine, Inje University Ilsan Paik Hospital, Goyang-si, Gyeonggi-do, South Korea*

**Background:** Many cancer survivors have been reported to have poor health related quality of life (HRQoL). This could be caused by various symptoms of cancer itself and treatment. For better understanding of cancer treatment and HRQoL, we investigated HRQoL and associating factors according to current treatment status and compared them with general population. **Methods:** Using national survey data in South Korea (KNHANES IV-V) from 2007 to 2010, we analyzed 14,396 subjects aged over 50years. Cancer survivors were defined as person diagnosed cancer by physician and divided into two groups, with current treatment and no treatment. Euro QOL was measured as HRQoL. Socioeconomic status (age, sex, education, having SSI), number of non-cancer disease, depressive mood, time since diagnosis and health behaviors (smoking, alcohol, physical activity) were collected as risk factors. EQ5D index and EQ_VAS of survivors receiving treatment were compared with no treatment group and general population, respectively. **Results:** Cancer survivors with treatment (N=191) showed lower EQ_VAS ($\beta$=-3.57, P=0.047) when compared to the general population, while group with no treatment (N=464) did not show the difference in multivariate analysis. Depressive mood was a consistent risk factor of poor HRQoL regardless current cancer treatment status (OR=3.73, 95% CI=1.18-11.78 in cancer treatment, 2.64 95% CI=1.37-5.09 in non-treatment), and same even in non-cancer group (OR=2.37, 95%=2.11-2.65). Except depressive mood, other risk factors influencing poor HRQoL could be attenuated among survivors with treatment. Survivors with no treatment still had a number of non-cancer morbidity and lower income as risk factors for low score of EQ5D index, similar to the non-cancer group. **Conclusions:** Current cancer treatment is a strong indicator for poor HRQoL in survivors. Cancer survivors had different risk factors for poor HRQoL according to current treatment status. Depressive mood was an important factor for poor HRQoL in both treatment and non-treatment groups. For evaluating HRQoL of cancer survivors even in long term group, the influence of current treatment status should be considered. Attention and management of depressive mood should be part of the care of cancer survivors.

**9598 General Poster Session (Board #248), Sun, 8:00 AM-11:45 AM**

**Association of physical activity with cardiorespiratory fitness and cardiac function in cancer survivors with chemotherapy-related heart failure.** *Presenting Author: Karen Basen-Engquist, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Studies have shown that physical activity can have a positive effect on cancer survivors, but there is scant research that addresses whether physical activity is beneficial to survivors who have chemotherapy related heart failure (CRHF). **Methods:** The purpose of this study was to evaluate the association between physical activity and cardiac function in cancer survivors with CRHF. There were 24 survivors, 20 were female, with a mean age of 54, 42% where white and the most common cancer site was breast (62.5%). The mean BMI was 30.5 and mean peak VO2 was 13.1. B-type natriuretic peptide (BNP), troponin, ejection fraction and peak VO2 were measured at a baseline assessment. Patients also filled out the CHAMPS physical activity questionnaire. Correlations and regression models were used to determine if physical activity measured by the CHAMPS was associated with the CRHF measures and peak VO2. All regression models included gender, age, race and BMI. Separate models were run for CHAMPS total hours and CHAMPS hours of moderate or greater intensity activity. **Results:** Both total hours and hours of moderate or greater activity from the CHAMPS were significantly correlated with peak VO2 (Total: R = .473, P = .026; Moderate or greater: R = .538, P = .010). There was no significant relationship between the CHAMPS activity variables and ejection fraction, BNP or Troponin. The regression models showed that BMI was a significant predictor of peak VO2 (B = -.253, P = .014) and CHAMPS moderate or greater intensity hours approached significance (B = .458, P = .062), but CHAMPS total hours was not a significant predictor. Age was the only variable to significantly predict BNP (B = 6.54, P = .017) and race (P = .05) was a significant predictor of ejection fraction with white subjects having higher values. There were no significant predictors of troponin. **Conclusions:** In this study, patients' current physical activity levels were not related to measures of cardiac function. Current exercise and BMI were related to peak VO2 suggesting that despite the CRHF, cardiorespiratory fitness may improve with exercise. Future randomized trials should test the effects of exercise in survivors with CRHF.

**9599 General Poster Session (Board #249), Sun, 8:00 AM-11:45 AM**

**Leukocyte telomere length and risk of secondary primary tumors in long-term breast cancer survivors.** *Presenting Author: Maria Alma Rodriguez, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Leukocytetelomere length (LTL) has been associated with cancer risk including breast cancer. Telomere shortening is observed in response to chemotherapy and/or ionizing radiation exposure. More recently, a report has shown a significant association between short LTL and increased risk of treatment-related thyroid cancer, whereas a suggestive, non-significant association was found between LTL and treatment-related breast cancer (Gramatges MA, et al. Clin Cancer Res, Nov. 2013). We hypothesize that LTL at diagnosis may be associated with breast cancer survival and risk of developing secondary primary tumors (SPT) in long-term breast cancer survivors. We used a case-control study to test this hypothesis. **Methods:** We used a quantitative real-time PCR method to measure LTL in 168 long term breast cancer survivors (including 68 with SPT, and 100 without SPT), 96 newly diagnosed breast cancer cases, and 97 controls. Cases and controls were matched by years since diagnosis, age at time of sample collection and race. Wilcoxon-rank sum test was used to compare LTL among these three groups and between those long-term survivors with and without SPT. **Results:** We found that LTL was significantly longer in long-term breast cancer survivors than newly-diagnosed breast cancer patients (Mean (SD), 1.31 ±0.26 vs 1.22 ±0.31; p=0.005), and healthy controls (1.31±0.26 vs 1.10±0.30, p<0.001). Overall, there were no significant differences in LTL between long term survivors with SPT and without SPT. However, in stratified analyses, we observed that breast cancer survivors with SPT had significantly or borderline significantly shorter LTL than those without SPT in individuals with low BMI (<=25) (1.23±0.19 vs 1.44±0.25; p<0.006) and in ever smokers (1.21±0.31 vs 1.36 ±0.32, p =0.071). **Conclusions:** Longer telomeres were observed in long term breast cancer survivors when compared to new diagnosed cases and healthy controls. A relation between short LTL and increased risk of SPT in long term breast cancer survivors was observed in individuals with low BMI and ever smokers. These results suggest a role of telomere dysfunction in long term breast cancer survivorship.

**9600 General Poster Session (Board #250), Sun, 8:00 AM-11:45 AM**

**Factors associated with bone fractures following hematopoietic stem cell transplantation.** *Presenting Author: Xerxes Pundole, Department of General Internal Medicine, Section of Rheumatology, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** The number of long-term survivors of hematopoieticstem cell transplantation (HSCT) is growing. These survivors have increased bone fragility and susceptibility to fracture, leading to death and long-term disability; however, risk factors associated with fractures in these survivors are unclear. **Methods:** We conducted a retrospective study of patients who received HSCT from January 1, 1997, to December 31, 2011, at The University of Texas MD Anderson Cancer Center. Kaplan-Meier survival function plots and Cox proportional hazard models were used. **Results:** A total of 7,650 patients underwent HSCT during the 15-year period. Among them, 631 (8%) developed at least 1 fracture after HSCT; approximately 11% (n = 440) of those who underwent autologous HSCT and 5% (n = 191) of those who underwent allogeneic HSCT developed a fracture. Univariate Cox proportional hazard analyses showed that age >50 years at the time of HSCT, multiple myeloma or solid organ tumors, and autologous HSCT were associated with a higher hazard of developing a fracture. In a multivariable model including all predictors of interest (age at HSCT, sex, and race) except type of HSCT, age >50 years at the time of HSCT (hazard ratio [HR], 1.31; 95% confidence interval [CI], 1.09-1.56), multiple myeloma (HR, 4.96; 95% CI, 4.13-5.95), and solid tumors (HR, 1.61; 95% CI, 1.18-2.21) were associated with an increased risk of developing a fracture. In another multivariable model with type of HSCT included, and indication not included showed that age >50 years at the time of HSCT (HR, 1.94; 95% CI, 1.64-2.30) and autologous HSCT (HR, 1.58; 95% CI, 1.33-1.88) were associated with an increased risk of developing a fracture. **Conclusions:** HSCT and its associated treatment particularly increase the risk of fractures in those who undergo autologous HSCT and are older than 50 years. Regular screening to prevent bone loss should be initiated early, and establishment of a new fracture risk assessment tool is warranted in this patient population.

**9601 General Poster Session (Board #251), Sun, 8:00 AM-11:45 AM**

**Risk factors and prevalence of cognitive deficits in women with gynecologic malignancies.** *Presenting Author: Anne Van Arsdale, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY*

**Background:** Cognitive impairment has implications in counseling, treatment, and survivorship for women with gynecologic malignancies. The purpose of our study was to evaluate prevalence and risk factors associated with cognitive impairment. **Methods:** After IRB approval, 165 women at an urban ambulatory facility were queried using a Montreal Cognitive Assessment (MOCA), Depression Scale, Wong-Baker pain scale, and neuropathy scale. The association of cognitive deficit with age, education, race/ethnicity, disease site, stage, treatment, pain, neuropathy, anxiety and depression was evaluated. **Results:** Mean MOCA score was 24.1 (range 13-30.) 24% of patients had MOCA scores less than 22. Low scores (<22) were associated with older age, non-white race/ethnicity, lower education level, uterine cancer, and pain > 5 ($p<0.05$). There was a trend toward lower scores for with chemotherapy and radiation treatment ($p=0.10$). Low cognition scores were not associated with pain medication use. **Conclusions:** There was a high prevalence of cognitive deficits in women with gynecologic malignancies. Further research is needed to evaluate the impact of deficits on treatment adherence and outcomes.

| Variable | Normal cognition (≥22) | Low cognition (<22) | p-value |
|---|---|---|---|
| Age at diagnosis (years -mean) | 56.7 (12.6) | 63.2 (11.6) | 0.005 |
| Time since diagnosis (weeks - median) | 129 | 108 | 0.36 (Wilcoxon – skewed distribution) |
| Ethnic background | | | |
| African American | 26 (63.4) | 15 (36.6) | 0.02 |
| Hispanic | 28 (68.3) | 13 (31.7) | |
| White | 67 (87.0) | 10 (13.0) | |
| Other | 4 (80.0) | 1 (20.0) | |
| Education | | | |
| Middle school or less | 4 (40.0) | 6 (60.0) | 0.004 |
| Any HS | 38 (69.1) | 17 (30.9) | |
| College and higher | 82 (83.7) | 16 (16.3) | |
| Disease site | | | |
| Uterus | 67 (70.5) | 28 (29.5) | 0.012 (Fisher Exact) |
| Ovary/fallopian tube/PP | 44 (89.8) | 5 (10.2) | |
| Cervix | 10 (83.3) | 2 (16.7) | |
| Vulva | 4 (50.0) | 4 (50.0) | |
| Stage | | | |
| I/II | 82 (78.1) | 23 (21.9) | 0.53 |
| III/IV | 33 (73.3) | 12 (26.7) | |
| Treatment variables | | | |
| No further treatment (surgery only) | 60 (79.0) | 16 (21.0) | 0.10 |
| RT only | 3 (50.0) | 3 (50.0) | |
| Chemo only | 38 (82.6) | 8 (17.4) | |
| Both chemo/RT | 22 (64.7) | 12 (35.3) | |
| Pain | | | |
| <5 | 106 (79.7) | 27 (20.3) | 0.03 |
| ≥5 | 19 (61.3) | 12 (38.7) | |
| Taking pain medications | | | |
| No | 92 (78.6) | 25 (21.4) | 0.22 |
| Yes | 32 (69.6) | 14 (30.4) | |

**9602 General Poster Session (Board #252), Sun, 8:00 AM-11:45 AM**

**Breast imaging two years post-breast conserving therapy (BCT): Do more frequent mammograms (MMG) yield benefits?** *Presenting Author: Jingjing Hu, Hematology/Oncology, Baystate Medical Center/Tufts University School of Medicine, Springfield, MA*

**Background**: High level evidence defining the optimal timing and frequency of MMG surveillance (6-monthly vs. annually) after breast-conserving therapy (BCT) is lacking. The purpose of this retrospective study was to determine the value of 6-monthly MMG in detecting cancer events after BCT. **Methods**: AJCC stage 0 to IIIC breast cancer and ductal carcinoma in-situ (DCIS) patients (n=492) treated with BCT from 2005-2009 who had two years of surveillance MMG were selected. MMG-associated events, additional imaging and biopsies (Bx) triggered by abnormal mammograms, and tumor recurrences were analyzed by time intervals. A 6-monthly MMG group (n=400) was compared with annual MMG group (n=92). MMG yield was defined as MMG detected events divided by total MMG. We analyzed results using simple frequencies and Fisher's exact test. **Results:** Of 1591 total MMG, 144 were pre-radiation; 69 additional imaging tests (38 ultrasounds, 22 magnification MMG and 9 MRIs) were performed. 1407 and 182 MMGs were performed in 6-monthly MMG group and annual MMG group respectively. 44 biopsies were triggered by abnormal MMGs (table). At 24 months after BCT, MMG detected 3 ipsilateral invasive cancers and 2 contralateral DCIS; 1 ipsilateral regional and 5 distant cancer events were found clinically. Two-year MMG yield was 0.31% (95%CI: 0.04-0.59%); First-year MMG yield was 0.10% (95%CI: 0-0.4%) and second- year MMG yield was 0.66% (95%CI: 0.02%-1.3%). MMG yields were 0.21% (95%CI: 0-0.45%) for the 6-monthly group and 1.0% (95%CI: 0-4.0%) for the annual group with no significant difference (p=0.11). **Conclusions:** The addition of 6-monthly MMG over annual screening did not significantly increase cancer detection, but was associated with unnecessary images and biopsies.

| Interval after BCT(mos.) | Positive ipsilateral MMG-triggered Bx (n) | Ipsilateral MMG-triggered Bx (n) | Positive contralateral MMG-triggered Bx (n) | Contralateral MMG-triggered Bx (n) | Total positive MMG-triggered Bx n,(%) | Positive non-MMG triggered Bx |
|---|---|---|---|---|---|---|
| 6-12 | 0 | 17 | 1 | 6 | 1,(4.4%) | 2 |
| 13-18 | 3 | 8 | 0 | 0 | 3,(37.5%) | 0 |
| 19-24 | 0 | 11 | 1 | 2 | 1,(7.7%) | 4 |
| First 24 mo. | 3 | 36 | 2 | 8 | 5,(11.4%) | 6 |

**9603 General Poster Session (Board #253), Sun, 8:00 AM-11:45 AM**

**Trends in health-related quality of life (HRQoL) and income over time in older adults with and without cancer: Evidence from the Surveillance, Epidemiology, and End Results–Medicare Health Outcomes Survey (SEER–MHOS) linked database.** *Presenting Author: Veena Shankaran, Seattle Cancer Care Alliance/Fred Hutchinson Cancer Research Center, Seattle, WA*

**Background:** The impact of cancer diagnosis (dx) on the financial health and HRQoL of older adults is not well understood. The goal of this study was to explore longitudinal changes in HRQoL and self-reported income in a population-based sample of older Medicare enrollees with and without cancer. **Methods:** SEER-MHOS links data on cancer patients (pts) dx in 1998–2007 with a longitudinal HRQoL survey of Medicare Advantage Organization enrollees. We identified pts age ≥ 65 with primary breast, colorectal, prostate, lung, or head and neck cancers who had completed at least 2 MHOS surveys (1 pre and 1 post dx). 2,514 cancer cases were matched 1:4 with 8,616 non-cancer controls by age, gender, race, and time between surveys (mean age 75.3); controls were assigned a pseudo-dx date when their age was the same as the dx age of the matched cancer case. Mean physical component score (PCS) and mental component score (MCS) were determined at various time intervals before and after dx. The proportions of individuals experiencing a decline in household income were also reported. **Results:** A similar proportion of cases and controls reported declines in at least 1 income category after dx (24.4% vs. 24.1%). More cancer pts than controls reported a transition from owning a home to rented housing after dx (2.9% vs. 1.9%, $p < 0.05$). Mean PCS and MCS scores were similar in the 2 years leading up to dx but dropped significantly in the 6 months after dx in cancer pts relative to controls. By 2 years post dx, mean PCS and MCS were again similar between groups (Table). **Conclusions:** Cancer dx has a significant and time-sensitive impact on HRQoL in older Medicare enrollees. While there is some evidence of instability in household income and home ownership in this population, further investigation into the factors associated with these changes is warranted.

| | Pre–Dx | | Post–Dx | | | |
|---|---|---|---|---|---|---|
| | -10–12 mo | -4–6 mo | 0–3 mo | 4–6 mo | 10–12 mo | 22–24 mo |
| Mean PCS | | | | | | |
| Non-cancer | 42.1 | 41.2 | 39.5 | 41.1 | 39.6 | 40.1 |
| Cancer | 41.8 | 42.0 | 37.1 | 36.1 | 38.2 | 39.4 |
| P | 0.7 | 0.3 | 0.003 | <0.001 | 0.1 | 0.3 |
| Mean MCS | | | | | | |
| Non-cancer | 52.8 | 52.4 | 51.5 | 51.8 | 51.9 | 52.2 |
| Cancer | 53.9 | 53.4 | 48.3 | 50.2 | 50.5 | 51.9 |
| P | 0.1 | 0.2 | <0.001 | 0.036 | 0.05 | 0.6 |

**9604 General Poster Session (Board #254), Sun, 8:00 AM-11:45 AM**

**Arterial elasticity in testicular cancer survivors.** *Presenting Author: Anne Hudson Blaes, University of Minnesota, Minneapolis, MN*

**Background:** Testicular cancer survivors are known to have an increased risk of cardiovascular (CV) disease. We aimed to explore the impact of platinum based chemotherapy on endothelial function. **Methods:** Survivors < 30 years at diagnosis who received platinum chemotherapy 2002-2012 and 17 similarly-aged healthy male controls were identified. A history of CV disease was excluded. Subjects underwent pulse wave analysis using the HDI/PulseWave CR-2000 Cardiovascular Profiling System and Pulse contour analysis using the Endo-PAT2000 system. Biomarkers were obtained to evaluate lipids and inflammatory markers. Comparisons were made using T-tests and Wilcoxon Rank-Sum tests. **Results:** 13 survivors (median age 30.2 years, body mass index [BMI] 27.3) and 17 health controls (median age 27.1 years, BMI 24.8) enrolled. Median time from chemotherapy was 4.7 (range 0.8-14) years. Four cases (30.8%) and no controls smoked. There was no difference in lipid profiles between cases and controls.* Median systolic blood pressure (SBP) was elevated (124.5 mmHg cases, 113.4 mmHg controls, p=0.010). Despite the young age of participants, cases had reduced small artery elasticity (9.0 vs 10.4 ml/mmHg x 10, p=0.086). Smoking appears to exacerbate SBP, lipids and artery elasticity. **Conclusions:** In this pilot study, testicular cancer survivors early after the completion of cancer therapy have elevations in SBP and reduced small artery elasticity, suggesting premature CV risk. Further follow up is warranted.

| Measure | Normals | All cases | Smoker cases | Non-smoker cases | Controls | p-value* |
|---|---|---|---|---|---|---|
| SBP (mmHg) | <140 | 124.5 (10.9) | 128.0 (13.7) | 122.1 (9.8) | 113.4 (10.9) | 0.010 |
| Diastolic blood pressure (mmHg) | <90 | 77.7 (9.9) | 83.8 (9.3) | 74.7 (9.1) | 73.4 (5.8) | 0.182 |
| Cholesterol (mg/dl) | <200 | 178.2 (45.4) | 184.5 (64.8) | 176.8 (38.4) | 168.4 (39.6) | 0.544 |
| Triglycerides (mg/dl) | <150 | 152.6 (124.5) | 246 (193.5) | 106.0 (49.1) | 119.7 (90.7) | 0.431 |
| HDL (mg/dl) | >45 | 43.0 (15.6) | 33.5 (8.2) | 48.6 (49.1) | 47.4 (9.4) | 0.377 |
| LDL (mg/dl) | <130 | 106.4 (43.7) | 109.0 (51.7) | 106.6 (44.0) | 97.1 (27.8) | 0.524 |
| Large artery elasticity (ml/mmHg x 10) | | 19.9 (6.6) | 16.7 (2.1) | 21.3 (7.5) | 18.6 (3.0) | 0.679 |
| Small artery elasticity (ml/mmHg x 10) | | 9.0 (2.5) | 8.0 (1.5) | 9.5 (2.7) | 10.4 (2.3) | 0.086 |

* Wilcoxon Rank Sum test, comparing all cases and controls.

**9605 General Poster Session (Board #255), Sun, 8:00 AM-11:45 AM**

**Patient-reported outcomes from adolescent/young adult (AYA) cancer survivors.** *Presenting Author: James M. Metz, Hospital of the University of Pennsylvania, Philadelphia, PA*

**Background:** AYA survivors may experience unique toxicites compared to older survivors, and these may be difficult to measure. This Internet based study evaluates patient-reported outcomes during cancer survivorship. **Methods:** Data were gathered via a convenience sample frame from cancer survivors voluntarily utilizing a publically available, free, Internet-based tool for creation of survivorship care plans. Available at www.livestrongcareplan.com and through the OncoLinkwebsite, it provides customized guidelines for survivor care. During use of the tool, survivors are queried regarding late effects for which they are at risk. All data have been maintained with IRB approval. **Results:** The tool has been used by over 35,000 persons, with PRO available for 11,301; 32% of these were AYA. Median age of AYA survivors was 30 (Range 18 – 35; median diagnosis age 27). Median age of older survivors was 54 (Range 36 – 93, median diagnosis age 50). AYA survivors were 70% female and older were 76% female. In the AYA cohort, most common cancer diagnoses were hematologic (30%), breast (25%), and genitourinary (GU) (18%), compared to breast (44%), gastrointestinal (11%), and GU (10%) in the older cohort. AYA survivors reported cognitive changes (54%), and sexual side effects most frequently. Among males, erectile dysfunction (ED) was reported by 7% of AYA survivors, all of whom denied ED prior to treatment; of these, 14% reported that they had not maintained an erection until completion of intercourse since cancer treatment, and 23% reported that they could do so about 50% of the time. Retrograde/dry ejaculation was reported by 53%. Among females, sexual concerns such as vaginal dryness and shrinkage were reported by 47%. Time since cancer diagnosis ranged from <1yr to 15 years for the AYA cohort (median 2.1 years). **Conclusions:** AYA survivors are prominent users of this tool, although their diagnosis profile differs from that of older users. They report significant late effects, including perceived cognitive changes and prominent sexual side effects, and these may warrant specific counseling and support.

**9606 General Poster Session (Board #256), Sun, 8:00 AM-11:45 AM**

**Dose delays, dose reductions, and relative dose intensity in patients with cancer who received (neo)adjuvant chemotherapy in community oncology practices.** *Presenting Author: Menaka Bhor, McKesson Specialty Health and the US Oncology Network, The Woodlands, TX*

**Background**: Neutropenic complications, such as febrile neutropenia (FN), often necessitate delays or reductions in doses of myelosuppressive chemotherapy. The resulting reduced relative dose intensity (RDI) may lead to poorer disease-free survival and overall survival. **Methods**: Using the McKesson Specialty Health/US Oncology iKnowMed electronic health record database, we retrospectively identified the first course of (neo)adjuvant chemotherapy received by patients without metastases who initiated treatment between 1/1/2007 and 3/31/2011. For each regimen, we estimated mean RDI and the incidences of reduced RDI (< 85% over the course), dose delays (≥ 7 days in any cycle of the course), and dose reductions (≥ 15% in any cycle of the course) relative to the corresponding standard regimens described in the National Comprehensive Cancer Network (NCCN) guidelines or in published phase 3 trials. We also estimated the proportion of patients who received colony-stimulating factor (CSF) prophylaxis in the first 5 days of cycle 1. **Results**: See Table. **Conclusions**: The incidences of chemotherapy dose delays, dose reductions, and reduced RDI varied greatly across tumor types and regimens. CSF prophylaxis also varied, but was most frequently associated with regimens with a high risk (> 20%) of FN according to the NCCN guidelines. Further research should evaluate the impact of reduced RDI on long-term survival.

| Tumor type and regimen | Sample size | Mean RDI, % (SD) | RDI < 85%, % | Dose delay ≥ 7 days, % | Dose reduction ≥ 15%, % | CSF prophylaxis in cycle 1, % |
|---|---|---|---|---|---|---|
| **Breast cancer** | | | | | | |
| TC | 3,392 | 89.8 (18.9) | 19.3 | 22.9 | 22.3 | 50.7 |
| TAC* | 1,566 | 85.7 (22.2) | 27.1 | 36.1 | 34.8 | 91.8 |
| Dose-dense AC→T* | 1,269 | 93.5 (9.0) | 15.6 | 38.2 | 27.0 | 89.1 |
| **Ovarian cancer** | | | | | | |
| Carboplatin, paclitaxel | 314 | 67.4 (27.0) | 66.9 | 67.2 | 77.4 | 21.0 |
| **NSCLC** | | | | | | |
| Carboplatin, paclitaxel | 391 | 57.1 (32.4) | 71.4 | 61.9 | 78.3 | 24.0 |
| Cisplatin, vinorelbine | 218 | 61.4 (24.2) | 82.1 | 61.5 | 91.3 | 1.4 |
| **Hodgkin lymphoma** | | | | | | |
| ABVD | 774 | 69.1 (24.6) | 64.1 | 72.6 | 69.9 | 24.8 |
| **NHL** | | | | | | |
| RCHOP/CHOP (Q3W) | 1,443 | 75.2 (25.3) | 52.6 | 57.2 | 54.1 | 73.1 |
| RCVP/CVP | 409 | 76.7 (26.1) | 48.9 | 54.5 | 46.2 | 28.9 |

* High risk of FN according to the NCCN.

**9607 General Poster Session (Board #257), Sun, 8:00 AM-11:45 AM**

**A multicenter observational study comparing physician-assessed febrile neutropenia (FN) risk and prediction-model severe neutropenia (SN) or FN risk in patients (pts) with nonmyeloid malignancies.** *Presenting Author: Gary H. Lyman, Hutchinson Institute for Cancer Outcomes Research, Fred Hutchinson Cancer Research Center, Seattle, WA*

**Background**: A prediction model was previously developed that estimates the risk of SN or FN during the first cycle of chemotherapy (ctx) based on pt characteristics, disease characteristics, and the myelotoxicity of the ctx regimen (Lyman, 2011). **Methods**: This prospective, multicenter, observational study (124 community-based oncologists; 944 pts) was directed at investigating the relationship between physician-assessed FN risk and prediction-model SN or FN risk. The subjects of this study were the physicians, not the pts. Pts were included if they were ≥ 18 years old, newly diagnosed, and candidates for initiating an NCCN intermediate (10%–20%) FN risk ctx regimen. Physicians entered clinical data about the pts into a database and made a clinical prediction of FN risk. Physician-assessed FN risk was then compared to prediction-model SN or FN risk. Physicians were blinded to the data elements collected by the model and the risk predicted by the model. No outcome data were collected. **Results**: Physicians were hematologists/oncologists (79.8%), oncologists (18.5%), and gynecologists/oncologists (1.6%). Median (Q1, Q3) years of clinical experience was 12.0 (6.5, 20.0). Pts were 65.5% women, median (Q1, Q3) age was 62.0 (53.0, 70.0) years, and the most common tumor types were breast (38.6%), colorectal (27.4%), and NSCLC (12.2%). Correlation estimates (approximate 95% CI) for physician-assessed FN risk and prediction-model SN or FN risk were 0.194 (0.000, 0.373) for NHL, 0.166 (0.027, 0.298) for breast, 0.130 (–0.068, 0.318) for colorectal, 0.121 (–0.134, 0.362) for NSCLC, 0.008 (–0.309, 0.323) for SCLC, and –0.050 (–0.483, 0.403) for ovarian. Correlation between risk estimates was highest for physicians with 8–17 years of clinical experience, oncologists, and those working in clinical settings with > 4 physicians. **Conclusions**: The lack of correlation between physician-assessed FN risk and prediction-model SN or FN risk suggests that community oncologists would benefit from use of a standardized and systematic approach to assess FN risk among pts receiving intermediate-risk ctx regimens.

**9608 General Poster Session (Board #258), Sun, 8:00 AM-11:45 AM**

**Palonosetron (PAL) in combination with 1-day versus 3-days dexamethasone (DEX) to prevent nausea and vomiting in patients receiving paclitaxel and carboplatin (TC).** *Presenting Author: Naoto Furukawa, Department of Obstetrics and Gynecology, Nara Medical University, Nara, Japan*

**Background:** According to current guidelines the combination of PAL and 3-days DEX is the standard antiemetic treatment in pts receiving TC. However, PAL has prolonged efficacy in preventing delayed nausea and vomiting, and pts receiving DEX reported moderate to severe problems in the week following chemotherapy. The aim of present study was to evaluate the efficacy and toxicity of PAL and DEX on day 1 only in pts with gynecological cancer receiving TC. **Methods:** This study is a prospective, randomized phase II study. Pts were stratified according to age (over 50 years or under 50 years) and habitual alcohol intake (yes or no). Chemotherapy-naïve pts >20 years old were randomly assigned to receive PAL (0.75mg iv) plus DEX (20mg iv) on day1 before receiving TC (D-1 group), or PAL (0.75mg iv) plus DEX (20mg iv) on day1 before receiving TC and DEX (8mg po) on days 2 and 3 (Std group). Primary endpoint was complete response (CR; defined as no vomiting episodes and no rescue medication) for 24-120 h after the first chemotherapy cycle initiation. Nausea and vomiting were evaluated with the MASCC Antiemesis Tool (MAT). Toxicity assessments were conducted using the NCI-CTC investigator guide (version 4.0). **Results:** Between April 2012 and December 2013, a total of 88 pts were randomized: 82 pts (D-1 group=43, Std group=39; median age D-1 group=59 years, Std group=62 years; habitual alcohol intake D-1 group=4, Std group=3) were available for the efficacy and toxicity analysis. 69.8% (30/43) and 76.9% (30/39) of pts reported delayed CR in D-1 and Std, respectively (P = 0.465). Acute and overall CR in D-1 and Std were similar (95.4% vs. 94.9%, P =0.920; 67.4% vs. 76.9%, P=0.340). The most common adverse event was grade 1 constipation (18.6% vs. 20.5%, P=0.828) and grade 1 insomina (16.3% vs. 12.8%, P=0.658). In logistic analysis, age under 50 years was associated with a lower incidence of delayed CR (odd ratio 3.79). **Conclusions:** The antiemetic treatment with DEX on day 1 only seemed as effective as the standard treatment for prevention of nausea and vomiting in pts receiving TC. In addition, in pts < 50 years old other antiemetic drugs may be necessary in addition to DEX and PAL. Clinical trial information: 000007491.

**9609 General Poster Session (Board #259), Sun, 8:00 AM-11:45 AM**

**Perceptions regarding the value of the physical examination in patients with advanced cancer: A survey study.** *Presenting Author: Kunal C. Kadakia, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Despite its clinical utility, progressive reliance on technology can lead to devaluing the physical examination in patients with advanced cancer. The primary objective was to determine whether these patients have a positive or negative perception of the physical examination. Secondarily, to determine if these perceptions are related to interpersonal/relational values (symbolic) or diagnostic/objective values (pragmatic). **Methods:** One-hundred and fifty patients with cancer receiving concurrent oncology and palliative care were administered a 26-item survey regarding their overall perception of the physical examination. The primary outcome, patient responses to "I believe my experience while undergoing physical examinations has been overall: very negative (-5) to very positive (+5)", was analyzed using the Sign test. Other items were predefined as symbolic or pragmatic statements and responses from strongly disagree (1) to strongly agree (5) were further analyzed. Multivariable logistic regression was utilized to test for associations between baseline characteristics and the primary outcome. **Results:** Most patients (83%) found the overall experience of being examined to be highly positive (median=4, interquartile range [IQR]=2-5, p=<0.0001). Patients valued both the pragmatic (median=5, IQR=4-5) and symbolic (median=4, IQR=4-5) aspects of the physical examination. Increasing age was independently associated with a more positive perception of the physical examination (odds ratio=1.07 per year, 95% confidence interval 1.02-1.12, p=0.01). **Conclusions:** Patients with advanced cancer find the physical examination to be a highly positive aspect of their care. These benefits are perceived as having both symbolic and pragmatic value. The physical examination should remain a cornerstone of clinical encounters.

**9610 General Poster Session (Board #260), Sun, 8:00 AM-11:45 AM**

**A randomized phase II study evaluating the use of prydoxine to prevent hand-foot syndrome associated with capecitabine therapy for advanced or metastatic breast cancer.** *Presenting Author: Akiyo Yoshimura, Department of Breast Oncology, Aichi Cancer Center, Nagoya, Japan*

**Background:** Pyridoxine (Pyr) is a drug of activated vitamin B6 and usually used for allergic dermatitis. Pyr is frequently used to prevent the HFS, although the evidence of benefit is lacking in Japan. The aim of this is to determine whether Pyr could reduce capecitabine (Cap)-induced HFS in advanced or metastatic breast cancer patients. This study is an open label, multicenter, randomized phase II study conducted by Tokai Breast Cancer Research Group (TBCRG) in Japan. **Methods:** All patients were received either concomitant pyridoxine (60mg P.O per day) or none with Cap containing regimens (Cap monotherapy, Cap plus cyclophosphamide, Cap plus weekly paclitaxel). Patients were stratified by chemotherapy regimens, line of therapy after metastases, and institutes. The study treatment was given until grade 2 HFS or incidence of other severe adverse events or progression disease. Primary endpoint is the period until the incidence of grade 2 or worse HFS from start of protocol treatment. The key secondary endpoints were incidence and period until all grade HFS and safety. **Results:** A total of 135 advanced and metastatic breast cancer patients were randomized the concomitant Pyr arm (n=67) and Cap alone arm (n=68). The baseline characteristics were well balanced in both arms. Grade 2 or worse HFS developed in 19 of 66 patients (28.8%) versus 21 of 67 patients (31.3%) in concomitant Pyr arm and Cap alone arm, respectively. The median HFS-free period (grade 2 or worse) was 13.6 and 10.6 months in concomitant Pyr arm and Cap alone arm, respectively (Hazard ratio=0.75 [95%CI: 0.40-1.40], P=0.364). Grade 1 HFS-free period were not significant difference in both arms (Hazard ratio=0.92 [95%CI: 0.61-1.38], P=0.659). HFS-free period in each regimens were not evaluated because of small events in combination regimens. Interestingly, leucocytopenia and neutropenia were significantly increased in concomitant Pyr arm (p=0.020 and 0.006, respectively). The ratio of other adverse events were similar with both arms. **Conclusions:** Prophylactic pyridoxine use may delay the period until the incidence of severe Cap-induced HFS in advanced and metastatic breast cancer patients. Clinical trial information: UMIN000002932.

**9611 General Poster Session (Board #261), Sun, 8:00 AM-11:45 AM**

**Prevention of irinotecan-induced diarrhea by probiotics: Randomized double-blind, placebo-controlled phase III study.** *Presenting Author: Michal Mego, Faculty of Medicine, Comenius University and National Cancer Institute, Bratislava, Slovakia*

**Background:** Diarrhea is one of the dose limiting toxicity of irinotecan. SN-38 is main irinotecan metabolite responsible for diarrhea development. SN-38 is excreted in glucuronidated form into the intestine. Due to the bacterial enzyme beta-D-glucuronidase in intestinal lumen it is deconjugated and in this form causes direct damage to the intestinal mucosa associated with the development of diarrhea. This study aimed to determine the effectiveness of the probiotics in the prevention of irinotecan induced diarrhea due to reduction of intestinal beta-D-glucuronidase activity. **Methods:** Between January 2011 and December 2013, 46 patients with colorectal cancer starting a new line of irinotecan based therapy were included. 5-flurouracil/capecitabine along with irinotecan was administered to 26 (56.5%) patients and 22 (47.8%) patients received biological therapy as well. Patients were randomized 1:1 to probiotics (PRO) or placebo (PLA). Probiotic formula Colon Dophilus, was administered at a dose of 10x $10^9$CFU of bacteria tid, orally for 12 weeks of chemotherapy. Primary endpoint was incidence of grade 3/4 diarrhea. The study was prematurely terminated due to slow accrual, when 46 of 220 planned patients were accrued. Herein, we report final analysis of the study. **Results:** 23 patients were randomized to PRO and 23 patients to PLA. Administration of probiotics compared to placebo led to a reduction in the incidence of severe diarrhea of grade 3 or 4 (0% for PRO vs. 17.4% for PLA, p = 0.11), as well as reduction of the overall incidence of diarrhea (39.1% for PRO vs. 60.9% for PLA, p = 0.24) and incidence of enterocolitis (0% for PRO vs. 8.7% for PLA). Patients on PRO used less loperamid compared to PLA (mean duration of loperamid use: 4.5 days for PRO vs. 10.4 days for PLA, p = 0.45; mean number of loperamid tablets: 5.9 for PRO vs. 37.7 for PLA, p = 0.49). There was no infection caused by probiotic strains recorded. **Conclusions:** Administration of probiotics in patients with colorectal cancer treated with irinotecan-based chemotherapy is safe and could lead to a reduction in the incidence and severity of gastrointestinal toxicity. Phase III clinical trials with adequate sample size are warranted. Clinical trial information: NCT01410955.

**9612 General Poster Session (Board #262), Sun, 8:00 AM-11:45 AM**

**A genome-wide association study (GWAS) of docetaxel-induced neutropenia in CALGB 90401/60404 (Alliance).** *Presenting Author: Daniel Louis Hertz, University of Michigan, Ann Arbor, MI*

**Background**: The objective of this analysis was to perform unbiased discovery of genetic variants that modulate neutropenia risk early in docetaxel treatment. **Methods**: Chemotherapy-naive metastatic castration-resistant prostate cancer (mCRPC) patients treated with docetaxel and prednisone ± bevacizumab on the CALGB 90401 trial who experienced grade 3+ neutropenia (ANC < 1,000 cells/mm$^3$) within the first two treatment cycles (cases) were compared with controls who completed two cycles without grade 3+ neutropenia. All single nucleotide polymorphisms (SNPs) genotyped on the Illumina HumanHap610-Quad platform that passed quality control were included in a genome-wide association study (GWAS) in genetically-defined European subjects. SNPs selected for future replication, based on p-value and biological relevance to neutropenia, were adjusted for treatment arm, age, baseline ANC, smoking status and palliative radiation. **Results**: The incidence of grade 3+ neutropenia within the first two cycles was 22.6% (172/761). 590 European subjects fulfilling the case or control criteria were evaluated in a discovery GWAS of 498,022 SNPs. The top hit was an intronic SNP (rs12431732) in *ACTN1*, which bundles actin in the neutrophil cytoskeleton. Actin specific antibodies have been detected in auto-immune neutropenia, providing a plausible biological mechanism. Ten SNPs, many in genes involved in leukocyte homeostasis such as *SERPINA3* and *BAALC*, were prioritized for future replication (Table). **Conclusions**: GWAS in a prospectively enrolled mCRPC patient cohort identified SNPs that may influence risk of docetaxel-induced neutropenia, adjusted for bevacizumab treatment. Replication in independent cohorts of docetaxel treated patients is necessary to verify the influence of these SNPs on neutropenia risk.

| GWAS rank | rsID | Gene | Minor allele frequency | Adjusted hazard ratio | Adjusted p value |
|---|---|---|---|---|---|
| **1** | rs12431732 | *ACTN1* | 0.07 | 3.58 | $5.18 \times 10^{-07}$ |
| **2** | rs533722 | *RNLS* | 0.22 | 2.14 | $4.88 \times 10^{-06}$ |
| **4** | rs926788 | *SERPINA3* | 0.29 | 2.14 | $3.38 \times 10^{-06}$ |
| **8** | rs12586591 | *ACTN1* | 0.20 | 2.24 | $3.02 \times 10^{-06}$ |
| **10** | rs6468861 | *BAALC* | 0.43 | 0.50 | $1.52 \times 10^{-05}$ |
| **25** | rs153166 | *ARHGAP26* | 0.32 | 1.69 | $8.30 \times 10^{-04}$ |
| **27** | rs16978131 | *SETBP1* | 0.16 | 0.41 | $4.72 \times 10^{-04}$ |
| **30** | rs2183938 | *DAPK1* | 0.21 | 1.94 | $7.81 \times 10^{-05}$ |

**9613 General Poster Session (Board #263), Sun, 8:00 AM-11:45 AM**

**Use of aprepitant in uncontrolled delayed nausea and vomiting associated with preparative regimens in stem cell transplantation: A retrospective analysis.** *Presenting Author: Linh Tran, Stanford Hospital/Clinics, Stanford, CA*

**Background:** Aprepitant, a well tolerated antiemetic, is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy in combination with other antiemetic agents. Aprepitant has not been studied for the treatment of established or refractory nausea and vomiting. We report the experience of an academic medical center in the treatment of uncontrolled delayed nausea and vomiting in the stem cell transplant (SCT) population. **Methods:** Between 2008-2013, 110 patients were identified retrospectively to have been treated with a 3-day course of oral aprepitant for uncontrolled delayed nausea and/or vomiting after receiving preparative regimen for SCT. Primary outcome was to determine the rate of complete response ($CR_{NV}$, defined as no vomiting with grade 0-1 nausea, using CTCAE 4.02 at 5 days) and partial response ($PR_{NV}$, defined as a reduction in grade of nausea and vomiting without achieving CR at 5 days). Further analysis to assess CR, PR and time to control (reduction in the grade) for nausea ($CR_N$, defined as grade 0-1 nausea at day 5; $PR_N$, defined as a reduction in grade of nausea without achieving CR at day 5) and vomiting ($CR_V$, defined as no vomiting at day 5; $PR_V$, defined as a reduction in grade of vomiting without achieving CR at day 5) was also performed. **Results:** Of 110 patients, 37% were female, average age was 46.9 years (range, 21-75 years), 46.4% received alloSCT (25.5% FTBI), 52.7% autoSCT, and 0.9% syngeneic SCT. After receiving aprepitant, $CR_{NV}$ was achieved by 23.6%, with 50% $CR_N$ and 51.8% $CR_V$. 14.5% achieved a $PR_{NV}$ with 24.5% $PR_N$ and 1.8% $PR_V$. Median time to control nausea was 2 days (range, 1-5 days) and vomiting was 1 day (range, 1-2 days). All but 2 patients received ondansetron and dexamethasone prior to aprepitant administration. Of 21 patients who received at least one agent from a new class of antiemetic after administration of aprepitant, 6 (29%) of those patients achieved $CR_{NV}$ and 2 (10%) achieved $PR_{NV}$. **Conclusions:** The use of aprepitant shows efficacy in the treatment of uncontrolled delayed nausea and vomiting associated with preparative regimens in SCT.

**9614^ General Poster Session (Board #264), Sun, 8:00 AM-11:45 AM**

**Multicenter randomized double-blind controlled phase III study of hhpg-19K as prophylactic therapy in patients with advanced non-small cell lung cancer (NSCLC) receiving myelosuppressive chemotherapy.** *Presenting Author: Caicun Zhou, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China*

**Background:** HHPG-19K (19K) is a long-acting pegylated recombinant G-CSF that can be dosed only once-per-chemo cycle. The aim of this phase III study was to investigate the efficacy/safety of HHPG-19K as prophylactic therapy in patients with advanced NSCLC treated with myelosuppressive chemotherapy. **Methods:** Patients were randomized (1:1:1) blindly to three treatment arms to receive 19K 100mg/kg, 6mg fixed dose or CONTROL (saline) in cycle 1. In cycles 2 to 4 following unblinding at the end of cycle 1, patients in CONTROL received short-acting G-CSF at dose of 5$\mu$g/kg once daily subcutaneously 48h after chemotherapy while patients randomized in 2 19K arms to receive the same doses as in cycle 1. All patients received 4 cycles of docetaxel (75mg/m$^2$) plus cisplatin (75mg/m$^2$) or carboplatin (AUC=5) per 21 days. The primary endpoint was the incidence of grade 3/4 neutropenia evaluated in cycle 1. **Results:** 151 chemo-naive patients with histopathology stage III/IV NSCLC enrolled into this study. The distribution of patients' baseline characteristics was well balanced among 3 arms. The incidence of grade 3/4 neutropenia was significantly decreased in patients received 19K 100$\mu$g/kg and 6mg-fixed compared to CONTROL in cycle 1 and showed no statistical difference in cycle 2 to 4. Mean duration of grade 3/4 neutropenia and median recovery time from neutropenia for two 19K arms were significantly shorter than that of CONTROL in cycle 1 and were similar in three arms in cycles 2 to 4. Four (8.00%) febrile neutropenia were observed in CONTROL in cycle 1 only. Nausea, fatigue and anorexia were the most common observed adverse events and no statistical difference among three arms in all cycles. **Conclusions:** This study demonstrated that the efficacy of HHPG-19K (either 100 $\mu$g/kg or 6 mg-fixed dose) was superior to placebo treatment and was comparable to short-acting G-CSF as prophylactic use in patients with NSCLC receiving chemotherapy. HHPG-19K was well tolerated and no unexpected adverse events were observed. The 6 mg-fixed dose is more convenient for administration and is recommended in further clinical practice. Clinical trial information: NCT01560195.

**9615 General Poster Session (Board #265), Sun, 8:00 AM-11:45 AM**

**A phase II study evaluating efficacy of zoledronic acid in prevention of aromatase inhibitor (AI)-associated musculoskeletal symptoms: The ZAP trial.** *Presenting Author: Cesar Augusto Santa-Maria, The Johns Hopkins University School of Medicine and The Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD*

**Background:** Aromatase inhibitor-associated musculoskeletal symptoms (AIMSS) contribute to significant morbidity and therapy discontinuation. Retrospective data suggest that bisphosphonates may reduce the prevalence of AIMSS. **Methods:** We conducted a single-arm prospective clinical trial in postmenopausal women with stage 0-III breast cancer scheduled to initiate adjuvant AI, designated ZAP. Eligible women received intravenous zoledronic acid 4 mg (ZA) at baseline and 6 months, and started letrozole 2.5 mg daily 1-2 weeks afterwards. We compared the percentage of women who developed AIMSS over 12 months to historical controls not taking bisphosphonates from the Exemestane and Letrozole Pharmacogenetics (ELPh) trial (NCT00263913). AIMSS were defined as an increase of 0.22 from a scale of 0-3 in the Health Assessment Questionnaire Disability Index (HAQ-DI) and/or 2.0 cm in the Visual Analog Scale (VAS). AIMSS were assessed at 1, 3, 6, and 12 months and compared between studies with a logistic regression model adjusting for patient age, body mass index, race, prior chemotherapy, and prior tamoxifen use. We also evaluated the probability of AI discontinuation or change to another endocrine therapy by 1 year using a Kaplan Meier approach. **Results:** From 2011 to 2013, 59 women enrolled in ZAP. All (100%) and 52 (88%) women received baseline and 6 month ZA, respectively. 435 of 502 women from ELPh were eligible as historical controls. Both cohorts had similar characteristics, except more women in ELPh received prior tamoxifen. Twenty-two (37%) and 267 (61%) women on ZAP and ELPh, respectively, reported AIMSS during the first year ($p<0.001$). Five (8%) and 67 (15%) women on ZAP and ELPh discontinued AI or changed endocrine therapy ($p=0.24$). The cumulative probability of discontinuing AI or changing endocrine therapy was 9% for ZAP and 21% for ELPh (log rank $p=0.05$). **Conclusions:** Compared to historical controls, ZA prophylaxis in the adjuvant setting is associated with reduced AIMSS and decreased probability of AI discontinuation or change. A prospective randomized control trial is required to confirm these findings. Clinical trial information: NCT01194440.

**9616 General Poster Session (Board #266), Sun, 8:00 AM-11:45 AM**

**Effects of fosaprepitant (Fosa) administered as single dose versus two doses, on nausea/vomiting (N/V) in patients receiving multiday chemotherapy (CT) with a highly emetogenic regimen of doxorubicin and ifosfamide (AI): Randomized cross-over study.** *Presenting Author: Saroj Vadhan-Raj, Section of Cytokines and Supportive Oncology, Department of Sarcoma Medical Oncology. The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background**: AI is multi-day regimen of highly emetogenic chemotherapy, with high incidence of delayed N/V. Fosa, NK1 receptor antagonist (RA), administered IV as single dose (FDA-approved), with 5HT3RA and dexamethasone has improved the control of emesis. However, delayed N/V still remains problematic. Purpose of the study was to examine the effects of fosa administered IV on day 1 vs days 1 and 4 on N/V and the effect on ifosfamide (Ifex) and its active metabolites, due to potential drug interactions via CYP450. **Methods**: Sarcoma pts, planned to receive AI, were randomized 1:1 to Arm A (single- dose Fosa on day 1) or Arm B (2-doses, on days 1 and 4). Within each arm, patients were randomized to Group-1: Fosa in cycle-1 (C-1) and no Fosa in cycle-2 (C-2), and group-2: no Fosa in C-1 and Fosa in C-2. Blood samples were drawn for levels of Ifex/metabolites to be analyzed at the end of study. All pts could receive 2 doses of Fosa during cycles 3-6. Pts were monitored for N/V with daily symptom diary and FLIE (functional living index -- emesis) score (days 1, 5 and 10). **Results:** Of 47 pts, 40 eligible pts were randomized. There were 13 men and 27 women, with median age of 45 years (range, 19-65) and KPS of 90 (80-100). At present, 34 pts have completed 2 CT cycles. As shown below, Fosa administered as 2 doses resulted in significantly better control of delayed N/V as compared to single-dose or the control cycle. Furthermore, in cycle-3 the higher CR rate for N/V was maintained with 2 doses. Treatment with Fosa (one or two doses) was well tolerated with no enhanced neurological toxicity. **Conclusions**: The results of this study showed for the first time that Fosa administered as 2 doses is well tolerated and more effective in the control of delayed N/V than single dose or no Fosa with 5HT3RA + Dexa in pts receiving multi-day CT. Clinical trial information: NCT01490060.

**Complete response (CR*) in C-1 and C-2.**

| Study groups | No. of pts | Day 1 N (%) | Days 2-5 N (%) | Days 1-10 N (%) |
|---|---|---|---|---|
| **Single-dose** | 18 | 13 (72) | 2 (11) | 2 (11) |
| **Two-doses** | 16 | 10 (63) | 8 (50) | 6 (38) |
| **Control (no Fosa)** | 34 | 27 (79) | 6 (18) | 4 (12) |
| **P value **** | | 0.44 | 0.015 | 0.06 |

* CR: No emetic episodes and no rescue medications. ** Chi-square test.

**9617 General Poster Session (Board #267), Sun, 8:00 AM-11:45 AM**

**Noninvasive liver fibrosis index changes during chemotherapy: Marker for oxaliplatin-induced hepatic sinusoidal obstruction syndrome.** *Presenting Author: Sehhoon Park, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea*

**Background:** Even though oxaliplatin (OXA) could induce hepatic sinusoidal obstruction syndrome (SOS), OXA-based regimes are still standard treatment for patients with colorectal (CRC) and advanced gastric cancer (AGC). The aim of the study was to evaluate the utility of non-invasive liver fibrosis index (NIFI) for monitoring OXA-induced hepatic SOS. **Methods:** From February 2004 to December 2013 patients with CRC or AGC who received OXA-based chemotherapy (CTx) were identified in the institutional electronic patient database. Liver fibrosis were evaluated before and after the OXA exposure with splenic volume index (SVI) and 4 different NIFIs: age-platelet index (API), AST to platelet ratio index (APRI), platelet to spleen ratio (PSR), Fibrosis-4 score (FIB-4). Adjusted odd ratio (aOR) with 95% confidence intervals (CI) were analyzed to evaluate risk after matching age, body mass index, cancer type, stage, previous chemotherapy cycle. **Results:** A total of 288 patients (pts) were eligible for evaluation: 211 pts were male and median age was 65; 206pts had CRC; 82pts had AGC; median OXA cumulative dose was 798.80mg/m$^2$and median duration of OXA based chemotherapy was 4.87 months. Increase in SVI were directly correlated with the cumulative OXA dose (p=0.005). Using a cutoff of SVI $\geq$ 0.3, 120 pts (41.67%) were positive for hepatic SOS. All of the 4 NIFIs were significantly correlated with SVI. aOR for each NIFI were show in the Table. **Conclusions:** Changes of NIFIs showed good correlation with SVI changes during OXA-based chemotherapy. NIFIs could be useful for non-invasive monitoring of OXA induced hepatic SOS.

| | N=288 (mean ± standard deviation) | SVI ≥ 0.3 N=120, (41.67%) | SVI<0.3 N=168, (58.33%) |
|---|---|---|---|
| **NIFIs changes before and after OXA-based chemotherapy** | | | |
| **API** | 2.40 ± 1.90 | 2.73 ± 1.91 | 2.17 ± 1.86 |
| **APRI** | 0.41 ± 1.59 | 0.64 ± 2.34 | 0.25 ± 0.60 |
| **PSR** | 1.10 ± 1.97 | 0.36 ± 1.72 | 1.63 ± 1.98 |
| **FIB-4** | 1.76 ± 3.24 | 2.41 ± 4.45 | 1.29 ± 1.84 |
| | **aOR** | **95% CI** | **P value** |
| **Adjusted OR for NIFIs** | | | |
| **API** | 1.16 | 1.01-1.32 | 0.032 |
| **APRI** | 1.98 | 1.12-3.50 | 0.018 |
| **PSR** | 0.67 | 0.58-0.79 | <0.001 |
| **FIB-4** | 1.28 | 1.11-1.49 | 0.001 |

**9618 General Poster Session (Board #268), Sun, 8:00 AM-11:45 AM**

**Enobosarm and lean body mass in patients with non-small cell lung cancer.** *Presenting Author: Jeffrey Crawford, George Barth Geller Professor for Research in Cancer, Duke University Division of Medical Oncology, Durham, NC*

**Background:** Cancer induced muscle wasting is a selective and progressive cancer related symptom that begins early in the course of malignancy. Greater than 50% of NSCLC patients have muscle wasting at diagnosis, increasing to >80% prior to death. Historically, interventions targeting muscle wasting and cachexia focused on weight, ignoring the importance of lean body mass (LBM).Enobosarm is a first-in-class, non-steroidal, oral, selective androgen receptor modulator (SARM). We report results for 2 Phase 3 clinical trials of enobosarm, POWER 1 (P1) and POWER 2 (P2), for the prevention and treatment of muscle wasting in patients with advanced NSCLC. **Methods:** Patients (pts) with Stage III or IV NSCLC were randomized at initiation of first-line chemotherapy based upon the planned chemotherapy regimen; platinum + taxane (P1, n=321) or platinum + non-taxane (P2, n=320). Pts (males and postmenopausal females ≥30y with ECOG ≤1) received either enobosarm 3mg or placebo (pbo) for 5 months. LBM was measured by Dexa and body weight (BW) by scale weight, w/hospital gown & w/o shoes, at baseline day (d)84 and 147. **Results:** In P1 and P2, decreases in BW were observed from baseline in both enobosarm and pbo groups. In P1, enobosarm treated pts had a lower rate of decline in BW as compared to pbo through d84 (p=0.053) and 147 (p=0.038). Despite declining BW, increases in LBM were still observed in enobosarm pts (+0.41 kg) compared to pbo (-0.92 kg) by continuous variable analysis at d84 (p=0.0002) and 147 (p<0.0001). In P2, there was no difference in loss of BW between groups; however, enobosarm pts demonstrated significant increases in LBM (+0.47 kg) compared to pbo (-0.37 kg) at d84 (p=0.0111) and 147 (p=0.0028). Additionally, a larger proportion of pts receiving enobosarm maintained or increased LBM at d84 and 147 in both trials (P1: p=0.036 and 0.026; P2: p=0.113 and 0.013; by responder analysis) as compared to pbo. The incidence of adverse events was similar between enobosarm and pbo in both trials. **Conclusions:** Overall, enobosarm was safe and well tolerated. Enobosarm had a clinically significant effect on muscle, despite decreases in BW, which may translate into improvement in physical function. Impact on survival will be evaluated. Clinical trial information: NCT01355497, NCT01355484.

**9619 General Poster Session (Board #269), Sun, 8:00 AM-11:45 AM**

**Effect of body mass index and menopausal disorders during menopause on vasomotor symptoms of postmenopausal Japanese breast cancer patients treated with anastrozole: A prospective multicenter cohort study of patient-reported outcomes.** *Presenting Author: Kaori Tane, Hyogo Cancer Center, Akashi, Japan*

**Background:** Although vasomotor symptoms induced by aromatase inhibitors are frequently recognized, risk factors are ill-defined. To identify risk factors for vasomotor symptoms of Japanese breast cancer patients treated with adjuvant anastrozole, we conducted a prospective cohort study based on patient-reported outcomes (PROs). Patients and **Methods:** For this prospective cohort study (SAVS-JP, UMIN000002455), 391 postmenopausal Japanese estrogen receptor-positive breast cancer patients who were treated with adjuvant anastrozole were recruited from 28 centers. The PRO assessment was obtained from a self-reported questionnaire at baseline, 3, 6, 9 and 12 months between August 2009 and April 2012. Vasomotor symptoms, comprising hot flashes, night sweats, and cold sweats, were categorized into four grades (none, Grade 1: mild, Grade 2: moderate, Grade 3: severe). Pre-existing symptoms were only included if they worsened post-baseline. **Results:** Hot flashes, night sweats, and cold sweats at baseline were reported by 80 (20.5%), 59 (15.1%), and 32 (8.2%) patients respectively. New or worsening symptoms were experienced by 139 (38.4%), 106 (29.3%), and 104 (28.7%) patients. About 80% of newly occurring symptoms were grade 1, and less than 5% were grade 3. Overall vasomotor symptoms were reported by 201 (55.5%) out of 362 patients. Patients with vasomotor symptoms were significantly younger, had higher body mass index (BMI), shorter time period aftermenopause, and more menopausal disorders during menopause. Multivariate analysis showed that BMI (odds ratio: 1.09, 95% confidence interval: 1.02-1.16, P=0.009) and experience of menopausal disorders (2.11, 1.35-3.30, P=0.001) were significantly associated with vasomotor symptoms. **Conclusions:** We found that high BMI and experience of menopausal disorders at menopause were significantly associated with occurrence of vasomotor symptoms. These data are expected to prove useful for management of postmenopausal Japanese women treated with aromatase inhibitors. Clinical trial information: UMIN000002455.

**9620 General Poster Session (Board #270), Sun, 8:00 AM-11:45 AM**

**Prediction of major complications in patients with solid tumors and apparently stable febrile neutropenia: Validation of the CISNE risk score.** *Presenting Author: Javier Espinosa, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain*

**Background:** In order to improve the risk stratification of patients with febrile neutropenia (FN), we previously developed a prognostic score predicting major complications in patients with solid tumors and apparently stable episodes (Br J Cancer. 2011;105[5]:612-7). **Methods:** On the basis of our previous multivariate analysis, 6 predictors were associated to serious complications [ECOG PS≥2 (2points), chronic obstructive pulmonary disease (1point), cardiovascular disease (1point), mucositis NCI grade≥2 (1point), monocytes <200 (1point) and stress-induced hyperglycemia (2points)]. We have integrated these factors into a score ranging from 0 to 8, which allows the classification of patients into 3 prognostic classes: low (0points), medium (1-2points) and high risk (≥ 3points). We present here a validation of this score (CISNE) and a comparison with MASCC and Talcott models. **Results:** From Oct/12 to Dec/13, we prospectively recruited 780 patients with apparently stable FN from 21 hospitals. The rate of infection-related complications and death was 15.6% (95%CI, 12.9%-18.6%) and 1.7% (95%CI, 0.9%-3%), respectively. CISNE classified 26%, 41% and 33% of the patients as low, medium and high risk, respectively. The rate of complications and death within each of these groups was 1.5%, 7.5% and 37.1% (p<0.001), and 0, 0.9% and 4.3%, respectively (p<0.001). The Table summarizes the comparison of the 3 scales to predict serious complications. The AUCs were 0.84 (95%CI, 0.81-0.86) for CISNE; 0.72 (95%CI, 0.68-0.75) for MASCC and 0.57 (95%CI, 0.54-0.61) for Talcott. **Conclusions:** CISNE is a valid score that classifies apparently stable FN episodes more accurately than MASCC and Talcott.

| Parameter | CISNE (<3 vs ≥3) | MASCC (<21 vs ≥21) | Talcott (I-III vs IV) |
|---|---|---|---|
| **Sensitivity % (CI-95%)** | 77.8% (69.4- 84.8) | 35.2% (26.8 - 44.4) | 27.8% (20.1-36.7) |
| **Specificity % (CI-95%)** | 75.5% (72-78.7) | 87.6% (84.9-90.1) | 87.5% (84.7-89.6) |
| **PPV % (CI-95%)** | 37.1% (31.1-43.3) | 34.6% (26.3-43.7) | 29.1% (21.2 -38.48) |
| **NPV % (CI-95%)** | 94.8% (92.5-96.5) | 87.9% (85.2-90.3) | 86.7% (83.9-89.2) |
| **pLR (CI-95%)** | 3.18 (2.7-3.75) | 2.86 (2.09-3.92) | 2.24 (1.58-3.17) |
| **nLR (CI-95%)** | 0.29 (0.21-0.41) | 0.74 (0.65-0.84) | 0.82 (0.74-0.92) |

**9621 General Poster Session (Board #271), Sun, 8:00 AM-11:45 AM**

**The impact of docetaxel-related toxicities on health-related quality of life in patients with metastatic cancer (The QoLiTax-Trial of the Arbeitsgemeinschaft Internistische Onkologie, AIO).** *Presenting Author: Claudia Pauligk, Krankenhaus Nordwest, University Cancer Center, Frankfurt, Germany*

**Background:** Docetaxel is a widely used cytotoxic agent. It causes a number of side effects, most frequently leukopenia and neutropenia, alopecia, nausea, diarrhea, and fatigue. This study evaluates the impact of docetaxel toxicities on patient's health-related Quality of life (QoL). **Methods:** We conducted a multicenter, prospective, non-interventional trial, in which the QoL was assessed using the EORTC QLQ-C30 questionnaire at baseline and every 4 weeks up to 40 weeks in patients receiving a docetaxel-based chemotherapy for metastatic disease. The primary endpoint was the 4-months ≥5% deterioration rate of the global health status/QoL scale in patients with vs. those without grade 3/4 leukopenia or neutropenia. Secondary endpoints were the effect of other treatment-related adverse events on QoL. Uni- and multivariate analyses were applied. **Results:** From January 2008 to June 2011 a total of 2,659 patients were included. The majority of patients (48.1%) had prostate cancer, followed by breast (17.1%) and non-small-cell-lung cancer (15.8%). Patients received a median of 5 docetaxel cycles with median dose of 75 mg/m$^2$. The 4 months ≥5% deterioration rate of the global health status/QoL was similar between patients with and without grade 3 or 4 leukopenia/neutropenia (adjusted odds ratio 1.024, p=.4). Among other treatment-related toxicities, the presence of grade 3/4 diarrhea showed the strongest effect on global health status/QoL average scores (50.91 vs. 33.06), followed by vomiting (50.91 vs. 35.17), dyspnea (50.94 vs. 35.81), stomatitis (50.88 vs. 36.41), nausea (50.91 vs. 36.68), infection (50.90 vs. 37.14), fatigue (50.90 vs. 43.82) and anemia (50.91 vs. 41.03), p<0.05 for all comparisons. Grade 3/4 leukopenia/neutropenia, alopecia, constipation, neuro- and nail toxicity had no significant impact on the global health status/QoL or other items. **Conclusions:** Docetaxel associated non-hematological toxicity, but not isolated leukopenia strongly impact patient's QoL. This has to be considered by clinicians while making therapeutic decisions.

**9622 General Poster Session (Board #272), Sun, 8:00 AM-11:45 AM**

**Scrambler therapy for treatment of chemotherapy-induced peripheral neuropathy.** *Presenting Author: Breanna L Weisbrod, Mayo Clinic, Rochester, MN*

**Background:** More effective treatment is needed for chemotherapy-induced peripheral neuropathy (CIPN). Preliminary data support the use of Scrambler therapy, a device which treats pain via non-invasive cutaneous electrostimulation, for the treatment of CIPN (Smith TJ et al. J Pain Symptom Manage 2010). The current abstract reports data from a pilot trial, performed to investigate the effect of Scrambler therapy for the treatment of established CIPN. **Methods:** Eligible patients: age ≥ 18 years, ECOG PS ≤2, life expectancy ≥3 months, CIPN symptoms of ≥1 month duration with tingling and/or pain ≥4/10 during the prior week. Patients were treated with Scrambler therapy to the affected area(s) for up to 10 daily 30 minute sessions. Symptoms were monitored using a neuropathy questionnaire consisting of numerical analogue scales ranging from 0-10, daily before therapy as well as weekly for 10 weeks after therapy. Descriptive summary statistics formed the basis of data analysis. During the daily therapy, last values carried forward were used. **Results:** We report on 37 patients enrolled between 7/18/2011 and 5/6/2013, 12 men and 25 women; the mean age was 58. While the study technically remains open to obtain more experience with this procedure, the first 37 accrued CIPN patients are the basis of our final CIPN-related manuscript from this project (in development). Patients had a history of exposure to various neurotoxic chemotherapeutic agents and the majority (78%) had symptoms ≥1 year. 25 patients were treated primarily on their lower extremities while 12 were treated primarily on their upper extremities. The table portrays data (average symptoms during the previous 24 hours) at baseline, on the last of the 10 planned days of therapy, and at the end of 10 weeks of follow up, regarding patient reported pain, tingling, and numbness. There were no substantial adverse events. **Conclusions:** Scrambler therapy appears to be effective for the treatment of CIPN: a prospective placebo-controlled clinical trial should be performed. Clinical trial information: NCT01347723.

| | Mean baseline score | Mean final Rx score (day 10) | Average percent drop in score (day 10) | Mean final Rx score (week 10) | Average percent drop in score (week 10) |
|---|---|---|---|---|---|
| **Pain** | 5.8 | 2.6 | 53% | 3.1 | 47% |
| **Tingling** | 6.0 | 3.3 | 44% | 2.9 | 26% |
| **Numbness** | 6.3 | 4.0 | 37% | 2.9 | 46% |

**9623 General Poster Session (Board #273), Sun, 8:00 AM-11:45 AM**

**Bone health in prostate patients: An opportunity for screening and intervention.** *Presenting Author: George A. Dawson, VA New Jersey Healthcare System, East Orange, NJ*

**Background:** Despite known risk factors, men are not routinely screened for bone health. Men with prostate cancer are at an increased risk of bone disease because of treatment with androgen deprivation therapy (ADT). Risk factors include family history, calcium and vitamin D deficiency, certain medications, being thin or small-boned, tobacco use, alcohol abuse. and lack of physical activity. We started a screening and management program to mitigate the effects of ADT on bone health in veterans beginning treatment for prostate cancer. This study evaluates the pre-existing risk factors in pts who had baseline dexa scans before ADT. **Methods:** We completed a retrospective chart review of 182 veterans diagnosed with prostate cancer and referred to Radiation Oncology for radical treatment from 2009 to 2013. This reports on the 160 pts who had baseline dexa scans. Clinical variables analyzed were demographics, tobacco and alcohol use, vitamin D levels, incidence of AODM (adult onset diabetes mellitus), and calcium or vitamin D use. Descriptive statistics as well as bivariate analysis including Chi Square tests and odds ratios were calculated. **Results:** The mean age of the study participants was 66.6 yrs (47-82.8 yrs); 52% were African American, 45% White, 3% Hispanic. Baseline dexa scans were abnormal in 63% of pts, showing osteoporosis and /or osteopenia. Vitamin D levels were abnormal in 61%. Abnormal vitamin D levels were found in 26% of pts with normal DEXA scans. Almost 99% pts received calcium and Vitamin D supplements. Twenty percent had a history of alcohol abuse, 56% used tobacco, and 33% had AODM. Ethnicity may be a factor ( p<0.05) but the sample sizes per group were not equivalent. Smokers with an abnormal Vitamin D level were at increased risk of bone disease as comparedto non smokers (p<0.01) . **Conclusions:** Pre-ADT screening confirms the risk of underlying bone disease in this previously unscreened veteran population. Guidelines for treatment and prevention of bone disease should be implemented in all patients over age of 50. An opportunity exists to identify and treat men at risk when seen for prostate cancer treatment whether they receive ADT or not.

**9624 General Poster Session (Board #274), Sun, 8:00 AM-11:45 AM**

**Clinical risk prediction in anthracycline cardiotoxicity.** *Presenting Author: Bonnie Ky, University of Pennsylvania, Philadelphia, PA*

**Background:** Anthracyclines are highly effective as anticancer therapies and have led to important survival gains. There are, however, significant concerns over cardiotoxicity. The overall objective of this study was to define the incidence and clinical predictors of anthracycline-induced cardiotoxicity in a prospective, community-based cohort. **Methods:** The PREDICT study included 586 patients undergoing an anthracycline-based chemotherapy across 24 community oncology programs. Participants underwent detailed cardiovascular (CV) evaluation including B-type natriuretic peptide (BNP) biomarker assessment and serial echocardiograms at baseline and multiple standardized intervals over a maximum followup of 12 months. A cardiac event was defined as asymptomatic left ventricular dysfunction (LVD), symptomatic heart failure (HF), symptomatic arrhythmia, acute coronary syndrome, or cardiac death. Multivariable logistic regression analyses, and specifically a backwards stepwise elimination procedure, were used to determine the relationships between baseline clinical risk factors and subsequent cardiac events. **Results:** The median age was 53 years (range 18-86), and 77% were non-Hispanic white and 81% female. At baseline, there was a high prevalence of CV risk factors including hypertension (21%), diabetes (13%), hyperlipidemia (25%), and tobacco use (39%). During follow-up, 11% of the participants experienced at least 1 cardiac event, primarily being LVD or HF. In multivariable analyses, the strongest predictors of subsequent cardiotoxicity were: number of CV risk factors at baseline (Odds Ratio [OR] 1.3, 95% CI 1.1-1.5, p=0.01); cancer type (OR 1.7, 95% CI 0.9-3.1, p = 0.10 for lymphoma compared to breast; OR 2.8, 95% CI 1.2-6.3, p=0.02 for other compared to breast); and a baseline BNP>100 pg/ml (OR 2.6, 95% CI 0.99-6.8, p=0.05). **Conclusions:** In a large, prospective community-based cohort, the number of CV risk factors, cancer type, and a baseline BNP>100 pg/ml were associated with cardiotoxicity. The significance of these predictors according to anthracycline dose and the potential differences according to sex remain to be further elucidated.

**9625 General Poster Session (Board #275), Sun, 8:00 AM-11:45 AM**

**Outcomes of early palliative care referrals for patients with advanced lung cancer.** *Presenting Author: Sriram Yennurajalingam, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background**: Despite previous studies showing benefits of early referral to palliative care in improving quality cancer care, late referral and underutilization are major concerns. The aim of this study was to determine the impact of early palliative medicine specialist referral (EPC) on quality cancer care outcomes in advanced lung cancer pts at a comprehensive cancer center. **Methods**: In this prospective non-randomized controlled study, pts with advanced non-small cell lung cancer with oncologist estimated survival of ≤ 6 months were referred to EPC, N=51. A control group of similar characteristics were recruited from pts with regular follow-up at the thoracic oncology clinic [standard oncology care,UC], N=52. Descriptive statistics and Wilcoxon rank sum tests were used to describe change in FACT-lung, Edmonton Symptom Assessment Scale(ESAS)-symptom distress scores and Hospital Anxiety and Depression Scale(HADS) at follow-up visit. **Results**: The median age was 61yrs; 52% were female. There was no difference in age, gender, race (p>0.1) at baseline between the two groups, but the EPC pts had a higher symptom burden (EPC 30.5 vs. UC 11.0 p=.001). At follow-up EPC pts had significant improvement in symptoms scores. EPC pts also were more likely to have improved QOL and EOL discussions (Table). **Conclusions**: EPC was associated with improved symptom distress scores and improved health utilization outcomes, although baseline symptom distress scores were worse in EPC at time of referral.

**Change in the symptom scores at follow-up and quality-care outcomes in UC and EPC.**

| | UC | | EPC | | |
|---|---|---|---|---|---|
| | Median change | IQR | Median change | IQR | p |
| **ESAS symptom distress** | 5.0 | (-2.0,16) | -2.5 | (-9.7, 6.7) | .02 |
| **HADS depression** | 1.0 | (0,5.0) | -1.0 | (-2.0, 3.0) | .04 |
| **FACIT lung cancer subscale** | -3.0 | (-5.0,1.0) | 3.0 | (-2.0,5.0) | .002 |
| **FACT_L TOI** | -9.0 | (-16.0,-1.3) | -5.0 | (-6.75,10.7) | .006 |
| **HADS depression (caregiver)** | .5 | (-1.0, 2.2) | -1.0 | (-4.0,1.0) | .025 |
| **Quality Metrics** | | | | | |
| **ICU sdmissions** | 4/51 | | 3/52 | | .68 |
| **Median ICU LOS** | 11 | | 5.0 | | .21 |
| **ICU deaths** | 1/51 | | 0/52 | | .38 |
| **Any chemotherapy within 14 days of death** | 3/51 (6%) | | 1/51 (1%) | | .3 |
| **Hospice referrals** | 5/51 (10%) | | 14/52 (27%) | | .02 |
| **Completion of advance directives** | 2/51 (4%) | | 9/52 (17%) | | .03 |
| **Discussion of advance care planning** | 2/51(4%) | | 34/51 (67%) | | .001 |

**9626 General Poster Session (Board #276), Sun, 8:00 AM-11:45 AM**

**Mortality from malignant bowel obstruction in hospitalized U.S. cancer patients.** *Presenting Author: Olatunji Boladale Alese, The Winship Cancer Institute of Emory University, Atlanta, GA*

**Background:** Malignant bowel obstruction (MBO) affects an estimated 3 - 15% of cancer patients globally, with a mean survival rate no longer than 4 weeks in inoperable MBO. We assessed predictors of survival and the influence of treatment modality in hospitalized MBO patients in the US. **Methods:** Data were obtained from all US states that contributed to the Nationwide Inpatient Sample (NIS) by Agency for Health Care Research and Quality in 2006 and 2010. MBO diagnoses and treatment variables were identified using Clinical Classification Software code based on ICD9 and CPT codes. Univariate and multivariate analyses were performed with a logistic model, weighted chi-square test, and a generalized linear model with the use of generalized estimated equation. Initial analysis in the 2006 NIS data was validated in the 2010 NIS data. **Results:** 942,014 and 1,103,528 eligible MBO patients were identified in 2006 and 2010 respectively. The in-hospital mortality was 24.5% in 2006, decreasing to 21.4% by 2010. The commonest concurrent condition was chronic lung disease (20.4%). Medical management (vs. surgical management), health insurance coverage, and obesity were significantly associated with better hospital survival in MBO patients. Adjusted analysis showed significantly increased odds of death with male gender, older age, stage IV disease, multiple co-morbid conditions (except obesity and AIDS) and weight loss. **Conclusions:** Lack of insurance coverage, weight loss and surgical management are associated with higher mortality in hospitalized MBO patients.

**Multivariable analysis of in-hospital mortality in 2010 (with covariates found significant in 2006).**

| | | Died during hospitalization | | |
|---|---|---|---|---|
| **Covariate** | **Level** | **Relative risk** | **95%CI** | **P-value** |
| **Management** | Medical | 0.78 | 0.72 - 0.86 | <.001 |
| | Surgical | 1 (Ref) | - | - |
| **Insurance status** | Insured | 0.63 | 0.48 – 0.82 | <.001 |
| | Noninsured | 1 (Ref) | - | - |
| **Metastasis** | Present | 1.65 | 1.52 – 1.78 | <.001 |
| | Absent | 1 (Ref) | - | - |
| **Weight loss** | Present | 1.49 | 1.36 – 1.63 | <.001 |
| | Absent | 1 (Ref) | - | - |
| **Obesity** | Present | 0.46 | 0.39 – 0.55 | <.001 |
| | Absent | 1 (Ref) | - | - |

**9627 General Poster Session (Board #277), Sun, 8:00 AM-11:45 AM**

**Predicting the risk of gastrointestinal (GI) toxicity in early colon cancer (CC) patients treated with adjuvant chemotherapy: Developing a GI toxicity scoring system.** *Presenting Author: Gillian Gresham, British Columbia Cancer Agency, Vancouver, BC, Canada*

**Background:** Baseline demographics and clinical factors may contribute to a patient's overall risk for developing chemotherapy-related GI toxicity, such as nausea, vomiting, and diarrhea. We aimed to develop a simple GI toxicity scoring system to better stratify early CC patients who may be at higher risk of developing GI toxicity from adjuvant FOLFOX chemotherapy. **Methods:** Patients diagnosed with early CC from 2005 to 2008 and treated with FOLFOX at any 1 of 5 regional cancer centers in British Columbia were reviewed. GI toxicities of interest included: (1) nausea/vomiting, (2) diarrhea, and (3) any GI side effects. Baseline variables that were analyzed consisted of age, sex, ECOG, time to adjuvant chemotherapy (TTAC) and laboratory parameters. Stepwise regression was used to develop a multivariate model for each toxicity and a weighted risk scoring system was subsequently devised based on the magnitude of the parameter estimates in the multivariate model. **Results:** In total, 475 pts were included: median age was 62 years (range 26-89), 16% were aged >70 years, and 55% were men. The majority (90%) was ECOG 0/1. Independent predictors for nausea/vomiting included age >70 years (OR 2.46, 95%CI 1.3-4.8, p=0.01), GFR <50 (OR 1.68, 95% CI 1.1-2.7, p=0.02), and TTAC >8 weeks (OR 1.33, 95% CI 0.9-2.1, p=0.14) whereas independent predictors for diarrhea included age >70 years (OR 1.44, 95% CI 0.79-2.62, p=0.12) and GFR <50 (OR 1.67, 95% CI 1.1-2.6, p=0.02). The multivariate model for the risk of any GI toxicity included age >70 years (OR: 2.61, 95% CI 1.1-6.1, p=0.04), GFR <50 (OR 1.69, 95% CI 1.1-2.6, p=0.004), and TTAC >8 weeks (OR 1.79, 95% CI 1.2-2.7, p=0.006). Points were assigned: 2 points for long TTAC and poor GFR and 1 point for advanced age. The study cohort was classified into their risk groups based on their score (Table). **Conclusions:** We developed a simple 5-point scoring system to stratify early CC pts receiving adjuvant FOLFOX into low and high risk groups for GI toxicity based on baseline clinical factors. Validation of this scoring system is currently underway.

| **Risk group** | **Risk (%) of any GI toxicity** | **P value** |
|---|---|---|
| **Low risk (0-2 points)** | 44.7 | 0.0075 |
| **High risk (3-5 points)** | 59.4 | |

**9628 General Poster Session (Board #278), Sun, 8:00 AM-11:45 AM**

**Randomized phase II pilot study of loratadine for the prevention of bone pain caused by pegfilgrastim.** *Presenting Author: Julia Moukharskaya, College of Medicine, Fletcher Allen Health Care, University of Vermont, Burlington, VT*

**Background:** Bone pain is a common side-effect of pegfilgrastim and can interfere with a patient's quality of life and treatment adherence. Antihistamine therapy may have analgesic activity in such patients. This study was designed to investigate the impact of antihistamine loratadine prophylaxis on pegfilgrastim-induced bone pain (PIP). **Methods:** This is a two stage trial design with the first stage identifying eligible patients who developed significant clinical PIP after receiving an initial dose of pegfilgrastim (6 mg SC) in the chemotherapy setting, and the second stage representing a randomized trial of a 7-day course of loratadine 10 mg daily or placebo starting on day 1 of pegfilgrastim administration. Significant PIP, assessed by Worst Pain Scale (0-10) of the Brief Pain Inventory, was defined as worst pain score >5 and a 2 point increase during the 7 days after pegfilgrastim. The primary end-point of the study was reduction of significant PIP with loratadine, defined as 2 point decrease in worst PIP between treatment and observation stages. Rescue use of other analgesics was allowed. Target sample size was based on the following assumptions: 30% incidence of significant pain, 10% benefit with placebo, 50 % benefit with loratadine, 89% power (chi-square test, 2-sided alpha=0.05) , and stratification by taxane use. **Results:** A total of 227 patients were enrolled in the observation stage, of whom 213 were included in the final analysis. Incidence of significant PIP was 30.5%. 45 patients with breast, lung and GI malignancy entered the randomization stage, male/female 11 /34, median age 56 (range 31-89). Gender, age, malignancy type, taxane use, and additional use of rescue NSAIDS and non-NSAIDS were all comparably distributed in loratadine vs. placebo groups (p=0.58). The rate of improvement in the significant PIP was 59.1% for loratadine arm and 54.5% for placebo arm (p=1.0). Results were unchanged after adjustment for rescue analgesic use or taxane therapy. **Conclusions:** Administration of prophylactic loratadine does not decrease the incidence of significant PIP. Clinical trial information: NCT01311336.

**9629 General Poster Session (Board #279), Sun, 8:00 AM-11:45 AM**

**The effects of oncologists' physical activity recommendations and information packages on level of physical activity and the quality of life in cancer survivors.** *Presenting Author: Ji-Hye Park, Yonsei University, Seoul, South Korea*

**Background:** Physical activity participation has been associated with reduced cancer-specific and all-cause mortality in breast and colorectal cancer survivors. The purpose of this study was to examine the effects of oncologists' recommendations of physical activity with and without information packages on physical activity on the amount of physical activity and quality of life in cancer survivors. **Methods:** A total of 161 stage I~III breast and colorectal cancer survivors, who were 52.08±8.21 years old were recruited for this study. They were assigned to one of three groups: 1) control group, 2) oncologists' recommendations for physical activity group, and 3) oncologists' recommendations for physical activity combined with information packages group. At baseline and after 4 weeks, the level of physical activity was measured using the Godin Leisure-Time Exercise Questionnaire. Quality of life, including self-reported physical function, was measured with the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30. **Results:** Out of 161 participants, 130 participants completed the trial (78.8%). Our study found that participants who received oncologists' physical activity recommendations with information packages significantly increased their levels of physical activity compared with the control group (pre: 9.91±7.75 vs. post: 14.21±11.89 Metabolic Equivalent of Task (MET) hours per week, p<0.01).Participants who only received oncologists' physical activity recommendations did not increase their physical activity levels. Furthermore, the pain levels of participants who received physical activity recommendations with information packages were significantly reduced after 4 weeks compared with those of the control group. **Conclusions:** It is important to provide physical activity information packages in addition to oncologists' recommendations in order to increase levels of physical activity among breast and colorectal cancer survivors. This research was supported by Basic Science Research Program through the National Research Foundation of Korea(NRF) funded by the Ministry of Education(2013R1A1A2005986).

**9630 General Poster Session (Board #280), Sun, 8:00 AM-11:45 AM**

**Effects of a 12-week home-based exercise program on quality of life, psychological health, and the level of physical activity in colorectal cancer survivors.** *Presenting Author: Ji Young Kim, Yonsei University, Seoul, South Korea*

**Background:** Although the importance of physical activity (PA) and exercise has been recognized, there are few randomized controlled trials which investigated the effects of exercise on psychological health of colorectal cancer survivors. Therefore, the purpose of this study is to examine the effects of home-based exercise program on quality of life (QOL), psychological health, and the level of PA in colorectal cancer survivors. **Methods:** One hundred twenty three colorectal cancer survivors were randomized into either home-based exercise (Intervention) group or control group. The home-based exercise program included unsupervised walking, stationary bike, or swimming for aerobic exercise and providence of resistance exercise DVD, pedometer, and exercise logs. QOL was measured by the Functional Assessment of Cancer Therapy - Colorectal (FACT-C) scale. The 7 Day physical activity recall (PAR) was used to assess the level of physical activity. In addition, the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue scale and Patient Health Questionnaire (PHQ) were administered. All assessments were conducted at baseline and 12 week. **Results:** Ninety nine participants completed the trial (80.5%). Both QOL and fatigue improved in the intervention group (QOL *p*-value =.020; fatigue *p*-value =.022), while they did not change in the control group (QOL *p*-value =.395; fatigue *p*-value =.265). The change in QOL and fatigue between intervention and control group was not statistically. The level of PA was significantly increased at 12-week in the intervention group, and the change was significantly different from the control group (*p*-value=.004). **Conclusions:** The 12-week home-based exercise program improves the QOL and psychological health in colorectal cancer survivors. In addition, we have demonstrated that home-based exercise program was effective to increase level of physical activity in stage II–III colorectal cancer survivors. This study was supported by the National Research Foundation of Korea (2013K2A1A2054437) and the National R&D Program for Cancer Control, Ministry of Health and Welfare, Republic of Korea (1120230).

**9631 General Poster Session (Board #281), Sun, 8:00 AM-11:45 AM**

**PROCAPP: A randomized, open-label phase III trial comparing mapisal and urea hand-foot cream as prophylaxis for capecitabine-induced hand-foot skin reaction (HFSR) in patients (pts) with gastrointestinal (GI) tumors or breast cancer—A study of the AIO Quality of Life Working Group.** *Presenting Author: Deniz Gencer, University Hospital Mannheim, Mannheim, Germany*

**Background:** HFSR is a frequently occurring dermatologic reaction associated with capecitabine (CAPE). Thus far, no effective prophylaxis has been established, but urea-containing skin ointments are frequently used. Mapisal (medac, Wedel, Germany) is a topically applied ointment with high radical protection factor currently investigated as a prevention strategy against HFSR. It has shown preliminary activity as prophylaxis against HFSR in patients treated with pegylated liposomal doxorubicin. **Methods:** This randomized phase-III study compared treatment with Mapisal and an urea (10%) containing cream as prophylaxis for HFSR in pts with GI tumors or breast cancer treated with CAPE. The primary endpoint was prevention of HFSR of any grade within 6 weeks based on a standardized patient diary. Pts were randomized in a 1:1 ratio and stratified according to sex and CAPE dose. The study had 80% power to show an absolute 20% reduction of the incidence of overall grade HFSR with Mapisal (30% -> 10%) with a type I error of 5%. Herein, we report on the first preliminary data. Secondary endpoints were time to develope HFSR >grade 1, CAPE dose intensity, and QoI analyses (EORTC QIQ C30 & DLQI). **Results:** Between 05/12 and 09/13, 160 pts were enrolled. 152 pts are evaluable for the current analysis. Median age was 65 years, 96 pts were female (60.0%). 63 pts had breast cancer (41.4%), 89 pts had GI tumors. In total, 47 / 152 pts experienced HFSR (30.9%). 30 out of 77 pts (39.0%) receiving Mapisal experienced HFSR (grades 1/2/3 [%]: 66.7 / 26.7 / 6.7 of total events). In the urea arm, 17 out of 75 pts (22.7%) reported HFSR (grades 1/2/3 [%]: 52.9 / 41.2 / 5.9). Using Mantel-Haenszel chi-squared test the stratified common odds ratio was 2.365 (95%-CI 1.154 – 4.848; p=0.027). **Conclusions:** Mapisal failed to show superiority over an urea-containing cream as prophylaxis for CAPE-associated HFSR. The final analysis will be presented at the meeting. Studies on the use of Mapisal as prophylaxis of HFSR in patients receiving pegylated liposomal doxorubicin are ongoing. Clinical trial information: NCT01626781.

**9632 General Poster Session (Board #282), Sun, 8:00 AM-11:45 AM**

**Pegfilgrastim (P) administration after 24, 72, or 96 hours (h) to allow dose-dense (DD) anthracycline- and taxane-based chemotherapy (CT) in breast cancer (BC) patients (pts): A single-center experience within the GIM2 randomized phase III study.** *Presenting Author: Matteo Lambertini, Department of Medical Oncology, U.O. Oncologia Medica 2, IRCCS AOU San Martino-IST, Genova, Italy*

**Background:** The GIM2 study (ClinicalTrials.gov number, NCT00433420) compared two different schedules of CT (DD versus standard duration) as adjuvant treatment of 2,091 node positive BC pts. DD arms were supported by P scheduled 24 h after CT. P can induce early leukocytosis after its administration with the potential risk of capillary leak syndrome and spleen rupture. To evaluate the best timing of P administration, 3 different cohorts of pts enrolled in the GIM2 study and treated at the coordinating center received P 24 or 72 or 96 h after CT. **Methods:** 5 pts were planned to be enrolled in each cohort; pts in cohort A received P after 24 h, pts in cohort B after 72 h and pts in cohort C after 96 h. After the preliminary results, cohort A and B were expanded up to 9 and 21 pts. A complete blood count was obtained 24 h after P and every 2 days for each cycle thereafter. **Results:** Median values of white blood cell (WBC) counts for all anthracycline and taxane cycles are reported in the table. Pts in cohort A showed WBC and neutrophil (N) counts 24 h after P higher than pts in the other cohorts; pts treated with P after 96 h showed a high WBC and N counts at day 13 (i.e. the day before the following CT cycle). No differences in CT delays were observed between pts treated with P after 24 h or 72 h. On the basis of these findings, the protocol was amended and pts in the DD arms received P after 72 h. **Conclusions:** The best timing of P administration in DD regimens is 72 h after CT. Clinical trial information: NCT00433420.

| | Cohort A P 24 h | Cohort B P 72 h | Cohort C P 96 h |
|---|---|---|---|
| | WBC count median x $10^3$/uL (range) | WBC count median x $10^3$/uL (range) | WBC count median x $10^3$/uL (range) |
| **Anthracycline-based CT** | | | |
| **Day 1** | 9.1 (4.3 – 17.3) | 9.2 (4.5 – 28.7) | 12.2 (5.2 – 32.8) |
| **24 hours after P** | 62.5 (23.3 – 116.4) | 35.0 (14.1 – 79.8) | 28.7 (14.4 – 64.4) |
| **72 hours after P** | 36.8 (27.5 – 53.2) | 15.9 (5.0 – 36.1) | 4.7 (0.8 – 24.3) |
| **Day 13** | 9.9 (2.9 – 16.3) | 12.7 (4.7 – 26.1) | 18.7 (9.0 – 37.5) |
| **Taxane-based CT** | | | |
| **Day 1** | 8.4 (4.7 – 15.0) | 10.5 (3.4 – 26.9) | 13.8 (5.2 – 30.7) |
| **24 hours after P** | 67.4 (29.5 – 92.9) | 53.8 (6.6 – 81.3) | 45.0 (23.7 – 61.9) |
| **72 hours after P** | 46.7 (27.0 – 78.7) | 36.9 (19.0 – 66.8) | 34.3 (15.7 – 58.6) |
| **Day 13** | 15.2 (7.7 – 25.6) | 20.5 (11.2 – 35.6) | 24.0 (13.1 – 49.3) |

**9633 General Poster Session (Board #283), Sun, 8:00 AM-11:45 AM**

**Phase 3 trial results for rolapitant, a novel NK-1 receptor antagonist, in the prevention of chemotherapy-induced nausea and vomiting (CINV) in subjects receiving moderately emetogenic chemotherapy (MEC).** *Presenting Author: Ian D. Schnadig, Compass Oncology and The US Oncology Network, Portland, OR*

**Background:** Rolapitant is a highly selective competitive long acting NK-1 receptor antagonist that demonstrated efficacy in a large randomized phase 2 dose-finding study. This study evaluated the 200 mg dose for efficacy and safety in the prevention of CINV in subjects receiving MEC. **Methods:** Randomized phase 3 double-blind active-control study. 1,369 chemonaïve patients treated with MEC (cyclophosphamide, doxorubicin, epirubicin, carboplatin, irinotecan, daunorubicin or cytarabine) were randomized 1:1 to either (1) rolapitant + granisetron + dexamethasone or (2) placebo + granisetron + dexamethasone. The primary endpoint was complete response (CR=no emesis and no rescue medication) in delayed phase (>24-120 hrs) post-chemo. Secondary endpoints included CR in acute (0-24 hrs) and overall (0-120 hrs) phases. Treatment comparisons were performed using Mantel-Haenszel chi-square test; to control for type 1 error testing for key secondary endpoints was conducted in a stepwise fashion. Subjects recorded episodes of emesis, nausea and rescue medication using a diary during 0-120 hrs post-chemo. **Results:** There were 1,344 evaluable patients (>50% received anthracycline-cyclophosphamide therapy). Subjects in rolapitant group had a significantly higher CR rate for the primary study endpoint during delayed phase compared to control (71.3% vs 61.6%, p<0.001, respectively). CR rates were also higher in rolapitant group for acute and overall phases (83.5% vs 80.3%, p=0.143; 68.6% vs 57.8%, p<0.001, respectively). The rolapitant group achieved higher rates of complete protection (no emesis, no rescue medication and maximum nausea VAS <25mm) in both delayed and overall phases compared to control (64.3% vs 56.9%, p=0.006; 62.0% vs 53.2%, p=0.001, respectively). AE rates were similar across both groups. **Conclusions:** Rolapitant in combination with a 5-HT3 receptor antagonist and dexamethasone was well-tolerated and demonstrated superior efficacy over control in the primary endpoint of the prevention of delayed CINV in subjects receiving MEC in a global phase 3 study. Clinical trial information: NCT01500226.

**9634 General Poster Session (Board #284), Sun, 8:00 AM-11:45 AM**

**Risk of severe diarrhea associated with ipilimumab in cancer patients.** *Presenting Author: Robert Charles Hendler, Stony Brook University Hospital, Stony Brook, NY*

**Background:** Ipilimumab is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody, which augments T-cell activation and proliferation and is thought to indirectly affect the T-cell mediated anti-tumor immune response. It has been approved by the FDA for treatment of unresectable or metastatic melanoma, and several trials have also shown promising results regarding ipilimumab's role in the treatment of other types of cancer. Ipilimumab has been associated in some individual studies with an increased rate of diarrhea, a serious adverse event associated with morbidity and treatment discontinuation. However the overall incidence and risk of diarrhea to ipilimumab is unknown. **Objective:** To conduct a systematic review of relevant clinical trials, and perform a meta-analysis to determine risk of diarrhea with ipilimumab. **Methods:** Articles from PubMed from January 1998 to November 2013 and abstracts presented at the American Society of Clinical Oncology up to 2013 were searched to identify relevant studies. The incidence and relative risk (RR) of diarrhea and its 95% Confidence Intervals were calculated using random effects or fixed effects models depending on the heterogeneity of included studies. **Results:** There were a total of 1571 patients across 10 clinical trials included in this meta-analysis. The overall incidence of all-grade diarrhea was 41.6% (95% CI: 33.6-50.0%). The overall incidence of high-grade diarrhea was 8.4% (95% CI: 5.5-12.7%). In comparison with controls, ipilimumab significantly increased the risk of all-grade diarrhea with an RR of 1.63 (95% CI: 1.37-1.97, P<0.001) and high-grade diarrhea with an RR of 2.19 (95% CI: 1.11-4.34, P=0.025). **Conclusions:** There was a significant risk of severe diarrhea in cancer patients treated with ipilimumab.

**9635 General Poster Session (Board #285), Sun, 8:00 AM-11:45 AM**

**Frequency, intensity, and correlates of financial distress (FD) among advanced cancer patients (AdCa).** *Presenting Author: Marvin Omar Delgado-Guay, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Financial problems are frequent and severe for AdCa. There is limited data on the effects of FD on suffering and quality of life(QOL) of AdCa. In this prospective cross sectional study, we examined the frequency of FD and its correlates in AdCa. **Methods:** We interviewed 149 AdCa, 77 at a Comprehensive Cancer Center(CCC) and 72 at a General Public Hospital-(GPH). AdCa completed self-rated FD(subjective experience of distress attributed to financial problems) numeric rating scale(0=best, 10=worst) and also validated questionnaires assessing symptoms(ESAS), psychosocial distress(HADS), and QOL(FACT-G). **Results:** Median age (Interquartile range:IQR): 60 years(55-65). 74/149(50%) were female. 78/149(52%) were married. 48/77 (62%) at CCC vs. 13/72(18%) at GPH were white (p<0.0001); 21/77(27%) vs. 32/72(38%) were African American(p<0.0001), and 7/77(9%) vs. 27/72(38%) were Hispanics(p<0.0001). 44/77(58%) at CCC vs. 14/72(19%) at GPH had college education and an advanced degree(p<0.0001). The median(IQR) current income was $3,000($1,400-$7,000) for CCC vs. $940($350-$1,300) at GPH, p=0.0017. 72(51%) AdCa self-reported as middle class before cancer diagnosis vs. 52(39%) at the time of the evaluation(p<0.0001). FD was present in 65/75[86% (95%CI=76-93%)] at CCC vs. 65/72[90% (81-96%)] p=0.45. However the median intensity of FD(IQR) at CCC was 4(1-7) vs. 8(3-10), p=0.0003. AdCa reported that FD was affecting their general well-being(0=not at all, 10=very much) with a median(IQR) of 5(1-8). FD was reported as more severe than physical distress, distress about physical functioning, social/family distress and emotional distress by 45(31%), 46(32%), 64(43%), and 55(37%) AdCa respectively (all significantly worse for GPH). Spearman Correlation of FD with financial burden r=0.53, p<0.0001; FACT-G r=-0.23, p=0.005; HADS-Anxiety r=0.27, p=0.001; ESAS-Anxiety r=0.2, p=0.01; and ESAS-depression r=0.18 p=0.03. **Conclusions:** FD was very frequent in both groups but intensity was double among GPH patients. FD was associated with worse anxiety, depression and poor QOL. More research is warranted to confirm these associations and establish interventions to improve this aspect of the care of AdCa.

**9636 General Poster Session (Board #286), Sun, 8:00 AM-11:45 AM**

**Safety of rolapitant, a novel NK-1 receptor antagonist, for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately or highly emetogenic chemotherapy (MEC or HEC).** *Presenting Author: Laszlo Urban, Matrahaza Healthcare Center and University Teaching Hospital, Matrahaza, Hungary*

**Background:** Rolapitant is a highly selective competitive long acting NK-1 receptor antagonist that successfully achieved the primary endpoint of complete response (no emesis and no rescue medication) in the delayed phase of CINV in two phase 3 studies in subjects receiving MEC or HEC. In addition, these studies evaluated the safety and tolerability of rolapitant in these subjects. **Methods:** Two separate phase 3 double-blind active control studies were conducted. 1369 subjects scheduled to receive MEC (cyclophosphamide, doxorubicin, epirubicin, carboplatin, ifosfamide, irinotecan, daunorubicin or cytarabine), and 555 subjects scheduled to receive HEC ($\geq$60 mg/m$^2$ cisplatin) were randomized 1:1 to either (1) rolapitant 200 mg + granisetron + dexamethasone or (2) placebo + granisetron + dexamethasone. Adverse events (AE) and serious adverse events (SAE) were collected for all subjects. **Results:** AE rates in cycle 1 were similar across rolapitant and control groups for both the MEC and HEC studies (63.9% vs 66.0%; 64.7% vs 60.2%, respectively). The most frequent AEs observed across both the rolapitant and control groups, respectively, for the MEC study were fatigue (16.3% vs 15.4%), constipation (10.3% vs 14.1%) and alopecia (11.3% vs 12.3%); and for the HEC study were constipation (7.4% vs 10.9%), asthenia (6.6% vs 11.3%) and neutropenia (9.9% vs 6.9%). SAEs rates in cycle 1 were also similar across rolapitant and control groups for both the MEC and HEC studies (6.6% vs 7.1%; 12.5% vs 14.2%, respectively). The most frequent SAEs across both the rolapitant and control groups, respectively, for the MEC study were febrile neutropenia (1.2% vs 2.1%), neutropenia (0.3% vs 0.9%) and neutrophil count decrease (0.3% vs 0.6%); and for the HEC study febrile neutropenia (0.7% vs 1.1%), neutropenia (0.7% vs 1.1%) and thrombocytopenia (1.1% vs 0.7%). No serious, related and unexpected AEs were reported for either study. **Conclusions:** Rolapitant 200 mg in combination with a 5-HT3 receptor antagonist and dexamethasone was demonstrated to be safe and well tolerated in two global phase 3 studies in subjects receiving HEC or MEC. Clinical trial information: NCT01500226.

**9637 General Poster Session (Board #287), Sun, 8:00 AM-11:45 AM**

**Symptoms in gastrointestinal stromal tumors.** *Presenting Author: Loretta A. Williams, Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** A major barrier to effective symptom management in gastrointestinal stromal tumors (GIST) is lack of recognition of the symptom burden of the disease and treatment. Symptom burden is the combined impact of disease- and treatment-related symptoms on daily functioning. Our aim was to describe the symptom burden of patients with GIST. **Methods:** After giving IRB-approved informed consent, 150 patients with GIST completed the 20 symptom severity and 6 interference items of the MD Anderson Symptom Inventory for GIST (MDASI-GIST) at least every 2 weeks for 1 year. Symptoms and interference were rated on 0-10 scales (0 = none or no interference, 10 = worst imaginable or complete interference). Patients also answered a single overall quality-of-life (QOL) question every 3 months. Demographic and disease information was collected on all patients. Trajectory analysis determined higher and lower symptom groups. Mixed modeling identified factors predictive of symptom burden. **Results:** Mean subject age was 59.2 years (standard deviation [sd] = 11.7). 51% (77) of the subjects were female, 83% (124) were white, 47% (70) were employed. Subjects had been diagnosed for an average of 48.3 months (sd = 63.2) and 52% (78) were receiving imatinib. Mean overall QOL rating was 7.7 (best = 10, sd = 2.4). Symptoms reported as most severe over the course of the year were fatigue (mean [M] = 2.95, sd = 2.60), drowsiness (M = 2.30, sd = 2.38), general weakness (M = 2.18, sd = 2.40), disturbed sleep (M = 2.16, sd = 2.46), and muscle soreness/cramping (M = 2.06, sd = 2.41). The mean severity of the 5 most severe symptoms, the interference items, and QOL were all significantly correlated (all $P < 0.001$). 36.5% of patients were in the higher symptom trajectory group. Younger age, having a primary diagnosis of gastric GIST, and not currently receiving imatinib were predictive of higher symptom burden. **Conclusions:** Approximately 1/3 of patients with GIST experience higher symptom burden primarily related to fatigue, sleep difficulty, weakness, and muscle discomfort. Higher symptom burden significantly impacts QOL. Additional research is needed to identify effective methods of symptom management. Clinical trial information: NCT01178307.

**9638 General Poster Session (Board #288), Sun, 8:00 AM-11:45 AM**

**Phase 3 trial results for rolapitant, a novel NK-1 receptor antagonist, in the prevention of chemotherapy-induced nausea and vomiting (CINV) in subjects receiving highly emetogenic chemotherapy (HEC).** *Presenting Author: Bernardo Leon Rapoport, The Medical Oncology Center of Rosebank, Johannesburg, South Africa*

**Background:** Rolapitant is a highly selective competitive long acting NK-1 receptor antagonist that demonstrated efficacy and safety in a large randomized phase 2 dose-finding study. This study evaluated the 200 mg dose for efficacy and safety in the prevention of CINV in subjects receiving HEC. **Methods:** Randomized phase 3 double-blind active-control study. 555 cisplatin-naïve subjects treated with HEC ($\geq$60 mg/m$^2$ cisplatin) were randomized 1:1 to receive either (1) rolapitant + granisetron + dexamethasone or (2) placebo + granisetron + dexamethasone. The primary endpoint was complete response (CR=no emesis and no rescue medication) in the delayed phase (>24-120 hrs) post-chemotherapy. Secondary endpoints included CR during the acute (0-24 hrs) and overall (0-120 hrs) phases. Treatment comparisons were performed using a Mantel-Haenszel chi-square test; to control for the type1 error, testing for the key secondary endpoints was conducted in a stepwise fashion. Subjects recorded episodes of emesis, nausea and rescue medication using a subject diary during 0-120 hours post-chemotherapy. **Results:** There were 544 evaluable subjects. Subjects in the rolapitant group had a significantly higher CR rate for the primary study endpoint during the delayed phase (70.1% vs 61.9%, p=0.043) compared to control. CR rates were also higher in rolapitant group for acute and overall phases (83.4% vs 79.5%, p=0.233; 67.5% vs 60.4%, p=0.084, respectively). The rolapitant group achieved higher rates of no nausea (maximum Visual Analog scale <5mm, 0-100mm) in both the delayed and overall phases compared to control (58.3% vs 46.9%, p=0.007; 55.0% vs 44.0%, p=0.009, respectively). AE rates were similar across both groups. **Conclusions:** Rolapitant in combination with a 5-HT3 receptor antagonist and dexamethasone was well-tolerated and demonstrated superior efficacy over control in the primary endpoint of the prevention of delayed CINV in subjects receiving HEC in a global phase 3 study. Clinical trial information: NCT01500213.

**9639 General Poster Session (Board #289), Sun, 8:00 AM-11:45 AM**

**Effect of baseline characteristics, including antihypertensive therapy, on survival and hypertension during treatment with vascular endothelial growth factor (VEGF) signaling pathway inhibitors (VSP-Is).** *Presenting Author: Ole-Petter Riksfjord Hamnvik, Brigham and Women's Hospital, Boston, MA*

**Background**: Oral VSP-Is are associated with a significant risk of hypertension (HTN), yet little is known regarding clinical predictors. We describe the association between baseline clinical characteristics, including antihypertensive (antiHTN) therapy, and increased blood pressure (BP) and survival in patients prescribed VSP-Is. **Methods:** Clinical data was obtained from1120 adults prescribed VSP-Is, identified from electronic medical records (Partners HealthCare, Boston, MA). The primary outcome was worsening HTN (BP$\geq$160/100 mmHg on $\geq$1 occasion or requiring intensification of antiHTN therapy) in patients with pre-existing HTN, or the development of new HTN in patients with no prior history. **Results:** The most common cancers wererenal cell (32.2%), hepatocellular (11.6%), GIST (12.5%), and other sarcomas (15.3%). Most patients received sunitinib (52%), sorafenib (25.9%) or pazopanib (18%). Pre-existing HTN was present in 65.4%. The primary BP outcome was identified in 49.9% (median follow-up 4.3 months). In a fully adjusted Cox model, risk factors for the BP outcome were increasing age (hazard ratio (HR) 1.01, 95% confidence interval (CI) 1.006-1.021), BMI (HR 1.02, 95%CI 1.01-1.03) and pre-existing HTN (HR 1.70, 95%CI 1.32-2.20), whereas tumor type, VSP-I prescribed, race and gender were not. The absolute BP increase was similar in patients with and without pre-existing HTN (21/15 mmHg). Improved survival was seen in patients who developed the BP outcome (11.1 months) vs. those who did not (4.2 months; HR 0.51, 95%CI 0.43-0.60). Patients taking angiotensin system inhibitors (ASIs) at baseline had improved survival vs. other antiHTN agents (HR 0.81, 95%CI 0.65-0.998, median survival 7.5 vs. 5.8 months). **Conclusions:** Pre-existing HTN is a risk factor for worsening HTN during therapy with VSP-Is, likely due to a higher baseline BP. Adequate BP control prior to VSP-I initiation may mitigate the risk. While the class of baseline antiHTN agents did not change the risk of worsened BP control, our finding that ASIs are associated with improved survival in patients starting VSP-Is warrants further study.

**9640 General Poster Session (Board #290), Sun, 8:00 AM-11:45 AM**

**Survival benefit with low-molecular-weight heparin in patients with advanced solid tumors: A post hoc analysis of PROTECHT trial.** *Presenting Author: Sandro Barni, Department of Medical Oncology, Treviglio and Caravaggio Hospital, Treviglio, Italy*

**Background:** Use of low molecular weight heparin (LMWH) are approved to reduce the thromboembolic events in patients with solid tumors. The effect of LMWH on overall survival (OS) has been debated but not demonstrated, and current guidelines recommend against its use to increase OS. We have conducted a post hoc analysis of PROTECHT (PROphylaxis of ThromboEmbolism during CHemoTherapy) randomized study that compared nadroparin to placebo in patients with metastatic or locally advanced solid tumors. **Methods:** In our post-hoc analysis, individual patient data (n=1,150) was reviewed and analyzed to assess response to chemotherapy and overall survival. Tumor response to chemotherapy was assessed using Response Evaluation Criteria in Solid Tumors. Survival analysis was performed through a Cox regression model with treatment, response to chemotherapy and their interaction term (treatment-by- response to chemotherapy) as covariates. A statistically significant interaction indicates that an overall comparison between the two treatments is inappropriate, and therefore hazard ratios (HRs) with associated 95% CI and p-values must be evaluated separately in each group (disease control / no disease control). **Results:** A statistically significant interaction between treatment and response to chemotherapy (P=0.0435) was found, suggesting the hypothesis that OS treatment difference depends on the response to chemotherapy. A statistically significant difference in OS in favour of nadroparin treatment was found in the subgroup of patients with disease control (HR=0.665 [95%CI 0.442 - 1.00], P=0.05), but not in the subgroup of patients without disease control (HR=1.077 [95%CI 0.857 - 1.35], P=0.525). In patients with disease control, 1-year survival rate was 83% [95%CI 79% - 87%] in nadroparin and 76% [95%CI 70% - 83%] in placebo respectively; conversely in patients without disease control 1-year OS was 49% [95%CI 44% - 53%] in nadroparin and 51% [95%CI 45% - 58%] in placebo. **Conclusions:** this post hoc analysis support the hypothesis that LMWH could increase survival albeit limited to patients responding to chemotherapy. Clinical trial information: NCT 00951574.

**9641^ General Poster Session (Board #291), Sun, 8:00 AM-11:45 AM**

**A randomized double-blind phase III pivotal study of febuxostat (FEB) versus allopurinol (ALL) in the prevention of tumor lysis syndrome (TLS): Florence study.** *Presenting Author: Michele Spina, National Cancer Institute, Aviano, Italy*

**Background:** Tumor lysis syndrome (TLS) is an oncologic emergency characterized especially by elevated serum uric acid (sUA). FEB is an orally administerd selective xanthine oxidase inhibitor to reduce sUA. **Methods:** This was a randomized, double blind phase III trial of FEB vs ALL in terms of control of sUA level and preservation of renal function in patients undergoing chemotherapy (CT) for hematologic malignancies at intermediate to high risk of TLS. Patients werestratified according to TLS risk and sUA level to FEB or ALL starting from 2 days prior CT and continued for 7-9 days. Assigned treatment was blinded, while daily dose level (low/standard/high containing ALL 200/300/600 mg or fixed FEB 120) was upon investigator's choice. Primary endpoints were sUA area under the curve (AUC $sUA_{1\text{-}8}$) and change in serum creatinine (sC) level both from baseline to Day 8, analyzed through ANCOVA including treatment and stratification factors as covariates. Secondary endpoints were response rate (sUA $\leq$ 7.5 mg/dL from CT start to Day 8), incidence of laboratory and clinical TLS and safety. The study was run in 79 sites in Europe and Brazil (NCT01724528). **Results:** 346 patients were included with similar baseline demographics in both groups. 82.1% of patients were at intermediate risk of TLS, 87.6% had a baseline sUA $\leq$ 7.5 mg/dl and 82.7% received standard dose level. Intention to treat (ITT) analysis: mean AUC $sUA_{1\text{-}8}$ (mgxh/dl) was significantly lower in FEB arm (514.0 $\pm$ 225.71 vs 708.0 $\pm$ 234.42; p $<$ .0001). No significant difference in mean sC change(%) occurred between FEB and ALL arms (-0.83 $\pm$ 26.98 vs -4.92 $\pm$ 16.70 respectively, p=0.0903). No significant difference was detected among secondary efficacy endpoints. Incidence of all adverse events (AEs) and related AEs was 67.6% vs 64.7% and 6.4% vs 6.4% in FEB and ALL arm, respectively. **Conclusions:** In this largest TLS prevention trial FEB proved to be significantly superior over ALL with a 28% lower exposure to sUA during CT. As no dose adjustment of FEB in patients with preexisting mild or moderate renal impairment is necessary makes FEB a preferable preventive measure of TLS. Clinical trial information: NCT01724528.

**9642 General Poster Session (Board #292), Sun, 8:00 AM-11:45 AM**

**Quality of life (QOL), mood, and prognostic awareness during hospitalization for hematopoietic stem cell transplantation (HSCT).** *Presenting Author: Areej El-Jawahri, Massachusetts General Hospital, Boston, MA*

**Background:** During HSCT, patients endure significant side effects in the hopes of curing their disease. While many studies have focused on the long-term outcomes of HSCT recipients, the acute impact of hospitalization for HSCT on patients' QOL and mood is unknown. Furthermore, data on patients' perception of their prognosis are lacking. **Methods:** We conducted a prospective longitudinal study of patients hospitalized at Massachusetts General Hospital for HSCT. At baseline and weeks 1, 2, and 3 of hospitalization, we assessed QOL (Functional Assessment of Cancer Therapy- Bone Marrow Transplantation [FACT-BMT]; higher scores indicate better QOL), fatigue (FACT-Fatigue; high scores indicate less fatigue), and mood (Hospital Anxiety and Depression Scale score $>$ 7 on anxiety or depression subscale considered clinically significant). Using a 10-item questionnaire, we measured patients' information preferences, and perception of their prognosis. **Results:** We enrolled 60 consecutive patients undergoing autologous (n=30), or myeloablative allogeneic (n=30) HSCT. Patients' QOL declined and fatigued increased throughout hospitalization [Table 1]. The proportion of patients with depression symptoms increased from baseline to week 3 (18.3% to 33.3%, p=0.002) whereas the proportion of patients with anxiety did not change significantly from baseline (22.6%, p=0.7). Although 90.0% of patients stated that it is 'extremely' or 'very' important to know about their prognosis, 86.2% reported inaccurate and overly optimistic perception of their prognosis compared to their physicians (p $<$ 0.0001). **Conclusions:** Patients undergoing HSCT report an overly optimistic perception of their prognosis and experience significant decline in QOL with increasing rates of depression throughout their hospitalization. Interventions to improve QOL, psychological outcomes, and prognostic awareness of patients hospitalized for HSCT are warranted.

| Outcome | Type HSCT | Week-1 | Week-2 | Week-3 | P-Value |
|---|---|---|---|---|---|
| QOL | Auto | 105.8 | 94.9 | 96.3 | **< 0.0001** |
| | Allo | 110.0 | 97.5 | 96.9 | **< 0.0001** |
| Fatigue | Auto | 34.4 | 27.0 | 27.3 | **< 0.0001** |
| | Allo | 38.5 | 34.3 | 30.9 | **= 0.002** |
| Depression | Auto | 23% | 40% | 43% | **= 0.002** |
| | Allo | 13% | 30% | 23% | **= 0.03** |

**9643 General Poster Session (Board #293), Sun, 8:00 AM-11:45 AM**

**Treating diabetic patients with chemotherapy: Single-center experience of toxicity and outcomes.** *Presenting Author: Jenny F. Seligmann, St. James's Institute of Oncology, Leeds, United Kingdom*

**Background:** Epidemiological evidence suggests diabetics are at increased risk of several cancers, with inferior cancer outcomes. There is little data to describe the experience of diabetic patients during chemotherapy. We have compared outcomes of diabetic patient(pts) with non-diabetics receiving palliative chemotherapy for advanced colorectal cancer (aCRC) in a single centre. **Methods:** We performed a retrospective case note analysis between 2004 and 2011. Diabetic pts starting first line chemotherapy for aCRC were identified using an electronic patient record database (Patient Pathway Manager) and chemotherapy prescription software (ChemoCare). Data for chemotherapy regimen, acute admissions, subsequent therapy and survival were compared, corrected for age, performance status (PS), comorbidity and initial regimen (single vs combination agent). **Results:** 146 diabetic pts and 730 controls were included. Median age was 66 years; 94% of diabetic pts had type 2 diabetes, 17% were receiving insulin. Performance status was similar (PS 0-1in 76% in diabetics vs 77% controls); more diabetic pts had comorbidity (61% vs 25%). Diabetics received less upfront combination chemotherapy (OR = 0.41, 95% CI=0.29-0.65, p$<$0.001). Only 5% of diabetic pts had upfront steroid reduction. Diabetes was associated with an increased risk of acute admission (OR=2.35, 95%CI 1.6-3.45, p$<$0.0001). A higher incidence of infective episodes requiring hospitalisation were observed in diabetics (OR = 3.79, 95% CI 2.25-6.38, p$<$0.001). No other factors predicted for increased risk of admission. Poor glycaemic control led to admission in 6.9% of diabetics. Subsequent treatment with second line chemotherapy (p=0.87) and overall survival (p=0.21) was similar in both groups. Increased age and poor PS were independently prognostic for survival. **Conclusions:** Diabetic pts with aCRC achieved the same survival with palliative chemotherapy as non-diabetic patients. However diabetic pts receiving chemotherapy have over double the risk of an acute admission during treatment, despite reduced use of combination chemotherapy. Awareness of this risk and consideration of potential contributing factors may enable these episodes to be avoided.

**9644 General Poster Session (Board #294), Sun, 8:00 AM-11:45 AM**

**Prediction and early detection of anthracycline-related cardiotoxicity using cardiac biomarkers.** *Presenting Author: Patrick Lawson Stevens, Vanderbilt University Medical Center, Nashville, TN*

**Background:** Anthracyclines (ANTH) are widely used as cancer therapies but carry a significant risk of heart failure (HF) and left ventricular dysfunction (LVD). Improved cardiovascular (CV) risk stratification is necessary to decrease the growing incidence of CV and oncologic morbidity during ANTH chemotherapy. The overall objective of this study was to define the utility of cardiac biomarkers, B-type natriuretic peptide (BNP) and Troponin I (TnI) in the identification of subsequent ANTH cardiotoxicity. **Methods:** The PREDICT study was a multicenter, prospective cohort of 586 patients initiating ANTH chemotherapy. Patients underwent serial biomarker evaluation at baseline, before each chemotherapy cycle, and at 6 and 12 months. Echocardiography was performed at baseline, 6 months, and 12 months, or for suspected CV events. CV events were defined as symptomatic HF, asymptomatic LVD, acute coronary syndrome, symptomatic arrhythmia, or cardiac death. **Results:** At baseline, the median BNP was 17pg/ml (range 0.5-188pg/ml) and 95% of participants had a TnI <0.05ng/ml. At baseline or during chemotherapy or follow-up, 17% had a BNP >100pg/ml and 41% had a TnI>0.05ng/ml. Overall, 63 patients (11%) suffered a CV event. In univariate analysis, a baseline BNP >100 pg/ml was associated with cardiotoxicity (OR 3.6, 95% CI 1.4-9.0, p=0.007) as was an elevated BNP >100 pg/ml at any time during or after therapy (OR 3.2, 95% CI 1.8-5.6, p<0.0001). Elevations in TnI at baseline or during therapy or follow-up were not associated with cardiotoxicity (p=0.52; 0.98, respectively). BNP demonstrated a high specificity and negative predictive value (Table), whereas TnI had less discriminative ability. **Conclusions:** Elevations in BNP were significantly associated with cardiotoxicity in patients undergoing ANTH chemotherapy and appeared superior to TnI. Cardiac biomarker assessment in addition to other clinical factors may assist in the identification of ANTH cardiotoxicity. Clinical trial information: NCT01311843.

**Diagnostic performance of BNP and TnI in predicting cardiac events.**

| Marker | Sensitivity (95% CI) | | Specificity (95% CI) | | PPV (95% CI) | | NPV (95% CI) | |
|---|---|---|---|---|---|---|---|---|
| BNP > 100 pg/ml | 35 | (23, 48) | 85 | (81, 88) | 22 | (14, 31) | 92 | (89, 94) |
| TnI > 0.05 ng/ml | 41 | (29, 54) | 59 | (54, 63) | 11 | (7, 15) | 89 | (85, 92) |

**9645 General Poster Session (Board #295), Sun, 8:00 AM-11:45 AM**

**Phase 3 trial of APF530 versus palonosetron (PALO) in preventing chemotherapy-induced nausea and vomiting (CINV): Efficacy in breast cancer patients (pts) receiving moderately (MEC) or highly (HEC) emetogenic chemotherapy.** *Presenting Author: Ralph V. Boccia, Center for Cancer and Blood Disorders, Bethesda, MD*

**Background:** APF530 provides controlled, sustained release of granisetron for preventing acute (0-24 h) and delayed (24-120 h) CINV. In a phase 3 trial measuring complete response (CR; no emesis or rescue medication), APF530 was noninferior to PALO in preventing acute and delayed CINV in MEC pts and acute CINV in HEC pts (defined by Hesketh, J Clin Oncol. 1997). We report data from 608 breast cancer pts in this trial. **Methods:** Pts receiving single-dose MEC or HEC were randomized to APF530 250 or 500 mg SC (granisetron 5 or 10 mg) or PALO 0.25 mg IV prior to cycle 1 (C1). In C2-4, PALO pts were randomized to APF530 250 or 500 mg; APF530 pts continued their C1 APF530 dose. Between-group comparisons used Fisher's exact test. **Results:** In C1, 78% of 423 MEC pts and 75% of 185 HEC pts received cyclophosphamide + doxorubicin or epirubicin. CRs with APF530 250 or 500 mg in C1 were not significantly different from those with PALO in preventing acute and delayed CINV with MEC or HEC (Table). There were no significant differences in within-cycle CRs between APF530 doses for acute and delayed CINV in MEC or HEC in C2-4. Both APF530 doses combined elicited high CRs during acute CINV in C2 (72%, 78%), C3 (75%, 84%), and C4 (82%, 85%) for MEC and HEC, respectively, trending toward higher CRs in later cycles. High CRs occurred in C2-4 during the delayed phase and overall risk period. **Conclusions:** APF530 has substantial activity in preventing CINV in first and subsequent cycles of chemotherapy in breast cancer pts receiving MEC or HEC. Clinical trial information: NCT00343460.

| | CINV | | APF530 250 mg | APF530 500 mg | PALO | Between-treatment *P* |
|---|---|---|---|---|---|---|
| MEC | | | N = 149 | N = 140 | N = 134 | |
| | Acute | CR, n (%) | 106 (71) | 102 (73) | 91 (68) | .661 |
| | | *P** | .605 | .427 | | |
| | | 95% CI* | -7.6, 14.0 | -5.9, 15.8 | | |
| | Delayed | CR, n (%) | 69 (46) | 67 (48) | 69 (52) | .677 |
| | | *P** | .406 | .629 | | |
| | | 95% CI* | -16.8, 6.6 | -15.4, 8.3 | | |
| | Overall | CR, n (%) | 63 (42) | 63 (45) | 61 (46) | .847 |
| | | *P** | .632 | 1.0 | | |
| | | 95% CI* | -14.8, 8.4 | -12.4, 11.4 | | |
| HEC | | | N = 60 | N = 67 | N = 58 | |
| | Acute | CR, n (%) | 46 (77) | 49 (73) | 38 (66) | .398 |
| | | *P** | .224 | .436 | | |
| | | 95% CI* | -6.1, 27.4 | -9.2, 24.0 | | |
| | Delayed | CR, n (%) | 35 (58) | 42 (63) | 30 (52) | .465 |
| | | *P** | .579 | .277 | | |
| | | 95% CI* | -11.9, 24.4 | -6.6, 27.9 | | |
| | Overall | CR, n (%) | 31 (51.7) | 37 (55.2) | 24 (41.4) | .288 |
| | | *P** | .275 | .152 | | |
| | | 95% CI* | -7.9, 28.1 | -4.1, 30.8 | | |

**P* and 95% CI vs PALO.*

**9646 General Poster Session (Board #296), Sun, 8:00 AM-11:45 AM**

**Management approaches and outcomes of lung cancer patients hospitalized for malignant pleural effusions.** *Presenting Author: Madhusmita Behera, The Winship Cancer Institute of Emory University, Atlanta, GA*

**Background**: Malignant pleural effusion (MPE) in lung cancer is associated with significant morbidity and poor prognosis. There has been a significant lack of progress regarding the current and recommended management of MPE. We studied MPE management in a large cohort of hospitalized lung cancer patients (pts). **Methods**: We utilized nationwide inpatient data from 2008-2010 from the Agency for Healthcare Research and Quality- Healthcare Cost and Utilization Project. All lung cancer pts with MPE among top 3 discharge diagnoses were selected. Therapeutic procedures used were identified using ICD 9-CM procedure codes. All analyses were performed using SPSS 20.0. **Results**: A total of 8570 pts, accounting for 2.5% of all lung cancer-related hospitalizations, had MPE (median age- 71 years, whites-66%, females- 48%, teaching hospitals-46%, urban locations-88%, elective admissions- 16%, median costs- $29,967). Median length of stay (LOS) was 5 days; mortality rate was 10.5% and 70% had major or extreme loss of function at discharge. Rural hospitals had a higher mortality compared to urban (14% vs. 10%, p=0.002). Thoracentesis(T), thoracostomy tubes(TT) and pleurodesis(P) were the top three procedures, with 48% having a T. Overall pneumothorax rate was 7.4%. There were significant differences in LOS and severity measures in pts sub-groups based on type of intervention (p<0.001). The TT group had higher mortality (Table). Univariate analyses showed significant difference in outcomes between elective and non-elective admissions in P group (p<0.001). **Conclusions**: Elective admissions for the management of MPE are associated with lower mortality and reduced loss of functional capacity over emergency hospitalizations. Pleurodesis is associated with longer length of stay, but lower mortality and better functional status at discharge.

| Outcomes | T (N=2860) | TT (N=1382) | P Total (N=1616) | P Elective (N=492) | P Nonelective (N=1120) |
|---|---|---|---|---|---|
| Mortality | 223(8) | 177(13) | 128(8) | 20 (4) | 108 (10) |
| Extreme/major loss of function | 2021 (71) | 992 (72) | 1044(64.6) | 238(48%) | 803(72%) |
| Cost ($10,000) | 3.8 (± 4) | 5.4 (± 5.4) | 6.2(± 5.6) | 4.6 (± 4) | 6.9 (± 6) |
| LOS (days) | 5.8 (± 4.8) | 8.5(± 6.2) | 9.7(± 6.4) | 7 (± 5) | 10.9 (± 6.5) |

Data are presented as N (%) or mean(± SD).

**9647 General Poster Session (Board #297), Sun, 8:00 AM-11:45 AM**

**A phase II randomized, double-blind placebo-controlled trial of an antiemetic, 6-gingerol in solid tumor patients receiving moderately to highly emetogenic adjuvant chemotherapy.** *Presenting Author: Jitprapa Konmun, Ramathibodi Hospital, Bangkok, Thailand*

**Background:** Several studies showed that ginger powder could reduce chemotherapy-induced nausea and vomiting (CINV). 6-gingerol is a natural compound extracted from ginger. It has an antagonistic activity to NK1, serotonin, and dopamine receptors. **Methods:** Patients who received moderately to highly-emetogenic chemotherapy were randomized to 6-gingerol 10 mg or placebo PO BID continuously, started 3 days prior to chemotherapy and continued for 4 cycles. 5-HT3 receptor antagonist and dexamethasone were given to all patients. The Likert scale was used to evaluate severity of nausea and loss of appetite. Vomiting was graded according to the CTCAE v.4. Quality of life (QoL) was measured by the FACT-G score. All parameters were evaluated at baseline and before each cycle. Primary endpoints were severity of acute (≤24 hours after chemotherapy) and delay (>24 hours) CINV between 2 groups. **Results:** 87 patients (median age of 53) were enrolled. Patient characteristics were equally distributed between 2 groups. Most patients received anthracyclines (64%) and platinum-doublets (20%). 6-gingerol group had significantly less CINV, improved QoL and appetite, correlated with cytokine changes (see Table). **Conclusions:** 6-gingerol significantly reduces CINV, improves appetite and QoL. A larger clinical trial is warranted to confirm these results.

| | 6-Gingerol N=41 (%) | Placebo N=46 (%) | p-value |
|---|---|---|---|
| Acute vomiting | 35 (85) | 26 (57) | 0.013 |
| None | 5 (12) | 18 (39) | |
| Gr. 1-2 | 1 (2) | 2 (4) | |
| Gr. 3-4 | | | |
| Delay vomiting | 31 (76) | 5 (11) | <0.001 |
| None | 9 (22) | 22 (48) | |
| Gr. 1-2 | 1 (2) | 9 (20) | |
| Gr. 3-4 | | | |
| Acute nausea | 22 (54) | 3 (6) | 0.002 |
| None | 14 (34) | 10 (22) | |
| Mild | 3 (7) | 16 (35) | |
| Moderate | 2 (5) | 7 (15) | |
| Severe | | | |
| Delayed nausea | 10 (24) | 4 (9) | <0.001 |
| None | 23 (56) | 9 (19) | |
| Mild | 5 (12) | 17 (37) | |
| Moderate | 3 (7) | 16 (35) | |
| Severe | | | |
| Mean FACT-G Score | 82.5 | 77.1 | 0.124 |
| Cyc2 | 86.2 | 72.4 | <0.001 |
| Cyc4 | | | |
| Mean super oxide dismutase (unit/mL) | 638 | 496 | 0.033 |
| Cyc2 | 786 | 448 | <0.001 |
| Cyc4 | | | |
| Mean catalase (Kunit/mL) | 61.2 | 47.9 | 0.001 |
| Cyc2 | 66.0 | 48.5 | 0.001 |
| Cyc4 | | | |
| Mean glutathione (unit/mL) | 18.5 | 13.2 | 0.016 |
| Cyc2 | 21.8 | 13.6 | 0.001 |
| Cyc4 | | | |
| Mean thiobarbituric acid reactive substance (nmol/mL) | 5.2 | 6.1 | 0.082 |
| Cyc2 | 5.2 | 6.8 | 0.002 |
| Cyc4 | | | |
| Mean appetite score | 2.0 | 3.6 | 0.008 |
| Cyc2 | 2.3 | 5.3 | <0.001 |
| Cyc4 | | | |

**9648 General Poster Session (Board #298), Sun, 8:00 AM-11:45 AM**

**A prospective, randomized, double-blind phase 3 trial of extended-release granisetron (APF530) versus palonosetron (PALO) for preventing chemotherapy-induced nausea and vomiting (CINV) associated with moderately (MEC) or highly (HEC) emetogenic chemotherapy: Does a reanalysis using newer ASCO emetogenicity criteria affect study conclusions?** *Presenting Author: Harry Raftopoulos, Hofstra North Shore-LIJ School of Medicine, Lake Success, NY*

**Background:** APF530 provides controlled sustained release of granisetron to prevent acute (0-24 h) and delayed (24-120 h) CINV. In a phase 3 trial in 1395 patients, single doses of subcutaneous (SC) APF530 250 and 500 mg were noninferior to intravenous (IV) PALO 0.25 mg in preventing acute CINV after MEC or HEC; APF530 500 mg was noninferior to PALO in preventing delayed CINV after MEC, but not superior in preventing delayed CINV after HEC (Grous et al. *J Clin Oncol* 2009, abs 9627). The primary efficacy endpoint was complete response (CR, no emesis or rescue medication). Chemotherapy emetogenicity was assigned by Hesketh criteria (Hesketh et al. *J Clin Oncol* 1997). However, ASCO reclassified some chemotherapy regimens in its 2011 antiemesis guidelines (Basch et al. *J Clin Oncol* 2011). **Methods:** Study data were reanalyzed with chemotherapy regimens reclassified as MEC or HEC using ASCO criteria. Noninferiority was shown if the CI difference in CR for APF530 – PALO had a lower confidence bound greater than −15%. **Results:** Using ASCO emetogenicity criteria (MEC = 609; HEC = 690), APF530 maintained noninferiority to PALO for all endpoints previously reported. The table shows CR rates by group, using ASCO criteria. **Conclusions:** Single-dose APF530 SC is an alternative to PALO for preventing acute and delayed CINV after MEC or HEC, with generally mild and manageable adverse events. In this post hoc analysis, reclassifying chemotherapy emetogenicity by ASCO criteria did not alter the initial study conclusions. Clinical trial information: NCT00343460.

| CINV | | | APF530 250 mg | APF530 500 mg | PALO | Between-treatment *P* |
|---|---|---|---|---|---|---|
| **MEC** | | | N = 193 | N = 205 | N = 211 | |
| | Acute | CR, n (%) | 158 (82) | 171 (83) | 187 (89) | .135 |
| | | P* | .067 | .157 | | |
| | | 95% CI* | −14, 0.2 | −12, 1.5 | | |
| | Delayed | CR, n (%) | 127 (66) | 142 (69) | 147 (70) | .674 |
| | | *P** | .456 | 1.0 | | |
| | | 95% CI* | −13, 5.3 | −9.4, 8.5 | | |
| **HEC** | | | N = 241 | N = 231 | N = 218 | |
| | Acute | CR, n (%) | 173 (72) | 172 (75) | 147 (67) | .254 |
| | | *P** | .360 | .118 | | |
| | | 95% CI* | −4.1, 12.8 | −1.4, 15.5 | | |
| | Delayed | CR, n (%) | 122 (51) | 129 (56) | 110 (51) | .420 |
| | | *P** | 1.0 | .258 | | |
| | | 95% CI* | −9, 9.4 | −3.9, 14.7 | | |

**P* and 95% CI vs PALO.

**9649 General Poster Session (Board #299), Sun, 8:00 AM-11:45 AM**

**Sleep problems and increased risk of mortality in the context of advanced cancer.** *Presenting Author: Kevin P Collins, University of Pittsburgh, Pittsburgh, PA*

**Background:** Sleep problems have been linked to increased mortality in the general population. The prevalence of sleep problems in those diagnosed with cancer is even higher than the general population. The aims of the proposed study were to examine the type and prevalence sleep problems, and to determine whether sleep problems are associated with survival, in advanced cancer patients. **Methods**: The study was prospective in design. A total of 355 patients with advanced cancers (stage III and IV) affecting the hepatobiliary and pancreatic systems were administered a battery of questionnaires including the Pittsburgh Sleep Quality Index (PSQI) and the Center for Epidemiological Studies-Depression (CES-D) scale. Descriptive statistics, Mann Whitney U test, and Cox regression analyses were performed to test the aims. **Results:** The majority of patients were male (64%) and the mean age 62 years (SD=11). Fifty-nine percent of patients reported poor sleep quality (PSQI $>$ 5); 43% reported sleeping $<$6 hours and 2% $>$ 10 hours; 27% reported sleep latency greater than 30 minutes for 3 or more nights per week; 80% reported poor sleep efficiency (less than 85% time in bed spent sleeping); and 19% reported taking a sleep aid 3 or more times per week. Fifty-eight percent of patients reported clinically significant levels of depression (CES-D $>$16) and those with clinically significant depressive symptoms reported shorter sleep duration (median=6) than those without clinical levels of depression (median=7; p=$<$0.001). Median survival for the entire sample was 7.6 months. After adjusting for factors known to contribute to survival (i.e., age, gender, vascular invasion, depression, and snoring), a curvilinear relationship was observed between sleep duration and mortality (Chi-square=27.8, p=$<$0.001). **Conclusions:** Consistent with findings in the general population, a curvilinear relationship between sleep duration and mortality was observed in advanced cancer patients.

**9650 General Poster Session (Board #300), Sun, 8:00 AM-11:45 AM**

**Cancer patients and their information needs for prediction of symptom burden during and after treatment: Implications for symptom management.** *Presenting Author: Luke Joseph Peppone, Department of Surgery, University of Rochester Medical Center, Rochester, NY*

**Background:** Throughout and after treatment, cancer patients often face a high symptom burden (e.g. fatigue, pain, cognitive difficulties, etc.). A high symptom burden can reduce QOL and treatment adherence, potentially reducing survival. However, predicting the symptom burden in cancer patients remains challenging. **Methods:** Cancer patients scheduled to receive chemotherapy and/or radiation therapy were prospectively surveyed at pre-treatment (n=972), during treatment (n=748), and 6-month follow-up (n=652). At pre-treatment, patients indicated symptom concern (Low, Moderate, or High) and the desire for additional information (Yes, No) on relieving symptoms. During treatment and at 6-month follow-up, patients reported on the severity (an 11-point scale: 0 "None" to 10 = "Worst") of 12 symptoms (fatigue, hair loss, memory, nausea, depression, sleep, pain, concentration, hot flashes, weight loss, skin problems, and dyspnea). Total Symptom Score (TSS) is the sum of all 12 symptoms. Mean symptom severity by symptom concern and additional information desire were determined by ANCOVA analysis. **Results:** Symptom concern at pre-treatment predicted symptom severity during treatment (Table). Patients who wanted more information on symptoms management before also had a significantly greater TSS (Yes = 46.7 vs No = 39.4; p=0.02) during treatment. Patients with high concern at pre-treatment also had a significantly higher TSS 6 months after treatment (High = 24.5 vs Low = 21.1; p$<$0.05). **Conclusions:** Pre-treatment patient symptom concern and wanting more symptom management information predicted symptom burden during treatment and 6 months after treatment. Clinicians should consider using these questions as indicator to which patients may require additional symptom management care.

| | Low | Moderate | High | P |
|---|---|---|---|---|
| **Total symptom score (TSS)** | 37.9 | 39.7 | 44.9 | $<$0.001 |
| **Fatigue** | 5.5 | 5.8 | 6.1 | 0.044 |
| **Pain** | 3.4 | 3.2 | 3.9 | 0.030 |
| **Concentration** | 2.8 | 3.0 | 3.6 | 0.014 |
| **Memory** | 2.7 | 2.9 | 3.4 | 0.021 |
| **Depression** | 3.2 | 3.5 | 3.9 | 0.028 |
| **Nausea** | 2.3 | 3.2 | 3.7 | $<$0.001 |

*Adjusted for severity of the respective symptom at pre-treatment.

**9651 General Poster Session (Board #301), Sun, 8:00 AM-11:45 AM**

**Understanding of early-phase clinical trials among a cohort of advanced cancer patients with limited standard treatment options.** *Presenting Author: Daniel Paul Dohan, University of California, San Francisco, San Francisco, CA*

**Background:** Early phase (EP) trials are typically offered to ACP once they exhaust standard treatment options. Limited knowledge exists about what patients understand regarding EP trials as they approach the end of standard treatments. **Methods:** ACP were recruited from five clinics at an academic medical center with an EP trials program. Patients were eligible if treating oncologists deemed them likely to exhaust standard treatment in 6-12 months. Eligible patients completed a 60 minute qualitative interview. Clinical research was only discussed if patients raised it during the interview. Interviews were audio recorded and transcribed; Atlas.ti was used for thematic coding. **Results:** 82 patients were recruited; 60 mentioned clinical research. Thematic analysis showed that understanding of clinical research differed along two dimensions: Accuracy and Specificity. Some ACP accurately described research; others had inaccurate understandings. Patients described the research process with different degrees of specificity (see Table). **Conclusions:** ACP with limited standard treatment options had mixed understandings of clinical research. Improving ACP understanding before EP trials are discussed may be appropriate.

| | Accurate | Inaccurate |
|---|---|---|
| **Specific** | It is randomized in the fact that there are three different levels to it. So you have somebody that's going to get the highest dosage of both drugs, you're going to have a group that's going to get the lowest dosage and then you're going to have a third group that's going to take the [study drug]. | The [study drug] appears to have put a second roadblock to cell division and I think it was January that they started this phase. So it may be just a carry-on from the first one or it may be a new phase [I] of a new study . . . to determine the efficacy of the drug and how it affects the patients. |
| **General** | One of them's about ready to be whatever the last phase is. I think that's the one we're going with. It's about ready to be approved, FDA approved, so it must be on the later phases. | I am still in a double-blind study so nobody knows if I'm getting the drug, which is a bummer. If I was in a Phase III, I would know I'm getting it. |

**9652 General Poster Session (Board #302), Sun, 8:00 AM-11:45 AM**

**Nervous system sequelae of chemotherapy treatment: Associations and proposed mechanisms.** *Presenting Author: Kelly N. H. Nudelman, IUPUI, Indianapolis, IN*

**Background:** Breast cancer treatment with chemotherapy often results in neurotoxic sequelae including chemotherapy-induced peripheral neuropathy (CIPN) and cognitive dysfunction. Although CIPN and cognitive dysfunction are often viewed as separate phenomena, we hypothesized that these effects may be related. **Methods:** Breast cancer patients treated with (Ctx+, n=27) and without (Ctx-, n=26) chemotherapy and healthy controls (HC, n=26) were assayed post-surgery, pre-treatment and one month post-treatment. All but one Ctx+ treatment included paclitaxel or docetaxel. Peripheral neuropathy symptom severity (PNS) was evaluated with the sum of the self-reported FACT/GOG-Ntx 11-item scale, cerebral gray matter density (GMD) and perfusion were assessed using MRI, and cognitive complaints, depression, and fatigue were assessed with the Multiple Ability Self-Report Questionnaire (MASQ), the Center for Epidemiologic Studies Depression scale, and the Fatigue Symptom Inventory. **Results:** Chemotherapy treatment was associated with increased PNS and cognitive complaints ($p<0.01$), which remained significant after adjusting for fatigue and depression. PNS was associated with increased cerebral perfusion in the left anterior cingulate (LAC) gyrus, a region associated with pain processing. Interestingly, a previously published Ctx+ frontal GMD decrease in this cohort was correlated with the LAC perfusion change ($p<0.01$) and PNS change ($p<0.01$). Individuals with GMD decrease showed lower LAC perfusion and fewer PNS, while increased PNS were correlated with increased cognitive complaints ($p<0.05$) and depression and fatigue (both $p<0.01$). **Conclusions:** This is the first study to identify cerebral perfusion change associated with peripheral neuropathy symptoms in a breast cancer cohort. Our findings suggest that chemotherapy-associated gray matter decrease may also reduce LAC perfusion and associated pain perception. This finding and the observed relationships between CIPN symptoms, depression, fatigue, and cognitive complaints highlight the importance of further research on the causal pathways underlying these effects, and of developing therapies targeting this symptom cluster.

**9653 General Poster Session (Board #303), Sun, 8:00 AM-11:45 AM**

**Prechemotherapy cognitive function in 362 breast cancer (BC) patients and 362 age-paired controls without cancer: A nationwide longitudinal trial conducted through the University of Rochester Cancer Center (URCC) Community Clinical Oncology Program (CCOP) Research Base (RB).** *Presenting Author: Michelle Christine Janelsins, University of Rochester Medical Center, Rochester, NY*

**Background:** Cancer-related cognitive impairment (CRCI) impairs quality of life. 15% of patients experience CRCI prior to chemotherapy (CT), 75% during CT and 35% after CT. Large studies are needed to confirm these results. **Methods:** We are conducting a large, nationwide, longitudinal observational study through the URCC CCOP RB and 23 CCOPs to elucidate the natural history of CRCI among BC patients receiving CT compared to similarly aged women without cancer. BC participant eligibility: 1) stage I-IIIc , 2) CT naïve, 3) ≥21 years, 4) no central nervous system disease, 5) scheduled to receive anthracycline or non-anthracycline-based CT with no concurrent radiation. Controls meet eligibility #2-4. CRCI is assessed within one week (wk) prior to CT, within 4 wks after CT and 6 months post-CT. Controls are assessed at the same time intervals. CRCI domains (i.e., memory, attention, processing speed, executive function) are assessed via patient report (Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog) and Behavior Rating Inventory of Executive Function (BRIEF)), and objective measures (computerized neuropsychological battery (CANTAB) and paper-based Trail Making Test (TMT-A)). **Results:** 362 BC patients were recruited (85% white, mean age=53) and paired with 362 controls.Adjusting for age, education, and WRAT-4 reading score (cognitive reserve), at pre-chemotherapy, BC patients performed less well than controls on FACT-Cog (Effect Size (ES)=0.4), BRIEF (ES=0.2;all $p<0.05$), CANTAB processing speed/attention and motor task tests (ES=0.2;all $p<0.05$), and the TMT-A (ES=0.2;$p<0.07$). There was no difference in these measures in BC patients scheduled to receive anthracycline-based CT vs. non-anthracycline-based CT. **Conclusions:** BC patients demonstrate poorer processing speed, attention, motor control, and perceived cognitive function prior to CT compared to women without cancer, suggesting it is clinically important to assess for CRCI before CT. NCI Grants: K07CA168886, U10CA037420. Clinical trial information: NCT01382082.

**9654 General Poster Session (Board #304), Sun, 8:00 AM-11:45 AM**

**Use, misuse, and overuse of white cell growth factors (GF) in community oncology practices in southeastern United States.** *Presenting Author: William J. Hrushesky, Oncology Analytics, Inc., Plantation, FL*

**Background:** Level 1 data, multiple national guidelines, and ASCO Choosing Wisely policy recommend that GFs be employed if the risk of febrile neutropenia (FN) exceeds 20%. Virtually every common chemotherapy regimen has been documented to put cancer patients at low (<10%) or intermediate (10-20%) or high risk (>20%) for FN. Oncology analytics (OA) screens all requests for GFs. If low risk regimens are employed, their use is challenged serially by: 1. electronically in initial request interaction, 2. informational fax bearing all relevant data, and 3. oncologist-to-oncologist peer review. We hypothesize that these agents are being overused in the community oncology setting among 2,800 practices we advise in the southeastern united states. **Methods:** During the 10 months between April 2013 and Jan 2014, we reviewed 1,700 requests for GFs: 894 for pegfilgrastim, 725 for filgrastim, and 62 for other GFs. **Results:** 355 of the 890 pegfilgrastim requests (40%) were made for patients receiving low-risk chemotherapy regimens; 455 (50%) intermediate risk, and 91 (10%) high risk regimens. Record reviews, educational faxes, and peer-to-peer reviews were serially instituted for all GF requests for low risk regimens. 113 (12%) of these were withdrawn or rescinded resulting in diminished cost of 2.1 million dollars in those 10 months. **Conclusions:** This ongoing pre-approval process results in more guidelines-compliant cancer care and diminishes waste.

**TPS9655 General Poster Session (Board #305A), Sun, 8:00 AM-11:45 AM**

**Single-center, prospective pilot study to evaluate advance care planning implementing the 3 Questions and 3 Elements to identify an informed health care proxy in an outpatient oncology palliative care clinic.** *Presenting Author: Eric Roeland, University of California, San Diego, Moores Cancer Center, La Jolla, CA*

**Background**: Despite the growing cancer therapeutics arsenal, the vast majority of advanced cancer patients will die. Consequently, understanding and communicating their end-of-life (EoL) care wishes is critical. Advance care planning (ACP) should occur in the non-emergent outpatient setting. However, given social and pragmatic challenges, these discussions are delayed until moments of crisis. In order to increase the probability that patients receive care consistent with their EoL wishes, health care providers require simple, effective, and efficient tools to initiate and complete meaningful ACP discussions. **Methods**: This is a single center, prospective, pilot study sponsored by the American Cancer Society to evaluate the average identification rate of an informed health care proxy by advanced cancer patients implementing a novel ACP tool in an academic oncology palliative care clinic over one year. Eligible subjects must have a known cancer diagnosis and a prognosis of less than 1 year. Consented subjects engage in a 1-hour ACP discussion initiated by the *3 Questions* which include: 1) the identification of potential health care proxy; 2) proxy's awareness about being designated as a health care proxy; 3) proxy's understanding of patient's wishes. The *3 Elements* define a meaningful ACP discussion and include: 1) the patient's personal definition of quality of life (QoL) 2) a specific plan if that personal QoL definition is not achieved 3) the patient's preferred location of death. Details of this ACP conversation are documented in the electronic medical record. The primary aim is to determine the proportion of advanced cancer patients who identify a health care proxy implementing the *3 Questions* and *3 Elements* versus a historical standard. Secondary aims include: 1) to determine the location of death of the subject 2) to determine if the subject's desired code status was honored. 3) to evaluate the health care proxy's satisfaction in understanding subject's wishes for EoL care after the subject's death.

**TPS9656 General Poster Session (Board #305B), Sun, 8:00 AM-11:45 AM**

**Quality of life (QOL) measurement in patients receiving neoadjuvant therapy in the I-SPY 2 trial.** *Presenting Author: Michael Hwang, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

**Background:** The I-SPY 2 TRIAL is a phase 2 trial investigating novel, targeted therapies in combination with standard chemotherapy in the neoadjuvant setting for stage 2 and 3 breast cancer. While the toxicities of chemotherapy alone are well characterized, introduction of experimental agents may significantly alter the toxicity profiles of these regimens, and could lead to short-term and long-term changes in QOL for patients. During the screening process, the trial informs patients of having either a tumor with a "low risk" (not eligible for the I-SPY 2 treatment phase) vs. "high risk" (eligible) profile, allowing the opportunity to study the impact on QOL of providing prognostic information prior to and throughout treatment. **Methods:** Patients who consent to the screening phase of I-SPY 2 are asked to participate in the QOL sub study. Patients complete a QOL questionnaire at baseline prior to treatment. For those patients who consent to the treatment phase of I-SPY 2, additional questionnaires are completed on the first day of treatment, after 12 weeks, prior to surgery, and then 1, 6, 12 and 24 months post-surgery. Questionnaires include established QOL measurements: the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and Breast 23 (EORTC QLQ BR23), the National Comprehensive Cancer Network Distress Thermometer and Fear of Recurrence scale, and items from the NCI Patient-Reported Outcomes Measurement Information System (PROMIS) in domains of physical, psychological, cognitive, and sexual function. The study will evaluate changes in QOL, distress, and fear of recurrence prior to surgery to two years post-operatively. The study will also allow comparison and validation of QOL measurement using PROMIS, a publicly available Web-based resource supported by the National Cancer Institute, to legacy EORTC QOL instruments. Since initiation of the QOL sub study, 520 patients have participated in the screening phase, with 311 patients initiating I-SPY 2 study treatment. With the accrual goal of 800 patients to the main I-SPY 2 TRIAL, up to 585 may be accrued to the prospective portion of the QOL sub study. Clinical trial information: NCT01042379.

**TPS9657 General Poster Session (Board #306A), Sun, 8:00 AM-11:45 AM**

**POWER-remote: A randomized study evaluating the effect of a remote-based weight loss program on biomarkers in women with early-stage breast cancer.** *Presenting Author: Cesar Augusto Santa-Maria, The Johns Hopkins University School of Medicine and The Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD*

**Background:** The majority of women diagnosed with breast cancer are overweight or obese, and gain weight with treatment, leading to inferior survival outcomes. The Practice-based Opportunities for Weight Reduction (POWER) investigators reported that, in an obese population with cardiovascular risk factors, a scalable remote-based weight loss intervention was equally effective to an in-person intervention (Appel NEJM 2011). We have adapted the remote intervention for breast cancer survivors. **Methods:** Randomized phase II single-blinded trial. Participants are women with stage 0-III breast cancer and a BMI $\geq$ 25 who have completed local therapy and adjuvant chemotherapy. Objectives:1.) Compare the proportion of participants who lose $\geq$5% of their baseline body weight after 6 and 12 months in the POWER-remote and self-directed (control) arms; 2.) Investigate the effects of weight loss on a panel of biomarkers relevant to obesity, inflammation, and breast cancer risk (insulin, IGF-1, hsCRP, IL-1, IL-6, TNF-$\alpha$, leptin, adiponectin, estradiol, and telomere length); 3.) Investigate the effects of weight loss on patient-reported outcomes (PROs), particularly physical function. Statistical Approach: We hypothesize that the proportion of women who experience $\geq$5% weight loss after 6 months will be greater in POWER-remote and will be similar to the results of the original POWER study (38.2% and 18.8% $\geq$5% weight loss in the remote and control groups, respectively). An interim futility analysis is planned after the first 80 patients are evaluable for the primary endpoint. The final analysis will conclude a significant benefit from POWER-remote if the one-sided p value is greater than 0.10 by Fisher's exact test. Changes in biomarkers and PROs from baseline to 6 months will be calculated and tested for differences by treatment arm and by response. We have enrolled 16 of the planned 200 patients. Future Directions: Results will be used to implement clinically based weight loss programs, and biomarker data will improve our understanding of energy dynamics in breast cancer survivors, leading to future studies investigating weight loss for primary and secondary breast cancer prevention. Clinical trial information: NCT01871116.

**TPS9658 General Poster Session (Board #306B), Sun, 8:00 AM-11:45 AM**

**Prevalence of hypogonadism in previously treated germ cell tumor patients.** *Presenting Author: Trent James Miller, Indiana University, Indianapolis, IN*

**Background:** Germ cell tumors (GCTs) represent a model for a curable malignancy. Most treated patients will live active lives. Patients treated with platinum combination chemotherapy may be left with clinically significant hypogonadism, causing signs and symptoms of erectile dysfunction, muscle weakness, insomnia, depression, increased sweats, and a greater risk for developing metabolic syndrome with resultant cardiovascular disease. It is thus important to identify the prevalence of hypogonadism in survivors of GCT, both in patient populations treated with chemotherapy as well as chemo-naïve patients. We will identify the incidence of hypogonadism and compare patients who have had chemotherapy versus those treated with surgery alone (orchiectomy +/- retroperitoneal lymph node dissection). We will correlate serum testosterone levels with physical & psychological quality of life (QoL) including symptoms of hypogonadism. We will assess these variables over time to determine if symptoms change relative to the time from treatment. Finally, we will develop a database of clinical information for future use. **Methods:** Patients who are at least 8 wks post-treatment with chemotherapy (Group 1) or at least 8 wks post-orchiectomy and/or other surgery for GCT (Group 2), who are between 18 and 50 yrs of age, and who are not receiving supplemental testosterone are eligible for enrollment. 100 patients will be enrolled in each group. Study participants will have a serum total testosterone, fasting lipid panel, serum human chorionic gonadotropin (hCG), and alpha-fetoprotein (AFP) measured at baseline. Testosterone, hCG, and AFP are repeated at 3, 6, and 12 mos. Supplemental testosterone may be prescribed per standard of care. Cancer diagnosis and treatment variables such as stage, type of surgery, chemotherapy, radiation treatment, hormonal treatment, age, and length of time since diagnosis/treatment will be obtained from medical records. Patients will complete a QoL questionnaire composed of items from the Aging Males' Symptoms (AMS) scale and the Patient Reported Outcomes Management Information System (PROMIS) at baseline, which is repeated at 3 and 6 mos. At the time of submission, there are 75 patients enrolled in Group 1, and 34 in Group 2.

**TPS9659 General Poster Session (Board #307A), Sun, 8:00 AM-11:45 AM**

**Phase II trial of inflammation markers and symptom control in metastatic lung cancer: Insync.** *Presenting Author: Chipman Robert Geoffrey Stroud, Leo Jenkins Cancer Center, Brody School of Medicine at East Carolina University, Greenville, NC*

**Background:** Palliative care with focused symptom management and control can improve quality of life outcomes and survival in metastatic non-small cell lung cancer (NSCLC) beyond standard chemotherapy. (Temel et al NEJM 2010) Many symptoms in cancer are related to inflammation. (Laird et al The Oncologist 2013) Smoldering inflammation in the tumor microenvironment is now a recognized 7$^{th}$ hallmark of cancer (Colotta et al Carcinogenesis 2009) as it regulates and escalates cancer invasion, angiogenesis, immune surveillance escape and the metastatic cascade. (Balkwill and Mantovani Lancet 2001) The Veristrat protein test is dominated by inflammatory proteins and is prognostic and predictive in metastatic NSCLC after treatment with platinum based chemotherapy. (Gregorc et al ASCO 2013 #LBA8005) C-reactive protein (CRP) is also a well studied inflammatory marker in cancer. The hypothesis of this study is that the remarkable survival benefit in the Temel study is mediated by reduced inflammation with symptom improvement and control. **Methods:** In this study, patients with metastatic NSCLC will be seen in consultation by our institutional Symptom Management Service PharmD upon presentation to our Thoracic Oncology Program and subsequently managed concurrently with the treating medical oncologist. Inflammatory protein marker studies with Versitrat and CRP will be evaluated at baseline, monitored at 4 and 10 months and correlated with ongoing symptom improvement and a quality of life (FACT-L) study. The primary objective is reduced inflammation markers with Veristrat 'poor' changing to Veristrat 'good' and a decreasing CRP. The secondary objectives are overall survival, quality of life FACT-L improvement and correlation with disease status.

**TPS9660 General Poster Session (Board #307B), Sun, 8:00 AM-11:45 AM**

**Scalp cooling alopecia prevention trial (SCALP).** *Presenting Author: Julie R. Nangia, Baylor College of Medicine, Houston, TX*

**Background:** Adjuvant chemotherapy treats micro-metastatic disease and decreases the risk of breast cancer recurrence. However, it may be associated with distressing adverse effects, including alopecia. Women with breast cancer rate chemotherapy-induced alopecia as one of the most severe, troublesome, and distressing side effects of chemotherapy. In many countries, scalp cooling has been introduced to prevent or reduce chemotherapy-induced alopecia. Scalp cooling causes cutaneous vasoconstriction, which reduces blood flow to the hair follicles during peak plasma concentrations of the chemotherapeutic agents and therefore reduces cellular uptake of these agents. It also results in reduced biochemical activity, which makes hair follicles less susceptible to the damage of the chemotherapy agents. Success rates are variable, but scalp cooling appears to be effective in preventing chemotherapy-induced alopecia especially in more recent studies. **Methods:** We are conducting a multi-center randomized non-blinded controlled prospective trial to demonstrate the safety and efficacy of the Orbis Paxman Hair Loss Prevention System in reducing the incidence of chemotherapy-induced alopecia. Women with stage I-II breast cancer will receive neoadjuvant or adjuvant anthracycline- or taxane-based chemotherapy, for at least four cycles are eligible. Participants will be randomized in a 2:1 ratio to scalp-cooling and will undergo scalp-cooling using the Orbis Paxman Hair Loss Prevention System prior to, during and after each chemotherapy administration. The primary efficacy endpoints are hair preservation, defined as CTCAE v4 alopecia $<2$, and device safety. Two hundred and thirty five (235) patients will be enrolled which will provide 85% power to detect a 20% difference in hair preservation, 15% in control group and 35% in scalp-cooling group . Secondary endpoints include: wig/scarf use and quality of life assessed by the EORTC QLQ-30, HADS and BIS. Study participants will be followed for 5 years post-study for time to first recurrence, overall survival, site of first recurrence, and incidence of isolated scalp metastasis. Clinical trial information: NCT01986140.

**TPS9661 General Poster Session (Board #308A), Sun, 8:00 AM-11:45 AM**

**SELECT-D: Anticoagulation therapy in selected cancer patients at risk of recurrence of venous thromboembolism.** *Presenting Author: Annie Young, Warwick Clinical Trials Unit, University of Warwick, Coventry, United Kingdom*

**Background:** Venous thromboembolism (VTE) in cancer patients is an important and increasingly frequent clinical problem. The impact of VTE on cancer patients can be considerable. Targeted selection by identifying patients with clinically relevant recurrent VTE may have wider health economic benefits whilst reducing patient risk through over-treatment. In the UK, dalteparin is the licensed anticoagulant for the extended treatment and prevention of recurrence of VTE in cancer patients and thus, the gold standard. Rivaroxaban is a highly selective direct Factor Xa inhibitor with oral bioavailability. **Methods:** Select-d is a prospective, randomised, open label, multicentre pilot trial comparing dalteparin (200 IU/kg daily subcutaneously for 1 month and 150 IU/kg months 2-6); and rivaroxaban (15 mg orally twice daily for 3 weeks and 20 mg once daily for 6 months in total) for cancer patients with VTE, with a second placebo-controlled randomisation (rivaroxaban vs placebo) comparing the duration of therapy (6 vs 12 months) in residual vein thrombosis (RVT) positive patients. 70% of patients are estimated to be RVT positive after initial treatment. 530 patients are being recruited toprovide reliable estimates of the primary outcome (VTE recurrence rates) to within the 95% confidence interval of 8% assuming VTE rates are 10% at six months. Secondary objectives include safety, acceptability, biomarker identification and health economics. The trial will recruit for two years with a minimum of one year follow up. Results will support optimal treatment for this key patient group. The independent TSC and DSMC fully support this important trial. At least 40 UK centres will participate in the trial. As of 1$^{st}$February 2014, 23 patients have been recruited from 24 open UK sites. Select-d is amongst the first randomised trials of the new oral anticoagulants in patients with cancer, following recent recommendations from the UK National Institute of Health and Care Excellence.(http://guidance.nice.org.uk/CG144, http://guidance-.nice.org.uk/TA261, http://publications.nice.org.uk/quality-standard-for-diagnosis-and-management-of-venous-thromboembolic-diseases-qs29). Clinical trial information: 86712308.

**TPS9662 General Poster Session (Board #308B), Sun, 8:00 AM-11:45 AM**

**A randomized placebo-controlled phase III study of duloxetine for treatment of aromatase inhibitor (AI)-associated musculoskeletal symptoms in women with early-stage breast cancer: SWOG S1202.** *Presenting Author: N. Lynn Henry, University of Michigan Medical Center, Ann Arbor, MI*

**Background:** Treatment with an aromatase inhibitor (AI) for 5 years improves outcomes for hormone receptor (HR)-positive breast cancer. However, up to 30% of patients discontinue treatment because of AI-associated musculoskeletal symptoms (AIMSS). Preliminary data suggest that treatment with the serotonin norepinephrine reuptake inhibitor duloxetine for 8 weeks decreases AI-associated pain. We are therefore conducting this placebo-controlled, randomized phase III trial of duloxetine for treatment of AIMSS. Specific Aims: To assess if duloxetine as compared to placebo causes a reduction in average pain in women with AIMSS at 12 weeks as measured by the Brief Pain Inventory (BPI). Additional measures include WOMAC, M-SACRAH, FACT-ES, PHQ-9, global rating of change, candidate gene variants, and inflammatory cytokines. Eligibility Criteria: Patients must have stage I-III HR-positive breast cancer and have undergone definitive breast cancer surgery. Patients must be postmenopausal, currently taking an AI (anastrozole, letrozole, or exemestane) for at least 21 days and not more than 36 months prior to registration, and plan to continue for at least 180 days after registration. Patients must have an average joint pain score of at least 4 out of 10 on the BPI, and pain must have started or increased after initiation of AI. Patients must not have a contraindication to duloxetine and must not require antidepressant therapy during study participation. **Methods:** Patients will be randomized to duloxetine 60 mg daily or matching placebo daily for 12 weeks, including a 7 day run-in period of 30 mg daily. Assessments will be performed at baseline, 2, 6, 12, and 24 weeks. Statistical Methods:We stipulate an alpha=0.05 two-sided test, with an estimated 5% non-adherence, 15% dropout, and 10% contamination rate at 12 weeks after randomization. For a one point difference in average joint pain and a 2.3 point SD at 12 weeks, 270 eligible patients would be required for 80% power under a two-arm normal design. To allow for an ineligibility rate of 8%, 294 total patients will be enrolled. The study was activated in May 2013 and is available on the CTSU. Clinical trial information: NCT01598298.

**TPS9663 General Poster Session (Board #309A), Sun, 8:00 AM-11:45 AM**

**Incidence of hypersensitivity reactions (HSR) in patients receiving reduced doses of dexamethasone as prophylaxis for carboplatin and paclitaxel in gynecologic malignancies.** *Presenting Author: Justin Liauw, Maine Medical Center, Portland, ME*

**Background:** Paclitaxel has been used in combination with a platinum agent as part of standard of care for the treatment of gynecologic malignancies. A major clinical concern with the use of paclitaxel is the potential for hypersensitivity reactions (HSRs). Dexamethasone is given in combination with other premedications to decrease the incidence of HSRs. The manufacturer-recommended premedication regimen includes dexamethasone 20 mg orally, taken 12 and 6 hours prior to the paclitaxel infusion. The cumulative dose of dexamethasone may be excessive and may decrease patient's quality of life (QOL). Several studies have omitted oral doses of dexamethasone and used a single 20mg dose of intravenous dexamethasone. These trials suggest that reduced doses of dexamethasone can result in a similar rate of HSRs compared with manufacturer-recommended premedication doses. Our study looks to eliminate the oral dexamethasone premedications, like the aforementioned studies, utilizing a single dose of 20 mg of intravenous dexamethasone. **Methods:** This is a prospective, single arm, interventional, feasibility study. Patients involved in this study will include women with a new diagnosis of ovarian or endometrial cancer that have been selected to receive 3-6 cycles of paclitaxel every 3 weeks with or without carboplatin. The primary endpoint is to document the incidence of paclitaxel HSRs of all grades and HSRs grades 3 and above. Grading of HSRs will be done utilizing the NCI Common Toxicity Criteria for Adverse Events (CTCAE) tool, version 3.0. QOL will be measured as a secondary endpoint using the FACT-O questionnaire, which will be administered prior to beginning paclitaxel chemotherapy, and at the end of paclitaxel chemotherapy. All premedication, excluding dexamethasone, will be chosen and dosed according to standard of care. The results of this study will be analyzed with descriptive statistics.

**TPS9664 General Poster Session (Board #309B), Sun, 8:00 AM-11:45 AM**

**Phase III design for a trial of single-dose fosaprepitant (FA) in preventing chemotherapy-induced nausea and vomiting (CINV) associated with moderately emetogenic chemotherapy (MEC).** *Presenting Author: Stephen Noga, Weinberg Cancer Institute, Baltimore, MD*

**Background:** CINV is a common side effect that may occur in acute (0-24 hours [h]) and delayed (25-120 h) post-chemotherapy phases. Aprepitant is a potent and selective oral NK1 receptor antagonist (RA) indicated for prevention of acute and delayed CINV associated with highly emetogenic chemotherapy (HEC) and MEC using a 3-day regimen combined with a 5HT3 RA and corticosteroid. FA, a water-soluble prodrug rapidly converted to aprepitant after intravenous (IV) administration, is approved as a single dose for HEC-related CINV. To further study FA with MEC, this study will evaluate the efficacy and safety of a single IV dose of 150mg FA given with a 5-HT3 RA and corticosteroid vs a 5-HT3 RA and corticosteroid alone in preventing MEC-associated CINV (NCT01594749). **Methods:** This is a global, phase III, randomized, double-blind, parallel-group study in 990 subjects ≥18 years of age naïve to HEC and MEC scheduled to receive an IV dose of MEC on treatment Day 1. Other moderate and low emetogenic chemotherapy agents may be added to the MEC through Day 3; there are no restrictions on the use of minimally emetogenic agents. Subjects are randomly assigned 1:1 to a control or treatment group. Control group consists of 8mg ondansetron and 20mg dexamethasone on Day 1, followed by 8mg ondansetron PO (by mouth) every 12 h on Days 2 and 3. The treatment group adds 150mg IV FA to the same dose of ondansetron PO and dose-adjusted dexamethasone (12mg PO) before the first dose of MEC on Day 1, followed by 8mg ondansetron PO 8 h after the first dose and no additional antiemetic beyond Day 1. Primary objectives will evaluate the proportion of subjects with a complete response (CR: no vomiting and no rescue medication use) during the delayed phase and FA safety/tolerability. Secondary objectives include CR in acute and overall (0-120 h post MEC) phases. Exploratory objectives further evaluate vomiting, nausea, rescue use, and impact on daily life. Treatment comparisons, stratified by gender, will include a formal test for superiority for the primary efficacy analysis. Primary and secondary efficacy analyses will be tested at a 2-sided significance level of 0.05. Clinical trial information: NCT01594749.

**10000 Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

**Real-time central review: A report of the first 3,000 patients enrolled on the Children's Oncology Group Renal Tumor Biology and Risk Stratification protocol AREN03B2.** *Presenting Author: Elizabeth Anne Mullen, Dana-Farber Cancer Center Institute/Boston Children's Cancer and Blood Disorders Center, Boston, MA*

**Background:** The Children's Oncology Group (COG) Renal Tumor (RT) Biology and Risk Stratification Protocol incorporates real-time central review to direct risk stratification and enrollment on COG therapeutic studies. We assessed the feasibility of the real-time central review process and its impact on the accuracy of risk stratification. **Methods:** 3,000 patients were enrolled on AREN03B2 between 2/2006 and 1/2012, with submissions from 214 COG institutions. Eligible diagnoses included any RT and extra-renal Wilms tumor or non-CNS rhabdoid tumor. Enrollment on AREN03B2 was required to enroll on a RT treatment study. Submission of pathology slides, radiology images, operative reports, and tumor and blood for analysis was required within 7 days of surgery to meet enrollment deadlines stipulated by the therapeutic studies. Central pathology review for histology and stage, radiology review for presence of bilateral lesions and pulmonary metastases, and surgical review for operative stage were completed electronically by a panel of expert reviewers. An initial risk assignment (IRA) was made by the study chairs based on the multidisciplinary central reviews. **Results:** 2,913/3,000 met all eligibility and submission requirements. The median time from enrollment to IRA was 8 days. 1,205 discrepancies between central and institutional review potentially impacting IRAs were observed; including differences in initial histology in 253 unilateral and 69 bilateral tumors, pathologic staging of 294 tumors, diagnostic imaging of 92 bilateral cases and 112 cases of pulmonary metastases, and the surgical review of 244 cases of rupture and 141 instances of node sampling. **Conclusions:** Real time central review is feasible in a large multi-center study. Discrepancies between local and central risk stratification were identified in a substantial number of participants. Communication of these findings in real time supported increased accuracy of enrollment on appropriate clinical trials and strengthened the comprehensive annotation of a rich RT biorepository. Expansion of this process to other pediatric tumor registry protocols should be strongly considered.

**10001 Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

**Treatment of stage IV favorable histology Wilms tumor with incomplete lung metastasis response after chemotherapy: A report from Children's Oncology Group study AREN0533.** *Presenting Author: David B. Dix, British Columbia Childrens Hospital, Vancouver, BC, Canada*

**Background:** National Wilms Tumor Study-5 showed that patients with stage IV Favorable Histology Wilms Tumor (FHWT) had 4-year event-free survival (EFS) and overall survival (OS) estimates of 75% and 86% when treated with Regimen DD4A (vincristine/dactinomycin/doxorubicin) and whole lung irradiation (XRT). To decrease relapse rates while subjecting fewer patients to XRT, the AREN0533 study evaluated whether therapy can be tailored based on the completeness of lung metastasis response after 6 weeks of DD4A chemotherapy. Patients showing complete resolution of lung metastases at week 6 continued DD4A without lung XRT. Patients with incomplete lung metastasis response ("slow incomplete response"=SIR) continued DD4A with the addition of cyclophosphamide/etoposide (Regimen M) and lung XRT. Interim analysis for the SIR group is the subject of this report. **Methods:** Patients were enrolled between February 2007 and February 2013 after undergoing risk assignment on the AREN03B2 Renal Tumor Biology and Classification study. The completeness of lung metastasis response was determined by central radiology review after 6 weeks of chemotherapy. The null hypothesis was that 4-year EFS for SIR when treated with DD4A therapy is 75%. The study was designed to detect a decrease in the risk of failure corresponding to 4-year EFS of 84%. **Results:** Among 391 patients enrolled, 279 had isolated lung metastases, of which 163 (58%) had SIR. At interim analysis in June 2013, the number of expected events under the null hypothesis was 38.6, yet only 15 events were observed. This difference was sufficient to reject the null hypothesis and conclude that Regimen M is superior to the historical standard ($p=0.0001$, Woolson 1-sample log rank test). The 3-year EFS and OS estimates for SIR patients were 88% (95% CI: 81%, 93%) and 92% (95% CI: 86%, 96%). Grade 3 or higher hematological toxicity was the most common toxicity observed with Regimen M, affecting 60% of patients. There were no unexpected toxicities. **Conclusions:** Patients with stage IV FHWT with SIR of lung metastases showed superior EFS with the addition of cyclophosphamide/etoposide compared to the historical standard. Clinical trial information: NCT00379340.

**10002 Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

**Outcome of localized blastemal-type nephroblastoma patients treated according to intensified treatment in the SIOP 2001 protocol: A report of the SIOP-RTSG.** *Presenting Author: Marry M van den Heuvel-Eibrink, Department of Pediatric Hematology and Oncology, Erasmus MC - Sophia Children's Hospital, Rotterdam, Netherlands*

**Background:** From previous pre-surgery chemotherapy based SIOP protocols, blastemal type Wilms tumor (BT-WT) has been identified as a poor prognostic subgroup. Therefore in SIOP 2001, post-operative treatment for BT-WT was prolonged and intensified (VCR/Act/Dox in stage I, VP16/Carbo/Cyclo/Dox in stage II-IV) aiming to improve survival. Here, we present characteristics and outcome of BT-WT patients treated on intensified regimen in SIOP 2001. **Methods:** Response and survival analysis of unilateral BT-WT (n = 238) patients treated from 2001-2012 (SIOP 2001) were compared with SIOP 93-01 (n = 113). **Results:** In SIOP 93-01 and SIOP 2001 trials, among 4061 unilateral non-metastatic Wilms tumor patients registered, 351 (8.6%) were BT-WT. Median age at diagnosis was 43 months (IQR 24-68). Stages were: I (n = 140, 40%), II (n = 106, 30%), III (n = 105, 30%). Pre-surgery chemotherapy reduced tumor volume from median 359 ml (IQR 174-611) to 123 ml (IQR 41-291). BT-WT were older, higher staged and showed less markedly volume decrease after pre-surgery chemotherapy. Univariate analysis of localised unilateral BT-WT cases in SIOP 2001 showed a 5-year event-free survival (EFS) of 80% (95% CI 75-86%) (67% in SIOP 93-01 (95% CI 59-76; p = 0.006)) and an overall survival (OS) of 88% (95% CI 83-93) (84% (95% CI 77-91; p = 0.4) in SIOP 93-01). Treatment protocol, volume at surgery, age and stage were prognostic variables for EFS in uni- and multivariate Cox regression analysis. Independent prognosticators for OS were stage, age and tumor volume at surgery. The most significant benefit of intensified treatment was found in Stage I BT-WT with 96% EFS in SIOP 2001 (OS 100%), compared to 71% EFS in SIOP 93-01 (OS 96%). **Conclusions:** BT-WT, defined after pre-operative chemotherapy, benefits from more intensive chemotherapy as reflected by reduction of relapse risk. However, OS mainly seems to be enhanced in stage I BT-WT patients underscoring the value of doxorubicin for relapse prevention in these tumors.

**10003 Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

**Randomized phase II trial of bevacizumab and temsirolimus in combination with vinorelbine (V) and cyclophosphamide (C) for first relapse/disease progression of rhabdomyosarcoma (RMS): A report from the Children's Oncology Group (COG).** *Presenting Author: Leo Mascarenhas, Children's Hospital Los Angeles, Saban Research Insititute, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA*

**Background:** Patients with RMS have a poor prognosis at first relapse/disease progression. VC has activity in RMS and preclinical data supports the use of bevacizumab and temsirolimus in RMS. **Methods:** Patients with biopsy proven RMS, $<$ 30 years of age and unfavorable prognosis at first relapse/progression were eligible. Entry criteria were: life expectancy $>$ 8 weeks, performance status $<$ 2, adequate organ function and written informed consent. Patients were randomized between two regimens administered every 3 weeks for a maximum of 12 cycles: Regimen A- V 25 mg/m$^2$ intravenously (IV) days 1 & 8, C 1.2 gms/m$^2$ IV day 1, bevacizumab 15 mg/Kg IV day 1; b) Regimen B- VC identical to regimen A, temsirolimus 15 mg/m$^2$ IV days 1, 8 & 15. Primary endpoint was event free survival (EFS) at 6 months. Disease response at week 6 was assessed using RECIST. The study had a phase 2 screening design and was powered to detect a 15% difference in EFS between the two regimens ($\alpha=0.2$, 1-$\beta=0.8$, 2-sided test). Interim analysis was planned when 30%, 50% and 75% of the expected events occurred. **Results:** 87 of the 100 planned patients were enrolled when the trial was closed following the second interim analysis after 46 events occurred in 68 patients with sufficient follow-up. The O'Brien Flemming boundary at this analysis corresponded to a 2-sided p value of 0.0582 with an observed 2-sided p value of 0.0031 favoring the regimen with temsirolimus. The 6 month EFS for regimen A was 50% (95% CI 32%, 66%) and for regimen B was 65% (95% CI 44%, 79%). The response rate observed for regimens A and B were 32% and 47% respectively ($p=0.22$). The rate of progressive disease on regimen A was 26% compared with 9% on regimen B. Treatment was well tolerated. No unexpected toxicities were observed. Febrile neutropenia was the most common adverse event on both regimens. Oral mucositis and hypertriglyceridemia were noted only on regimen B. **Conclusions:** Patients randomized to VC+ temsirolimus had a superior EFS compared to VC+ bevacizumab. Temsirolimus has been selected by COG for further investigation in newly diagnosed patients with intermediate risk RMS. Clinical trial information: NCT01222715.

**10004 Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

**Vincristine, dactinomycin, cyclophosphamide (VAC) versus VAC/V plus irinotecan (VI) for intermediate-risk rhabdomyosarcoma (IRRMS): A report from the Children's Oncology Group Soft Tissue Sarcoma Committee.** *Presenting Author: Douglas S. Hawkins, Seattle Children's Hospital, Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA*

**Background:** The long-term event free survival (EFS) for IRRMS is 65%. Since VI had significant activity in metastatic and recurrent RMS, we tested whether adding VI to VAC would improve EFS for IRRMS. **Methods:** Patients (pts) with alveolar (A)RMS or incompletely resected (Group III) embryonal (E)RMS arising in an unfavorable primary site (Stage 2/3), both without distant metastases, < 50 years, and adequate organ function were eligible to be randomized to 42 weeks of VAC (V=1.5 mg/m$^2$, A=0.045 mg/kg, C=1.2 g/m$^2$ every 3 weeks) vs VAC/VI (I=50 mg/m$^2$/day x 5 days) intravenously; doses were adjusted for children < 3 years; radiation therapy (36-50.4 Gy) was started at week 4, with individualized local control for children < 2 years allowed. The primary study endpoint was EFS. The study was designed with 80% power (5% 1-sided alpha level) to detect an increase in 5 yr EFS from 65% to 76%, a relative risk of 0.64. **Results:** 481 pts were entered between 12/2006-12/2012, with 461 confirmed eligible. Clinical features included ERMS 53%, ARMS 43%; age < 1 year 6%, 1-9 years 62%, 10+ years 32%; Group III 85%; Stage 3 61%. The most common primary tumor sites were parameningeal (44%), extremity (13%), and bladder/prostate (13%). With median follow up of 2.46 years in surviving pts, EFS and overall survival (OS) with 95% confidence intervals (CI) were similar overall and by histologic subtypes (Table). Grade 3/4 febrile neutropenia, anemia, and thrombocytopenia were less common with VAC/VI, particularly after the first 15 weeks of therapy, while diarrhea was more common with VAC/VI. **Conclusions:** The addition of VI to VAC did not significantly improve EFS or OS compared to VAC alone for IRRMS. The lower rate of hematologic toxicity and cumulative C dose with VAC/VI (8.4 g/m$^2$ vs 16.8 g/m$^2$) support the use of VAC/VI as the standard arm in future IRRMS trials. Clinical trial information: NCT00354835.

| Treatment | n | 2-year EFS (95% CI) | 2-year OS (95% CI) |
|---|---|---|---|
| VAC | 227 | 64% (56%, 70%) | 84% (78%, 89%) |
| VAC/VI | 234 | 64% (56%, 70%) | 86% (80%, 90%) |
| ERMS: VAC | 118 | 67% (56%, 76%) | 86% (76%, 92%) |
| ERMS: VAC/VI | 128 | 68% (58%, 76%) | 89% (81%, 93%) |
| ARMS: VAC | 102 | 58% (48%, 69%) | 81% (71%, 88%) |
| ARMS: VAC/VI | 95 | 57% (45%, 67%) | 83% (72%, 90%) |

**10005 Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

**Which patients with rhabdomyosarcoma (RMS) do need radiotherapy (RTX)? The long-term results of the CWS studies -81, -86, -91, and -96.** *Presenting Author: Ewa Koscielniak, Olgahospital Klinikum Stuttgart, Stuttgart, Germany*

**Background:** RTX is an essential therapy modality in the treatment of RMS. However, RTX is associated with severe late effects, therefore the indication and the optimal dose are still a matter of controversy. The stratification for the RTX indication and cumulative dose has been optimized in the consecutive CWS trials. Here we report the long-term results of four consecutive prospective trials. **Methods:** A total of 998 patients enrolled in the CWS-81, 86, -91 and -96 met the inclusion criteria for this analysis: 1) RMS histology 2) localized tumor (IRS Group I-III) 3) complete RTX data set and 4) follow up of minimum 10 yrs. 171 patients were classified as IRS Group I, 171 as IRS Group II and 656 as IRS Group III. 200 tumors (20%) had alveolar histology (RMA). The indication for RTX and the doses of 32Gy, 40Gy, 45Gy, 48Gy, 50Gy and 54Gy were stratified according to patient and tumor related factors. **Results:** The 5yrs event free survival (EFS) and overall survival (OS) did not differ between the trials included in the analysis. 630 pts were irradiated (63%).There was no major difference in proportion of irradiated patients between the trials 81-96 (62%, 59%, 71%, 61%). The 5yrs EFS by IRS Groups and RTX vs. no RTX were as follows: IRS I 60% vs. 84%, IRS II 73% vs. 72%, IRS III 62% vs. 57% (n.s.). The 5yrs EFS by RTX dose (32±2Gy vs. > 34Gy) were: IRS II 80% vs. 69%, IRS III 70% vs. 61%. Restricting the analysis to alveolar type: the 5 yrs EFS of patients irradiated with 32±2Gy vs. > 34Gy were as follows: IRS II 50% vs. 59%(n.s.), IRS III 30% vs. 41% (n.s.). There was no difference in EFS when splitting the RMS patients irradiated with > 34Gy into 40Gy vs. 45Gy, vs. 48Gy vs. 50 vs. 54Gy. **Conclusions:** The stratification criteria for RTX seem to compensate for different risk factors and allowed for reducing the cumulative dose to 32Gy in the lower risk group. However, the proportion of irradiated patients could not be reduced significantly. Further improvement in identification of patients who do not need RTX is needed.

**10006 Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

**Maintaining outstanding outcomes using response- and biology-based therapy for intermediate-risk neuroblastoma: A report from the Children's Oncology Group study ANBL0531.** *Presenting Author: Clare Twist, Stanford University, Palo Alto, CA*

**Background:** This Phase III prospective reduction of therapy study used tumor biologic features to determine the minimal treatment needed to achieve excellent outcomes in patients with intermediate risk (IR) neuroblastoma (NB). **Methods:** Between 10/8/2007 and 6/30/2011, 464 patients enrolled; 401 had evaluable IR NB. Eligibility included newly diagnosed single copy *MYCN* NB and: age <12 years with stage 2A/B <50% resected or stage 3 with favorable biology, age <365 days with stage 3 or 4, and all patients <365 days with stage 4S, including those too ill to undergo biopsy. Toddlers age 365-<547 days with favorable biology stage 4 NB and age 365-<547 days with stage 3 and unfavorable histology (UH) received isotretinoin in addition to chemotherapy. Risk-stratification and therapy assignment utilized age, INSS stage, INPC, *MYCN*, and tumor ploidy. Therapy reduction was prescribed for tumors without loss of heterozygosity (LOH) at 1p36 and/or 11q23. Therapy included 2-8 courses of chemotherapy +/- surgery. Treatment endpoint for localized favorable biology tumors was partial response. **Results:** The 3-year EFS/OS for all IR patients was 83±3%/95±2%. The presence of 1pLOH and/or unbalanced 11qLOH was detected in 18% of IR tumors. To date, there were no deaths due to disease in patients with localized favorable biology tumors. Among 124 stage 4 patients <365 days, 3-year EFS/OS for favorable biology (n=60) was 90±5%/95±4%; for unfavorable biology (diploid and/or UH, irrespective of LOH, n=24) was 63±16%/76±13% and 65±14%/95±7% for tumors with LOH (n=20). Among 9 stage 4 toddlers there were 3 relapses; 3-year OS 100%. Eight of 46 patients with stage 4S NB died; 5 were due to complications of hepatomegaly. **Conclusions:** Further reduction of therapy and prospective refinement of treatment using genomic stratification achieved excellent survival in the majority of IR NB patients. Some unfavorable biology IR tumors may benefit from novel treatment strategies. Clinical trial information: NCT00499616.

**10007 Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

**Tandem high-dose chemotherapy with stem cell rescue followed by risk-adapted radiation in children with high-risk cerebral primitive neuroectodermal tumor: Results of the prospective SFCE-trial PNET HR+5.** *Presenting Author: Christelle Dufour, Gustave Roussy, Villejuif, France*

**Background:** To assess the 3-year progression-free survival (PFS) rate of patients with newly diagnosed high-risk medulloblastoma (MB) or supratentorial primitive neuroectodermal tumor (sPNET) between 5-20 years treated according to the prospective multicenter trial PNET HR+5. **Methods:** Children received as postoperative induction chemotherapy two cycles of etoposide (500mg /m$^2$) - carboplatine (800mg/m$^2$), followed by two courses of thiotepa (600mg/m$^2$ per course) with autologous stem cell rescue. Risk-adapted conventional radiotherapy (RT) was delivered around day 45 after second transplantation. Craniospinal RT dose was 36 Gy for patients with metastatic disease or with unfavourable histology (anaplastic MB, large cell MB, MB with *myc* amplification) followed by a tumor bed boost of 18 Gy. Patients with localized sPNET received focal RT at the dose of 54 Gy. Maintenance treatment with 6 cycles of temozolomide was planned to start between 1-3 months after the end of RT. **Results:** From January 2009 to February 2012, 64 patients (MB=51; sPNET=13) between 5 and 19 years (median age, 9 years) were enrolled. Five patients didn't received RT due to progressive disease. Maintenance treatment was administered in 44 patients. The median follow-up was 32 months (range, 16-54 months). The 3-year PFS and overall survival (OS) were 80% (95% CI: 68-88%) and 85% (95% CI: 74-92%), respectively. The 3-year PFS was 79% (95% CI: 65-88%) for children with MB and 85% (95% CI: 58-96%) for those with sPNET. No major unexpected toxicities and no treatment-related deaths were reported. **Conclusions:** This treatment based on high-dose chemotherapy and conventional RT resulted in a high overall survival rate in children and adolescent with newly diagnosed high-risk cerebral PNET. Clinical trial information: NCT00936156.

**10008** **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

**Risk-based treatment for nonrhabdomyosarcoma soft tissue sarcomas (NRSTS) in patients under 30 years of age: Children's Oncology Group study ARST0332.** *Presenting Author: Sheri L. Spunt, Lucile Packard Children's Hospital at Stanford, Palo Alto, CA*

**Background:** NRSTS comprise ~4% of childhood cancer but only 3 prospective clinical trials have been performed in the U.S. in the past 40 years. Tumor grade, size, resection potential, and extent of disease influence outcome. ARST0332 evaluated a risk-based treatment strategy for young NRSTS patients designed to limit therapy for low-risk disease and to test a combined chemoradiotherapy approach for unresected higher risk disease. **Methods:** Newly diagnosed NRSTS patients < 30 years old were assigned to 4 treatment arms based on risk: A (surgery only): grossly excised low-grade and ≤ 5 cm widely excised high-grade tumor; B (55.8 Gy radiotherapy [RT]): ≤ 5 cm marginally resected high-grade tumor; C (ifosfamide/doxorubicin chemotherapy + 55.8 Gy RT): > 5 cm grossly resected tumor ± metastases; D (neoadjuvant ifosfamide/doxorubicin chemotherapy and 45 Gy RT, then surgery and an RT boost based on margins): > 5cm unresected tumor ± metastases. **Results:** 551 eligible patients were enrolled on Arm A (212), B (19), C (120), and D (200). Most common subtypes were synovial sarcoma (149), malignant peripheral nerve sheath tumor (60), and undifferentiated sarcoma (48). Tumors were 53% extremity, 72% high grade, 76% > 5 cm, and 14% metastatic. There were no toxic deaths; 2% had unexpected grade 4 adverse events. By treatment arm, at a median follow-up of 2.6 years, estimated 3-year event-free survival was: A 91%, B 79%, C 68%, D 52% and overall survival was: A 99%, B 100%, C 81%, D 66%. **Conclusions:** This novel risk-based treatment strategy segregated patients into clinically meaningful risk groups and produced outcomes similar to or slightly better than historical controls while using RT less frequently and at lower doses. This study defines the new standard of care for pediatric NRSTS against which future interventions should be compared. Clinical trial information: NCT00346164.

**10009** **Oral Abstract Session, Sun, 9:45 AM-12:45 PM**

**Breast cancer in childhood cancer survivors not treated with chest-directed radiation in the Childhood Cancer Survivor Study (CCSS).** *Presenting Author: Tara O. Henderson, Pritzker School of Medicine, The University of Chicago, Chicago, IL*

**Background:** While chest radiation (CRT) is strongly associated with risk of breast cancer (BC) in childhood cancer survivors (CCS), there are BC cases among survivors not exposed to CRT. We sought to examine if BC risk is elevated in non-CRT exposed women to inform surveillance recommendations. **Methods:** Using the CCSS cohort, BC risk was assessed among 3,768 female 5-yr CCS (median follow-up 25.5 yr, range 8-39) not treated with CRT. Cumulative incidence was examined treating death as a competing risk. BC risk was assessed using standardized incidence ratios (SIR) and 95% confidence intervals (CI) using incidence from the Surveillance, Epidemiology, and End Results Program, and by calculation of absolute excess risk (AER) per $10^4$person-yrs (py). **Results:** 47 CCS developed BC at a median age of 38 yrs (range 22-47) and median of 24 yrs (range 9.6-34.3) from primary diagnosis. Primary cancers included: 14 leukemia; 10 bone tumor; 10 soft tissue sarcoma; 6 Ewing's sarcoma (EWS); 2 CNS; and, 1 each of neuroblastoma, Wilms, Hodgkin, NHL. Among non-CRT exposed survivors, the cumulative incidence of BC was 2.5% (CI 1.6-8.8) at 35 yrs from diagnosis and 1.6% (CI 1.0-2.3) by age 40 yrs. Non-CRT survivors had a 3.8-fold increased risk of BC (SIR=3.8, CI 2.8-5.0) with an AER of 4.8/$10^4$ py, CI 2.9-6.2. Survivors with potential Li-Fraumeni (LF)-associated malignancy (leukemia, CNS, sarcoma except EWS) had an SIR of 3.8 (CI 2.7-5.2) and AER of 5.1/$10^4$ py (CI 3.0-7.4). Leukemia and sarcoma survivors were at highest risk (SIR=3.9, CI 2.3-6.6 and AER=3.5/$10^4$ py, CI 1.0-5.9 and SIR 5.3, CI 3.6-7.8; AER=14.2/$10^4$ py, CI 7.5-20.9, respectively). Among sarcomas, EWS survivors had a significant risk (SIR=9.5, CI 4.3-21.7; AER=29.3/$10^4$ py, CI 3.2-55.3). Survivors of all other cancers (excluding EWS and LF cancer) did not have an elevated BC risk (SIR=2.2, CI 0.9-5.3; AER 1.5/$10^4$py, CI -0.8 – 2.3). **Conclusions:** Although overall incidence is low, CCS not treated with chest-directed radiation are at increased risk for BC. The elevated BC risk is predominantly among leukemia and sarcoma survivors, potentially due to a genetic risk, and support consideration of early BC surveillance and genetic risk assessment.

**10010** **Oral Abstract Session, Sun, 9:45 AM-12:45 PM**

**Alkylating agent exposure and sperm concentration in adult survivors of childhood cancer: A report from the St. Jude Lifetime (SJLIFE) Cohort Study.** *Presenting Author: Daniel M. Green, St. Jude Children's Research Hospital, Memphis, TN*

**Background:** Male survivors of childhood cancer treated with alkylating agents (AA) are at risk for azoospermia; however, the long-term dose-risk relationship is unknown. **Methods:** Of the 287 SJLIFE participants treated with AA but no radiation therapy, 214 provided an evaluable semen sample (mean age at diagnosis: 7.9 years, mean age at evaluation: 29.8 years, and mean years from diagnosis to evaluation: 21.6 years). Survivors were categorized as azoospermia, oligospermia (sperm concentration > 0 and < 15 million/ml), or normospermia (sperm concentration ≥ 15 million/ml). AA exposure was estimated using the cyclophosphamide equivalent dose (CED). Risks were estimated using the odds ratio (OR) and 95% confidence intervals (CI) from multinomial logistic regression analyses. **Results:** Among survivors 24.8% had azoospermia, 27.6% oligospermia, and 47.6% normospermia (Table). CED was negatively correlated with sperm concentration ($r = -0.25$, $p < 0.001$). Neither age at diagnosis nor age at evaluation was significantly associated with increased risk for azoospermia. Treatment with cis-platinum or carboplatinum did not increase the risk of azoospermia or oligospermia. Adjusting for age at diagnosis and at follow-up, CED was statistically significantly associated with azoospermia (OR= 1.22, 95% CI 1.11, 1.34) and oligospermia (OR=1.14, 95% CI, 1.04, 1.25) for each 1000 mg/m$^2$increase of CED. **Conclusions:** We identified neither a threshold dose, below which impaired spermatogenesis was unlikely, nor a dose above which azoospermia was uniformly present. This result suggests that other factors, including genetic variation in drug metabolizing pathways, may modulate the impact of AA exposure on spermatogenesis.

| | | CED (mg/m$^2$) | | | | |
|---|---|---|---|---|---|---|
| Outcome | No. | Mean | SD | Range | Median | Interquartile range |
| Azoospermia | 53 | 10,830 | 7,274 | 1,000 - 41,311 | 9,234 | 6,354-10,916 |
| Oligospermia | 59 | 8,480 | 4,264 | 2,100 - 31,894 | 8,000 | 5,650-9,872 |
| Normospermia | 102 | 6,626 | 3,576 | 1,016 - 15,645 | 6,137 | 3,386-9,396 |

**10011** **Oral Abstract Session, Sun, 9:45 AM-12:45 PM**

**Multicenter study assessing tumor molecular profiles in advanced pediatric solid tumors.** *Presenting Author: Katherine A. Janeway, Dana-Farber Cancer Institute, Boston, MA*

**Background:** The role of molecular profiling in the clinical care of children with advanced solid tumors is unknown. Key questions are: do pediatric solid tumors have a sufficient rate of actionable alterations to warrant prospective assessment for clinical use; and, if potentially actionable alterations are identified are targeted drugs accessible for use in children with recurrent solid tumors? **Methods:** We conducted a multi-institution study to determine whether it is feasible to identify actionable alterations and make an individualized cancer therapy (iCat) recommendation using currently available clinical genomic technologies. Patients(pts) were eligible if they had a diagnosis of a high risk or recurrent/refractory solid tumor. Tumor profiling consisted of: a)mutation detection by either a Sequenom assay or targeted next-generation sequencing; b)copy number assessment by array CGH; and c)validation with IHC/FISH in some cases. Tumor profiling results were reviewed by a multi-disciplinary expert panel. iCat recommendations were made if an actionable alteration was present and if a targeted drug was available. Recommendations were tiered from 1 (strongest) to 5 (weakest) based upon strength of supporting evidence. **Results:** 100 pts were enrolled in 14 months. The most common diagnoses were neuroblastoma and Ewing sarcoma. 43% of pts had rare solid tumors. With 54 pts resulted and reviewed at the time of submission, profiling was technically feasible in 81%. Overall, 16 of 54 (30%) pts received an iCat recommendation (1 tier 1; 5 tier 3; 8 tier 4; 2 tier 5). The most common molecular aberrations in the 16 pts receiving an iCat recommendation were cancer-associated signaling pathway gene mutations (n=9), *MYC*/*MYCN* high copy number gain (n=4), and Cyclin D/CDK4/Rb pathway gene alterations (n=3). Additional pts had a potentially actionable alteration, but an iCat recommendation was not made due to lack of available drug. **Conclusions:** It is feasible to conduct a multi-institution clinical genomics study. A substantial proportion of relapsed, refractory pediatric solid tumors have actionable alterations. Additional research is required to determine whether applying genomics in this setting has an impact on pt outcome.

**10012 Oral Abstract Session, Sun, 9:45 AM-12:45 PM**

**What's in an exome? Diversity of diagnostic and incidental findings revealed by clinical tumor and germline sequencing of 100 children with solid tumors.** *Presenting Author: D. Williams Parsons, Texas Children's Cancer Center, Houston, TX*

**Background:** Whole exome sequencing (WES) can identify a wide spectrum of tumor and germline genetic findings. Before WES is incorporated into oncology practice, it is necessary to gain an understanding of the nature and frequency of these genetic results in cancer patients. **Methods:** The BASIC$^3$ (Baylor Advancing Sequencing in Childhood Cancer Care) study investigates the clinical implementation of CLIA-certified WES for sequentially diagnosed children with CNS and non-CNS solid tumors. Blood and frozen tumor samples undergo WES, with the resulting germline and tumor reports deposited into the medical record and disclosed to families by their oncologist and a genetic counselor. Germline reports include: (1) deleterious mutations and variants of uncertain significance (VUS) in disease genes related to cancer or other patient phenotypes, (2) incidental medically-actionable mutations, (3) FDA-approved pharmacogenetic (PGX) variants, (4) mitochondrial (mtDNA) mutations, and (5) carrier status for recessive disorders if requested by parents. **Results:** Of the first 124 eligible families, 100 (81%) consented to participate. At least one somatic mutation of proven or potential clinical relevance was reported in 22/80 (28%) patients with tumor available (e.g. *ALK, CTNNB1*, *BRAF*, *KRAS*, *KIT, TSC2*). Diagnostic germline findings were found in 11 cases: 8 pathogenic mutations in dominant cancer susceptibility genes (*TP53* x 2, *MSH2*, *BRCA1*, *WT1*, *BRCA2*, *DICER1*, *VHL*) and 3 mutations underlying non-oncologic diagnoses. There were 7 patients with medically-actionable incidental findings (2 in mtDNA). Nearly all patients harbored VUS in cancer genes (98%; median of 3) and PGX variants (89%; median of 1). Carrier mutations were reported in 76/89 (85%; median of 2) patients. **Conclusions:** Clinical tumor and germline WES revealed diagnostic and potentially actionable results in nearly 40% of pediatric solid tumor patients, including both cancer and non-cancer-related findings. Successful incorporation of genomic methods into the care of oncology patients will require preparation of clinicians to disclose and manage these diverse results. Supported by 1U01HG006485.

**10013 Oral Abstract Session, Sun, 9:45 AM-12:45 PM**

**Factors associated with nonadherence to oral 6-mercaptopurine (6MP) in children with acute lymphoblastic leukemia (ALL): A report from Children's Oncology Group (COG) study AALL03N1.** *Presenting Author: Wendy Landier, City of Hope, Duarte, CA*

**Background:** We have previously shown that poor adherence (adherence rate <95%) to oral 6MP is prevalent in children with ALL, and increases relapse risk (JCO 30[17]:2094-101). However, behavioral predictors of non-adherence to oral 6MP have not been examined. **Methods:** We addressed this gap in 462 children (non-Hispanic Whites: 34%; Hispanics: 36%, Asians: 15%, African-Americans: 15%) with ALL diagnosed at age ≤21 years, and receiving maintenance therapy. 6MP adherence was measured over 6 months using Medication Event Management System (MEMS) that recorded dates/times of 6MP bottle opening (adherence rate=days bottle opened/days 6MP prescribed). A 37-item questionnaire assessed barriers/facilitators (addressing the Health Belief Model [HBM]) to adherence. **Results:** Median age at study was 6 years (2-20); 67% were males; 40% had high-risk disease. MEMS monitoring for 76,174 person-days yielded a non-adherence rate of 44.4%. Multivariable analysis identified the following predictors of non-adherence: i) age ≥12 years (Odds ratio [OR]=2.2, p=0.02); ii) Hispanic ethnicity (OR=2.1, p=0.005); iii) African-American race (OR=4.2, p<.001); iv) parental education ≤high school (OR=1.8, p=0.02); v) annual household income <$50,000 (OR=1.6, p=0.05); vi) involvement of ≥2 adults in 6MP supervision (OR=2.4; p=.004); vii) failure (on part of parents/patients) to understand the purpose of 6MP (OR=2.8; p<.001); viii) failure to take 6MP at the same time each day (OR=1.8; p<.01); and ix) taking 6MP with milk/dairy (OR=1.9; p=.03). **Conclusions:** In addition to sociodemographic predictors, we identified behavioral determinants of 6MP non-adherence that align with HBM. Lack of perceived benefits (not understanding the purpose of 6MP), absence of cues to action (not taking medication at same time each day), low self-efficacy (absence of a designated adult assuming primary responsibility for 6MP administration), and presence of barriers (dietary restrictions) contributed to non-adherence. These findings identify vulnerable populations that could benefit from targeted interventions to improve adherence in pediatric ALL. Clinical trial information: NCT00268528.

**10014 Oral Abstract Session, Sun, 9:45 AM-12:45 PM**

**The significance of minimal residual disease (MRD) in relapsed childhood B-lymphoblastic leukemia (B-ALL): A report from Children's Oncology Group (COG) protocol AALL0433.** *Presenting Author: Glen Lew, Emory University School of Medicine, Atlanta, GA*

**Background:** Relapsed childhood B-ALL has a poor prognosis. Few risk factors beyond immunophenotype, timing, and site of relapse are known to affect outcome. MRD is a powerful predictor of outcome in newly diagnosed ALL, but its significance after relapse is less clear. We report an analysis of MRD and outcome from the AALL0433 protocol for childhood B-ALL with intermediate-risk relapse. **Methods:** AALL0433 is a Phase 3 study of intermediate-risk relapsed childhood B-ALL, defined as CNS/testicular relapse <18 mo. or bone marrow (BM)/combined relapse >36 mo. from diagnosis. Therapy is based upon the AALL01P2 / 9412 platforms. BM MRD was measured by flow cytometry at end-induction; results were blinded to investigators. Only matched family donor SCT was allowed on protocol. 271 eligible patients were enrolled. Outcome by treatment received remains blinded at this time. **Results:** The 3-yr. EFS/OS for the entire cohort of 271 patients were 60.7 ± 4.6% and 71.3 ± 4.3%, respectively. All 29 patients with isolated extramedullary relapse had MRD <0.01% at end-induction. Further analyses focused on patients with BM/combined relapse (n=242). The 3-yr. EFS/OS for this group of patients was 62.8 ± 4.8% and 73.6 ± 4.4%, respectively. 175 patients had available end-induction MRD data: 84 patients had MRD levels <0.01%, 28 were between 0.01-0.1%, and 63 had MRD > 0.1%. These three groups had 3-yr. EFS of 83.4 ± 5.4%, 70.4 ± 12.8%, and 40.9 ± 8.4% respectively (p=0.001), and 3-yr. OS of 88.5 ± 4.6%, 83.0 ± 10.3%, and 56.2 ± 9.0%, respectively (p = 0.0019). An MRD cutoff of 0.1% provided the best discriminator of outcome, with 3-yr. EFS 80.2 ± 5.2% vs. 40.9 ± 8.4%, and 3-yr. OS of 87.1 ± 4.3% vs. 56.2 ± 9.0% for those below (n=112) or above (n=63) this cutoff. **Conclusions:** Preliminary efficacy of the AALL0433 platform for intermediate-risk relapse of childhood B-ALL is encouraging. An end-induction MRD cutoff of 0.1% was the best predictor of outcome for patients with late BM/combined relapse. Because of the major survival difference at the 0.1% MRD cutoff, it will be used to stratify late BM relapse patients to receive chemotherapy vs. SCT in the next COG relapsed ALL trial. Clinical trial information: NCT00381680.

**10015 Oral Abstract Session, Sun, 9:45 AM-12:45 PM**

**Outcome of childhood T-cell acute lymphoblastic leukemia (T-ALL): Results from DFCI protocol 05-001.** *Presenting Author: Andrew E. Place, Dana-Farber Cancer Institute, Boston, MA*

**Background:** T-ALL accounts for ~ 15% of pediatric ALL; in general, outcomes have been less favorable than those for B-ALL. Methods: Between 2005-11, 97 evaluable patients (pts) aged 1-18 years (yrs) with newly diagnosed T-ALL were enrolled on DFCI ALL Consortium Protocol 05-001. Early T-cell precursor (ETP) subtype was retrospectively assessed in 90 pts by flow cytometry. End-Induction minimal residual disease (MRD) was assessed by PCR. All 97 pts were initially treated as high-risk regardless of other presenting features; 2 pts were assigned more intensive post-induction therapy based on cytogenetics (MLL-R:1; BCR-ABL: 1). **Results:** Presenting features and outcomes are shown in Table 1. The 4-yr EFS and OS for all T-ALL pts was 83% and 89%, respectively (median follow-up: 4.3 yrs). End-induction MRD was evaluable in 58 (67%) pts achieving CR; high MRD (>0.001) was associated with an inferior DFS (high MRD (N=15): 79%, low MRD (N=43): 95%, p=0.047). ETP subtype was identified in 16 pts (18%). ETP pts had a higher rate of induction failure (31% vs. 4%, p<0.01) and an inferior EFS (62% vs. 89%, p<0.01). None of the ETP pts who achieved CR after the 1$^{st}$ month of treatment subsequently relapsed. **Conclusions:** Overall outcome for T-ALL pts on Protocol 05-001 was favorable, especially for non-ETP pts with low MRD (4-yr DFS 98%; 95% CI:[84-99%]). Future studies should focus on intensifying post-induction treatment for pts with high end-induction MRD and modifying induction regimens for ETP pts. Clinical trial information: NCT00400946.

**Outcome and presenting features for T-ALL on DFCI 05-001.**

| | Total T-ALL N (%) | non-ETP T-ALL N (%) | ETP N (%) | p-value* |
|---|---|---|---|---|
| No. Pts. | 97 | 74 | 16 | |
| Age | | | | |
| <10 yrs | 54 (56) | 42 (57) | 6 (38) | 0.18 |
| ≥10 yrs | 43 (44) | 32 (43) | 10 (62) | |
| Median (range) yrs | 8.5 (1.2, 17.9) | 7.2 (1.2, 17.9) | 12.1 (2.9, 17.9) | 0.07 |
| Sex, Male | 71 (73) | 55 (74) | 10 (62) | 0.37 |
| WBC K/uL, median (range) | 64.3 (0.9, 905.0) | 81.1 (2.9, 905.0) | 13.4 (1.8, 259.2) | <0.01 |
| Mediastinal mass present | 43 (44) | 37 (50) | 3 (19) | 0.03 |
| 4 yr EFS (%) [95% CI] | 83 [74-90] | 89 [79-94] | 62 [35-81] | <0.01 |
| 4 yr DFS [95% CI] | 93 [85-97] | 94 [85-98] | 100 [NA] | 0.46 |
| 4 yr OS (%) [95% CI] | 89 [80-94] | 92 [83-97] | 81 [51-93] | 0.09 |
| Induction failure | 8 (8) | 3 (4) | 5 (31) | <0.01 |
| Induction death | 2 (2) | 1 (1) | 1 (6) | 0.33 |
| Achieved CR | 87 (90) | 70 (95) | 10 (62) | <0.01 |

* Non-ETP T-ALL *vs* ETP; Pts achieving a CR.

**10016 Oral Abstract Session, Sun, 9:45 AM-12:45 PM**

**The impact of initial cerebrospinal fluid (CSF) findings on outcome among patients with NCI standard (SR) and high-risk (HR) B-lymphoblastic leukemia (ALL): A report from the Children's Oncology Group (COG) Studies AALL0331 and AALL0232.** *Presenting Author: Naomi Joan Winick, The University of Texas Southwestern Medical Center; Center for Cancer and Blood Disorders, Children's Medical Center Dallas, Dallas, TX*

**Background:** To determine the prognostic significance of variable numbers of white cells (WBC), blasts and/or red cells (RBC) in diagnostic CSF samples of ALL patients, COG protocols, AALL0331 (SR)/AALL0232 (HR) incorporated a uniform CSF and risk group classification schema for all newly diagnosed patients. **Methods:** Patients, 1-31 years, were enrolled on the classification protocol, AALL03B1. CSF status was designated as: CNS1-no blasts; CNS2a- < 5 WBC + blasts + < 10 RBC/ml; CNS2b-< 5 WBC + blasts + > 10 RBC/ml; CNS2c- > 5 WBC + blasts, with excess WBC proportional to RBC; CNS3a- > 5 WBC + blasts + < 10 RBC/ml; CNS3b - > 5 WBC + blasts + > 10 RBC/ml, with excess WBC not proportional to RBC; CNS3c- clinical signs of CNS leukemia (e.g. cranial nerve deficits, hypothalamic disease). Only CNS1 patients could be allocated to the SR-low risk arm. CNS2 status did not impact therapy but CNS3 patients received augmented therapy and 1800 cGY cranial radiation. **Results:** In multivariate analysis that includes age and WBC at diagnosis and Day 29 MRD < 0.1%, the presence of CSF blasts, regardless of the number of CSF WBC or RBC is an independent adverse predictor of outcome for NCI SR (all of whom received dexamethasone) and HR patients. The EFS difference reflects a significant difference in the incidence of CNS, not marrow relapse in CNS1vs CNS2/3 patients (see Table). Conclusion: Even low levels of CNS leukemia, regardless of the number of RBCs, are associated with a lower EFS/OS and an increase in the likelihood of CNS relapse. The use of dexamethasone in NCI SR patients did not negate the impact of CSF blasts. Further augmentation of CNS directed therapy is needed for patients with CNS2/3 disease. Clinical trial information: NCY00482352.

| | CNS 1 | | CNS 2 a, b, c | | CNS 3 a, b, c | | |
|---|---|---|---|---|---|---|---|
| Cohort | 5 yr EFS | N | 5 yr EFS | N | 5 yr EFS | N | p-value |
| Overall NCI SR/HR | 85.3 ± .56% | 7214 | 76 ± 2% | 836 | 75.7 ± 5.2% | 124 | < 0.0001 |
| NCI SR-AALL0331 | 89.9% ± .59% | 4721 | 85 ± 2.3% | 415 | 82 ± 7.1% | 52 | 0.0003 |
| NCI HR-AALL0232 | 76.5 ± 1.2% | 2493 | 67.1± 3% | 421 | 70.5 ± 7.2% | 72 | < 0.0001 |
| Cumulative Incidence of Marrow relapse | 6.3 ± .3% | 7395 | 7.1 ± .9% | 857 | 9.3 ± 2.9% | 127 | 0.18 |
| CNS relapse | 2.9 ± .21% | | 7.8 ± 1% | | 5.9 ± 2.2% | | < 0.0001 |

**10017 Oral Abstract Session, Sun, 9:45 AM-12:45 PM**

**The effects of sodium thiosulfate (STS) on cisplatin-induced hearing loss: A report from the Children's Oncology Group.** *Presenting Author: David Robert Freyer, Children's Hospital Los Angeles, Los Angeles, CA*

**Background:** Cisplatin frequently causes irreversible hearing loss in children treated for cancer. STS is a thiol reducing agent shown in preclinical studies to protect hearing but not the tumor with its timed administration post-cisplatin. **Methods:** The primary aim of ACCL0431 was to evaluate the efficacy of STS, compared with observation (Obs), for preventing cisplatin-induced hearing loss. Eligible subjects were 1–18 years old with normal audiometry and planned cisplatin infusions of ≤ 6 hours with cumulative dose ≥ 200 mg/m$^2$. Subjects were randomized either to Obs or treatment with STS 16 grams/m$^2$ IV over 15 minutes 6 hours after each cisplatin dose. Hearing was measured using standard audiometry for age; data were reviewed centrally using American Speech-Language-Hearing Association criteria. The proportion of subjects with hearing loss ($\chi^2$ test) assessed at 4 weeks post the final cisplatin dose (primary endpoint) and EFS/OS (log-rank test, 2-year cumulative estimates and Cox proportional hazards model) were compared between the two groups. **Results:** 126 eligible subjects were enrolled with germ cell tumor (32), osteosarcoma (30), neuroblastoma (26), medulloblastoma (26), hepatoblastoma (7) or other (5). 105 subjects (64 male, 30 <5 years old) were evaluable for the primary aim. The proportion of hearing loss for STS vs. Obs was 28.6% vs. 55.4%, respectively (p=0.006). Including all 126 subjects at median post-diagnosis follow-up of 2.1 years, EFS for STS vs. Obs was 60.1% vs. 70.0% (p=0.53); OS was 74.5% vs. 88.8% (p=0.050). Subset analysis by extent of disease (determined post hoc) was performed. For subjects with localized disease, EFS was 72.5% vs. 67.1% (p=0.61); HR (hazard ratio) 0.81 (p=0.61); OS was 89.7% vs. 89.2% (p=0.73); HR 1.26 (p=0.73). For those with disseminated disease, EFS was 35.8% vs. 75.0% (p=0.047); HR 2.51 (p=0.055); OS was 49.0% vs. 88.3% (p=0.010); HR 4.03 (p=0.017). **Conclusions:** STS protects against cisplatin-induced hearing loss in children. However, the potentially lower survival seen in those with disseminated disease receiving STS raises the concern of a tumor protective effect when the drug is administered on this dose and schedule. Clinical trial information: NCT00716976.

**10018 Poster Highlights Session (Board #319), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**Phase I study of the MEK1/2 inhibitor selumetinib (AZD6244) hydrogen sulfate in children and young adults with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PNs).** *Presenting Author: Brigitte C. Widemann, Pediatric Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD*

**Background:** Lack of functional neurofibromin in NF1 leads to dysregulated Ras and tumorigenesis. Selumetinib (AZD6244; ARRY-142886), an oral selective inhibitor of MEK1/2, may inhibit PN growth by blocking Ras signaling. **Methods:** We are conducting a phase 1 trial (NCT01362803) to determine the maximum tolerated dose (MTD) and plasma pharmacokinetics (PK) of selumetinib in patients (pts) 3-18 years old with NF1 and inoperable PNs. The MTD is determined based on cycle (C) 1-3 toxicities. Selumetinib is administered BID on a continuous dosing schedule (1 C = 28 days) at dose level (DL) 1: 20 mg/m$^2$/dose, and 2: 30 mg/m$^2$/dose. Response evaluation with volumetric MRI analysis occurs after C 5, 10, and then after every 6 C (partial response [PR] = ≥20% decrease in the PN volume). **Results:** Eighteen pts (10 M:8 F, median age 12.9 years, range 5.3-18.5) with a median PN volume of 1204 mL (range 47-10,269 mL) have enrolled. DL2 exceeded the MTD with DLT in 2/6 pts: grade (gr) 3 creatine kinase (CK) elevation (n=1), and gr 3 decrease in left ventricular ejection fraction (n=1). DL1 was tolerated with DLT in 2/12 pts: gr 3 cellulitis (n=1), and grade 3 urticaria (n=1). The most frequent toxicities (all grades) are acneiform rash, asymptomatic CK elevation, nausea, vomiting, abdominal pain, diarrhea, and fatigue. All DLTs have been reversible. Preliminary median (range) selumetinib C1 day 1 PK parameters [DL1 (n=2), DL2 (n=5)] were: $C_{max}$ DL1 513 ng/mL (487-539), DL2 841 ng/mL (576-1770); $AUC_{0\text{-}24h}$DL1 2068 (2046-2089) ngxh/mL, DL2 2702 (2088-6008) ngxh/mL; half-life DL1 7.7 h (6.8-8.5), DL2 7.6 h (5.4-9.8). Of 11 pts with ≥ 1 restaging MRI, all had a decrease in PN volume (median maximal decrease 24%, range 8-39), and 3/5 at DL1, and 3/6 at DL 2 had a PR. All pts remain on trial after a median of 9 C (range 4-30). **Conclusions:** In children with NF1 PNs selumetinib is tolerated at 20 mg/m$^2$/dose BID on a continuous dosing schedule, approximately 50% of the adult recommended dose (75 mg BID). Preliminary activity is observed at DL1 and DL2. Enrollment is being expanded at 25 mg/m$^2$/dose, the MTD in study PBTC-029 for pediatric low grade gliomas, and a phase II trial is in development. Clinical trial information: NCT01362803.

**10019 Poster Highlights Session (Board #320), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**A phase I study of ruxolitinib in children with relapsed/refractory solid tumors, leukemias, or myeloproliferative neoplasms: A Children's Oncology Group Phase I Consortium study (ADVL1011).** *Presenting Author: Sarah K. Tasian, The Children's Hospital of Philadelphia, Philadelphia, PA*

**Background:** Ruxolitinib, an orally bioavailable inhibitor of the JAK family of kinases, may play a role in the treatment of childhood cancers with *JAK1*, *JAK2*, *CRLF2,* or other *BCR-ABL1*-like (Ph-like) alterations. We performed a phase 1 and pharmacokinetic (PK) study of ruxolitinib in children with relapsed/refractory solid tumors (STs) or hematologic malignancies (HMs; leukemias or myeloproliferative neoplasms). **Methods:** Ruxolitinib was administered orally twice daily (BID) continuously in 28 day cycles. The starting dose (15 mg/m$^2$; dose level 1, DL1) was equivalent to the recommended adult dose of 25 mg/dose BID. Using the rolling six design, subsequent 20% dose escalations were 21 (DL2), 29 (DL3), 39 (DL4), and 50 (DL5) mg/m$^2$/dose. Patients with HMs were enrolled at one dose level below ST patients. PK and pharmacodynamic analyses of phosphorylated (p) JAK2, STAT5, and S6 were performed in Cycle 1. **Results:** Twenty-eight ST and 21 HM patients were enrolled (median age 14.4 years; range 2.4 - 21.4). Twenty-seven ST and 10 HM patients were evaluable for toxicity. Ruxolitinib was generally well-tolerated, although there was 1 grade 5 event at DL2 in a ST patient (multi-system organ failure). During the dose escalation phase in STs, there was 1 dose-limiting toxicity at DL3 (neutropenia), DL4 (neutropenia), and DL5 (increased CPK). Grades 3 and 4 non-dose-limiting adverse events related to therapy in STs included cytopenias, nausea, and elevated transaminases and creatinine. PK parameters were similar to those in adults with marked inter-patient variability in the $C_{max}$ and AUC. Median peak plasma inhibitory activity of pJAK2 (44.8%), pSTAT5 (58.9%), and pS6 (62.3%) appeared generally dose-independent with the exception of greater pSTAT5 inhibition at DL5. **Conclusions:** The recommended phase 2 dose of ruxolitinib is 50 mg/m$^2$ orally BID. A trial of ruxolitinib with chemotherapy for children with acute lymphoblastic leukemia harboring activating JAK mutations or fusions or other Ph-like alterations is in development. Clinical trial information: NCT01164163.

**10020 Poster Highlights Session (Board #321), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**Results of nimotuzumab and vinorelbine, radiation, and re-irradiation for diffuse pontine glioma in childhood.** *Presenting Author: Maura Massimino, Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy*

**Background:** Radiotherapy is the only treatment definitely indicated for diffuse pontine gliomas (DIPG). Findings on the role of EGFR signaling in the onset of childhood DIPG has prompted the use of nimotuzumab, an anti-EGFR monoclonal antibody. Assuming a potential synergy with vinorelbine and radiotherapy, a pilot phase 2 protocol launched in 2009 combined nimotuzumab with concomitant radiation and vinorelbine. A protocol amendment in July 2011 introduced re-irradiation at relapse. The primary endpoint for first-line treatment was objective response rate (CR+PR+SD) according to the RECIST. This report concerns the outcome of this whole strategy. **Methods:** Vinorelbine 20 mg/m$^2$ was administered weekly, with nimotuzumab 150 mg/m$^2$ in the first 12 weeks of treatment; radiotherapy was delivered from weeks 3 to 9, for a total dose of 54 Gy. Then vinorelbine 25 mg/m$^2$and nimotuzumab were given every other week until the tumor progressed or for up to two years. Re-irradiation consisted of 19.8 Gy, fractionated over 11 days. Baseline and latest MRIs were assessed blindly by an outside neuroradiologist. **Results:** 25 children (mean age 7.4 years) were enrolled from August 2009 (median follow-up 29 months). A response was observed in 24/25 patients (96%). The nimotuzumab/vinorelbine combination was very well tolerated, with no acute side-effects. Eleven of 16 locally-relapsing patients were re-irradiated. One-year PFS and OS rates were 30±10% and 76±9%, respectively; 2-year OS was 27±9%; the median OS was 15 months. **Conclusions:** This strategy generated interesting results and warrants further investigation.

**10021 Poster Highlights Session (Board #322), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**Hearts too small for body size after doxorubicin for childhood ALL: Grinch syndrome.** *Presenting Author: Steven E. Lipshultz, Children's Hospital of Michigan, Wayne State University, Detroit, MI*

**Background:** Cross sectional studies show that cardiac abnormalities are common in survivors of doxorubicin (DOX)-treated childhood cancers. Longitudinal data, however, are rare. **Methods:** Serial echocardiograms (N = 900) from 115 DOX-treated childhood ALL (DFCI protocols 72-01 – 85-01) survivors were reported as indexed Z scores, indicating SDs above or below the normal mean for body size. Central single observer remeasurement minimized variability. Median individual and cumulative DOX doses were 30 mg/m$^2$/dose and 352 mg/m$^2$, respectively. **Results:** During 21 yrs median follow up (range 3-39), left ventricular (LV) fractional shortening remained decreased after DOX (mean LVFS >24 yrs: -2.42 [P<.05]). Both reduced LVFS and wall thickness related to cumulative dose (P<.05). LV dimension was initially above normal, but fell to become significantly decreased by last follow up (≤ 3yrs: +.53 [P<.05], > 12, ≤ 15yrs: +.08, > 24yrs: -.62 [P<.05], change over time: P<.001). The LV thickness-dimension ratio was significantly reduced until 21 yrs of follow up, following which it increased secondary to a fall in dimension and increasing wall thickness. However, the rise in wall thickness was accompanied by a progressive significant reduction in LV mass (≤ 3yrs: -.09 [NS], ≤ 24 yrs: -1.65 [P<.05]), indicating that increasing wall thickness was secondary to decreasing chamber size rather than myocardial hypertrophy. **Conclusions:** Progressive DOX cardiotoxicity transitions from an early subclinical dilated cardiomyopathy to a potentially restrictive cardiomyopathy detectable by 15+ years after exposure. The restrictive phase manifests as a relative decrease in LV dimension with a geometrically consequent rise in wall thickness leading to a normal thickness-dimension ratio at latest follow up. There is also a progressive fall in LV mass and cavity size that becomes inadequate for body size. Cardiomyopathy marked by shrinking myocardial and cavity size (Grinch Syndrome) appears to be a long term risk in this population. Monitoring for late clinically significant cardiotoxicity is essential. Symptomatic restrictive cardiomyopathy medical management failures are common, requiring use of early surgical therapeutic options.

**10022 Poster Highlights Session (Board #323), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**Risk and impact of pulmonary complications in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS).** *Presenting Author: Andrew Charles Dietz, Rady Children's Hospital San Diego, University of California, San Diego, San Diego, CA*

**Background:** Pulmonary complications from exposure to radiation, bleomycin and the nitrosureas have been well-documented among adult survivors of childhood cancer. However, the magnitude of condition-specific risks, compared to a non-cancer population, and the long-term impact on physical activity have not been well described. **Methods:** This analysis includes 13,208 five-yr survivors of childhood cancer (53% male, age 8 yrs [range: 0-21] at diagnosis, 33 yrs [6-59] at last follow-up), diagnosed ≤ 21 yrs between 1970-1986. Self-reported pulmonary outcomes were compared to a sibling control group (N=4,023) using Poisson regression to estimate rate ratios (RR) and 95% confidence intervals (CI) adjusted for attained age, sex, race, body mass index, congestive heart failure, and smoking status. Logistic regression was used to estimate associations (odds ratios, OR) between pulmonary outcomes and daily physical activity (walk one block, carry groceries, climb stairs, etc). **Results:** Compared to siblings, fewer survivors ever smoked (21.2% vs. 34.3%, p<0.001) but were more likely to report asthma (RR 1.4, CI 1.2-1.6), bronchitis (RR 1.2, CI 1.1-1.3), chronic cough (RR 2.2, CI 1.9-2.5), emphysema (RR 2.5, CI 1.2-5.2), need for extra oxygen (RR 2.2, CI 1.8-2.6), pulmonary fibrosis (RR 3.9, CI 2.7-5.8), pleurisy (RR 1.3, CI 1.1-1.7), and recurrent pneumonia (RR 2.8, CI 1.9-4.0). Cumulative incidence of any pulmonary condition by age 40 was 78.7% (CI 78.3-79.2). Lung cancer was reported in 17 (0.1%) with a standardized incidence ratio of 3.9 (CI 2.3-6.2). The standardized mortality ratio for death due to a pulmonary condition was 9.1 (CI 7.4-11). Limited daily physical activities were more likely among survivors with a pulmonary condition vs. those without: asthma (OR 1.6, CI 1.4-1.8), bronchitis (OR 1.5, CI 1.4 - 1.7), chronic cough (OR 2.8, CI 2.5 - 3.1), emphysema (OR 2.6, CI 1.5 - 4.3), need for extra oxygen (OR 3.3, CI 2.9 - 3.7), lung fibrosis (OR 2.3, CI 1.9 - 2.8), pleurisy (OR 1.9, CI 1.6 - 2.3), and recurrent pneumonia (OR 3.6, CI 2.9 - 4.4). **Conclusions:** Pulmonary complications are substantial among cancer survivors, significantly impacting daily activity and increasing risk of death.

**10023 Poster Highlights Session (Board #324), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**Exercise and risk of major cardiovascular events in adult survivors of childhood Hodgkin lymphoma: A report from the Childhood Cancer Survivor Study (CCSS).** *Presenting Author: Lee Jones, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Adult survivors of childhood Hodgkin's lymphoma are at elevated risk of treatment-related major cardiovascular (CV) events. We investigated whether exercise modified this association in HL survivors participating in the CCSS. **Methods:** HL survivors (n=1,187), median age 31.2 (range 18.0-48.9 years) and free of CV disease at baseline completed a questionnaire evaluating vigorous-intensity exercise behavior over the past week. Subsequent CV events were collected in follow-up questionnaires and graded according to the CTCAE (v. 4.03). The primary end point was incidence of any major (grade 3 to 5) CV event. Secondary end points were incidence of grade 3 to 5 CV events [coronary artery disease (CAD), heart failure, valve replacement, arrhythmia, and CV death]. Poisson regression analyses were used to estimate the association between exercise exposure [metabolic equivalent task-hrs·wk$^{-1}$(MET)] and risk of major CV events after adjustment for important clinical covariates (age, smoking, education, CV risk factors, and baseline grade 3-4 health conditions) and cancer treatment (anthracycline exposure and chest radiation). **Results:** A total of 135 major CV events were reported after median follow-up of 11.9 (range 1.7 - 14.3) years. In multivariable-adjusted analyses, the incidence of any CV event declined across increasing MET categories ($P_{trend}$=0.002). Compared with survivors reporting 0 METs, the adjusted RR for any CV event was 0.87 (95% CI, 0.56 to 1.34) for 3 to 6 METs, 0.45 (95% CI, 0.26 to 0.80) for 9 to 12 METs, and 0.47 (95% CI, 0.23 to 0.95) for 15 to 21 METs. A similar pattern was observed for the incidence of CAD (adjusted $P_{trend}$=0.005). The cumulative incidence of any CV event was 12.2% at 10 years for survivors reporting 0 METs, compared to 5.2% for those reporting ≥9 METs. Adherence to national exercise guidelines (i.e., ≥9 METs) was associated with a 51% reduction in the risk of any CV event, in comparison with not meeting the guidelines (p=0.002). **Conclusions:** Vigorous exercise reduces the incidence of CV events in a dose-dependent mannerbeyond CV risk profile and treatment exposure in adult survivors of childhood HL.

**10024 Poster Highlights Session (Board #325), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**Late mortality and relapse after dexrazoxane (DRZ) treatment: An update from the Children's Oncology Group (COG).** *Presenting Author: Eric Jessen Chow, Fred Hutchinson Cancer Research Center, Seattle Children's Hospital, Seattle, WA*

**Background:** DRZ use as a cardioprotectant in pediatric oncology has been limited by concerns regarding its efficacy and possible induction of second cancers, both of which may compromise overall long-term survival. **Methods:** COG protocols P9404 (T-cell acute lymphoblastic leukemia/lymphoma, n=537), P9425 (advanced stage Hodgkin lymphoma, n=216), and P9426 (low/intermediate stage Hodgkin, n=255) were conducted between 1996 and 2001. Patients were randomly assigned to treatment with or without DRZ (10:1 DRZ:doxorubicin alone given as IV bolus before each doxorubicin dose); cumulative protocol-specified doxorubicin dose: 100-360 mg/m$^2$. Data from all 3 trials were aggregated to examine overall relapse rates, and also linked with the US National Death Index to determine overall and cause-specific mortality by DRZ status (intent-to-treat). The combined sample had 80% power to detect differences in mortality and relapse rates of 5-7% and 6-8%, respectively. **Results:** Among 1,008 patients (DRZ+, n=507) with a median follow-up of 8.3 years (range 0-16.7), 132 died (DRZ+ n=67). With similar duration of follow-up by DRZ status, DRZ did not affect overall mortality (DRZ+, 12.8% vs. DRZ-, 12.2% at 10 years; HR 1.02, 95% CI 0.72-1.43) or relapse (10-year cumulative incidence: DRZ+, 15.6% vs. DRZ-, 18.8%; HR 0.82, 95% CI 0.60-1.10). Findings were similar when each protocol was examined separately. DRZ also was not associated with differential causes of death, with the original cancer accounting for 75.8% of all deaths (DRZ+/-, n=48/52; HR 0.91, 95% CI 0.61-1.34), followed by second cancers (DRZ+/-, n=10/9; HR 1.08, 95% CI 0.44-2.67), toxicity (DRZ+/-, n=7/3; HR 2.30, 95% CI 0.60-8.91), and other/unknown causes (DRZ+/-, n=2/1). There was no detectable difference in deaths due to acute myeloid leukemia/myelodysplasia (DRZ+/-, n=6/5) or with a cardiovascular event as a contributing cause (DRZ+/-, n=4/2). **Conclusions:** DRZ was not associated with a differential risk of mortality or relapse among randomized pediatric leukemia and lymphoma patients. Whether DRZ reduced cardiotoxicity is the focus of an ongoing prospective study. Clinical trial information: NCT01230983, NCT00005578, NCT00002827.

**10025 Poster Highlights Session (Board #326), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**Cardiac outcomes in aging survivors of childhood cancer exposed to cardiotoxic therapy: A report from the St. Jude Lifetime (SJLIFE) Cohort Study.** *Presenting Author: Daniel A. Mulrooney, St. Jude Children's Research Hospital, Memphis, TN*

**Background:** Cardiac studies among adult survivors of childhood cancer have generally relied on self-report or registry data; few have systematically performed comprehensive clinical assessments. **Methods:** We assessed 1,831 childhood cancer survivors, ≥ 18 yrs. of age and ≥10 yrs. from cardiotoxic therapy (radiation and/or anthracyclines). Cardiomyopathy (CMP), coronary artery disease (CAD), valve and conduction abnormalities, poor fitness (6-minute walk test < 490 minutes) and health status (SF-36 Physical Component score ≤ 40) were assessed. Cumulative prevalence was calculated by the Kaplan-Meir method. Cox proportional hazard models were used to calculate rate ratios (RR) and 95% confidence intervals (CI). **Results:** Survivors (52% male) were on average 8.3 yrs. (range: 0-21) at diagnosis and 32 yrs. (18-60) at evaluation. CMP was diagnosed in 6.7% (yield from screening 3.4%), CAD in 7.1% (yield 4.5%), valve disorders in 52% (yield 44%), and conduction abnormalities in 11% (yield 8%). By age 50 yrs. the estimated cumulative prevalence of CMP, CAD, valve and conduction disorders was 24% (CI 18-30%), 25% (CI 18-32%), 86% (CI 81-90%), and 42% (CI 34-49%), respectively. Diastolic dysfunction was present in 12%, and 18% of survivors had > 1 cardiac condition. Anthracycline exposure ≥ 250 mg/m$^2$ increased the risk of CMP (RR 4.1, CI 2.3-7.2), valve disorders (RR 1.4, CI 1.1-1.9), and conduction abnormalities (RR 2.0, CI 1.3-3.2) compared to unexposed survivors. Radiation to the heart increased the risk of CAD (RR 3.5, CI 1.8-6.7), valve disorders (RR 1.3, CI 1.1-1.6), and conduction abnormalities (RR 1.5, CI 1.1-2.1) compared to those unexposed. Survivors with CMP and CAD had poorer physical fitness compared to those without (31% vs. 19%, p=0.006 and 37% vs. 20%, p=0.003), and lower health status among those with CMP (46% vs. 16%, p<0.001), CAD (49% vs. 16%, p<0.001), valve (27% vs. 18%, p<0.002) and conduction abnormalities (36% vs. 15%, p<0.001). **Conclusions:** A substantial proportion of survivors exposed to cardiotoxic therapy have cardiac disease by 50 years of age. Systematic screening of adult survivors of childhood cancer identified considerable subclinical disease.

**10026 Poster Highlights Session (Board #327), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**Immunotherapy (IT) with ch14.18/CHO for high-risk neuroblastoma: First results from the randomised HR-NBL1/SIOPEN trial.** *Presenting Author: Ruth L Ladenstein, St. Anna Children's Cancer Research Institute, Vienna, Austria*

**Background:** The HR-NBL1/SIOPEN trial randomised 2 essential treatment concepts: Randomisation R1 investigated BUMEL superiority (plenary session ASCO 2012), whilst the R2 randomisation tested the benefits of adding subcutaneous interleukin 2 (scIL2) to ch14.18/CHO mAB immunotherapy(IT) and 13 cis retinoic acid (13-cis RA). The R2 population reached the target population of 400 patients (pts) in August 2013. **Methods:** After Rapid Cojec induction pts were randomised in R1 (296 BuMel, 302 CEM) till 09/2010. Median follow up is 6.2 years. Eligibility included complete bone marrow remission and ≤3, but improved mIBG positive spots. Local control included surgery and radiotherapy of 21 Gy. Eligibility to R2 included previous R1 eligibility. R2 was initiated in 2009 aiming at 400pts receiving ch14.18/CHOmAB as 8-hour infusion with 20mg/m$^2$ over 5 days and 13 cis RA over a total of 5 IT cycles. The schedule requires high dose morphine to control for neuropathic pain. R2 addressed a scIL2 question, using a dose of 6x10E6/m$^2$/day over 5 days twice in a weekly interval, given in week 2 in parallel with ch14.18/CHOmAb. **Results:** The superiority of BuMel in EFS and OS over CEM (3-years EFS&OS 50%/61% vs. 38%/52%; p<0.001) is maintained with a significantly lower relapse and progression rate with BuMel (48% vs. 58%) as major factor. Severe toxicity rates (ICU, toxic deaths) are below 10%, but are higher for CEM (p=0.012). Hence the MAT toxicity profile still favours BuMel in spite of a VOD rate of 24% (grade 3: 4%) vs. 10% in CEM (Grade3: 1%). Having reached the R2 target in August 2013, the randomisation is currently suspended expecting "last patient out" in 02/2014 with liberation of the randomised R2 data by the DMC thereafter. The R2 population undisclosed for treatment arms currently reveals a 2 year EFS/OS of 56%/68%. The scIL2 arm carries a significantly higher toxicity burden related to IL2 associated side effects like fever and capillary leak with a number of pts in the IL2 arm stopping treatment early. **Conclusions:** BuMel is maintained as SIOPEN standard treatment whilst R2 results will have a major impact on the future management of immunotherapy. Clinical trial information: NCT01704716.

**10027 Poster Highlights Session (Board #328), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**Genetic modification of T cells with a novel bispecific chimeric antigen receptor to enhance the control of high-grade glioma (HGG).** *Presenting Author: Meenakshi Hegde, Texas Children's Cancer Center, Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, TX*

**Background:** Highly targeted immunotherapy with adoptively transferred chimeric antigen receptor (CAR) T cells has shown considerable efficacy against some refractory childhood malignancies. Downregulation/mutation of targeted antigen can however create antigen loss escape variants. Multispecific T-cell approach could therefore further improve their therapeutic efficacy. **Methods:** We created a novel bispecific CAR that incorporates two extracellular antigen-recognition domains; one for HER2 (from HER2 monoclonal antibody FRP5) and the other for IL-13R$\alpha$2 (a mutated IL-13 molecule), in tandem (TanCAR). TanCAR was rationally designed by in silico modeling. Intracellular domain consists of a CD28/zeta-signaling chain. TanCAR encoding DNA was then synthesized and force expressed on T cells using retroviral system. Surface expression of extracellular domain of the TanCAR in its entirety was confirmed using HER2/IL-13R$\alpha$2 specific methods on flowcytometry. Functionality of TanCAR T cells was evaluated using standard immunoassays. Orthotopic murine model of HGG was used for in vivoexperiments. **Results:** 50-80% of T cells expressed the TanCAR on cell surface. In cytotoxicity assays, bispecific TanCAR T cells showed improved killing of IL-13R$\alpha$2 and HER2 positive HGG cell lines and autologous HGG cells over the control T cells from the same donor. Though TanCAR T cells were effectively activated and secreted immunostimulatory cytokines on recognizing HER2 and IL-13R$\alpha$2 proteins individually, cytokine secretion was significantly higher on simultaneous exposure to both target antigens. Adoptively transferred TanCAR T cells induced regression of established HGG xenografts. **Conclusions:** TanCAR T cells can distinctly target HER2 or IL-13R$\alpha$2 individually as well as both antigens simultaneously.TanCAR T cells exhibit enhanced effector functionality in vitro and anti-tumor activity in vivo, demonstrating their potential for therapeutic application. Targeting the heterogeneity in HGG with such a multi-specific T-cell approach could potentially achieve near complete targeting of tumor subpopulations and reduce the risk of recurrence.

**10028 Poster Highlights Session (Board #329), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**Immune activation and clinical responses following long-term infusion of anti-$GD_2$ antibody ch14.18/CHO in combination with interleukin-2 in high-risk neuroblastoma patients.** *Presenting Author: Holger N. Lode, University Medicine Greifswald, Greifswald, Germany*

**Background:** A less toxic treatment using long-term infusion (LTI) of anti-$GD_2$antibody ch14.18/CHO and subcutaneous interleukin-2 (IL-2) may improve outcome in high risk neuroblastoma (NB). **Methods:** 53 NB patients received 5/6 cycles of $6x10^6$ IU/$m^2$ s.c. IL-2 (d1-5; 8-12), LTI of 100 mg/$m^2$ ch14.18/CHO (d8-17) and 160 mg/$m^2$ oral 13-cis-RA (d19-32) in a single center program. Usage of i.v.-morphine and scores established for pediatric pain assessment were documented. Effector cells (NK- and T-cell subsets), ch14.18/CHO levels and $GD_2$ specific killing of neuroblastoma cells by ADCC, CDC, and whole blood were analyzed. KIR/KIRL mismatch and Fc$\gamma$-receptor polymorphisms were determined with a validated PCR-based method for KIR, HLA, FCGR2A (H131R), -3A (V158F) and -3B (NA1/NA2). Clinical response was assessed following INRG criteria by mIBG, MRI/CT, BM and catecholamines. **Results:** LTI of ch14.18/CHO translated into a decreasing degree of i.v. morphine usage allowing for treatment in the outpatient setting. The expansion of effector NK- (3x) and T-cells (2x) was combined with a pro-inflammatory cytokine response (IL-2, IL-6, IL-8, IFN$\gamma$). Effective levels of ch14.18/CHO (12.48 $\pm$ 0.93 $\mu$g/ml) at the end of antibody infusion translated into $GD_2$specific activity against NB cells in functional assays (CDC, ADCC, WBT). Interestingly, ch14.18/CHO levels and functional parameters before subsequent treatment cycles indicate persistent anti-NB activity measurable for the entire treatment period of 6-7 months. Response rates were 41.7 % in mIBG (15/36), 31.8 % MRI/CT (7/22), 28.6 % bone marrow- (6/21) and 38.1 % in catecholamines (8/21). An overall response of 30% (12/40), EFS of 32.4 % (observation 3.2 years, mean: 1.6 years) and an OS of 66.8% (observation 3.9 years, mean: 3.1 years) was observed. Patients with KIR/KIRL mismatch and high affinity FCGR alleles are associated with a longer event-free survival (P = 0.025), which supports NK-cell mediated ADCC as the mechanism of action. **Conclusions:** LTI of ch14.18/CHO shows anti-NB activity over the entire treatment period and objective clinical responses.

**10029 Poster Highlights Session (Board #330), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**Validation of the MIBG SIOPEN scoring method in two independent high-risk neuroblastoma trials.** *Presenting Author: Ariane Boubaker, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland*

**Background:** Harmonised evaluation standards of MIBG scintigraphy for (re)staging of neuroblastoma (NB) are an international aim. In the HR-NBL1/SIOPEN trial population a SIOPEN score (SISCO) >3 was associated with a significantly poorer event free survival (EFS) on pre and post induction mIBG. This analysis validates the SISCO prognostic value in the independent dataset (DS) of the Children's Oncology Group (COG) protocol A3973. **Methods:** SIOPEN scoring evaluates mIBG uptake over 12 skeletal regions (scored 0-6/region, maximum of 72), not considering extra-osseous disease nor the primary site. MIBG scans from mIBG-avid stage 4 NB pts in 2 collaborative trials were reviewed and judged evaluable by the SIOPEN Nuclear Medicine review committee: the COG-A3973 (DSA; n=216) and SIOPEN HR-NBL1 trial (DSB; n=343). Predefined categories from DSB were used with a SISCO of 0, 1-3, 4-17 and ≥18. In addition, the YOUDEN index was used to identify single cut points (CPY). The median follow-up time was 7.1 and 5.5y, respectively. **Results:** Both DS showed a significantly superior EFS with a SISCO ≤3 at diagnosis [5-yr EFS in DSA: 51%±7% vs 34%±4%, p= 0.047 and in DSB 47%±7% vs 26%±3%, p=0.007]. However, the YOUDEN index yielded different results at diagnosis with a CPY of 40 in DSA and 10 in DSB and failed to identify a consistent poor prognosis group. A post induction SISCO of ≤3 also revealed a significant superior outcome [5-yr EFS in DSA: 43%±5% vs 16%±6%, p=0.004 and in DSB 36%±4% vs 14%±4%, p< 0.001]. The post induction CPY was 3 in DSB (in line with the DSB stratification criterion of ≤3 mIBG positive spots to proceed to high dose chemotherapy) and 0 in DSA. Pts with a SISCO of 0 post induction have the best outcome in both DS. In MYCN amplified pts, the pre and post-induction SISCO of ≤3 showed a significant impact in both groups, whilst in MYCN non-amplified pts this effect is only seen post induction. A SISCO ≤3 has independent statistical significance in Cox models including age and MYCN. **Conclusions:** A SIOPEN score ≥ 3 of mIBG scans carries relevant prognostic significance for the management of patients with high-risk NB at diagnosis and at the end of induction chemotherapy in the HRNBI1/SIOPEN trial and was confirmed in the independent COG A3973 data set. Clinical trial information: NCT01704716.

**10030 Poster Highlights Session (Board #331), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**A neuroblastoma risk classification model for developing countries: A study from the International Neuroblastoma (NB) Risk Group (INRG) database.** *Presenting Author: Wendy B. London, Dana-Farber Cancer Institute/Boston Children's Hospital, Boston, MA*

**Background:** Current methods for stratifying NB patients (pts) at diagnosis to INRG risk/pre-treatment groups are based on prognostic clinical, genomic, and histologic factors [Cohn et al, JCO 2009]. In developing countries, testing tumors for genomic biomarkers or histologic features is not possible; however, clinical tests serum ferritin and serum lactate dehydrogenase (LDH) are likely available. **Methods:** Retrospective analysis included INRG pts with sufficient data for clinical risk factors and event-free survival (EFS). Survival tree regression was performed, considering only age (<18 months; ≥18 months), INSS stage (4; not 4), ferritin (<92; ≥92ng/mL), and LDH (<587; ≥587U/L). Pts were categorized into clinical pre-treatment risk groups, categorized by 5-yr EFS: very low (>85%), low (>75-≤85%), intermediate (≥50-≤75%), or high risk (<50%). EFS time was calculated from diagnosis until first event (relapse/progression, second malignancy, death), or until last contact if no event occurred. **Results:** From 8,800 INRG pts, 7,679 were able to be risk classified according to INRG definitions, including genomic and histological factors. Of 7,679, 3,509 had known age, stage, LDH and ferritin and a clinical pre-treatment risk group was assigned: very low (n=1319), low (n=379), intermediate (n=550), and high (n=1261). 5-yr EFS for very low-, low-, intermediate-, and high-risk groups were 90±1%, 80±3%, 65±3%, 27±2%, respectively. The clinical risk classification was the same as (58.1%) or similar to (12.8%) the INRG in 70.9% of pts. Based on 5-year EFS: INRG overestimated risk but clinical factors correctly assigned risk in 18.9% of pts; clinical factors overestimated (3.7%) or underestimated (6.4%) risk but INRG correctly assigned risk in 10.1% of pts. **Conclusions:** In 89.9% of pts, clinical factors (age, stage, ferritin, LDH) do as well or better than clinical, genomic, and pathologic factors currently used in INRG risk/pre-treatment group assignment. The INRG-clinical pre-treatment risk stratification shows promise for developing countries to assign treatment intensity, whereby very low-risk pts can be spared unnecessary, expensive chemotherapy.

**10031 Poster Highlights Session (Board #332), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**Validation of postinduction Curie scores in high-risk neuroblastoma.** *Presenting Author: Gregory A Yanik, University of Michigan Medical Center, Ann Arbor, MI*

**Background:** A semi-quantitative MIBG scoring method (Curie scoring, CS) has been previously examined in the Children's Oncology Group (COG) high-risk neuroblastoma trial, COG A3973, with a post-induction CS >2 associated with poor event-free (EFS) and overall survival (OS). We now examine the impact of Curie scoring in an independent data set, the SIOPEN-HR-NBL1 (SIOPEN-NB) high-risk study. **Methods:** MIBG scans from patients with MIBG avid, INSS stage 4 neuroblastoma enrolled on SIOPEN-NB were evaluated at diagnosis (n=345) and post-induction (n=330). Scans were evaluated in 10 different anatomic regions by 2 reviewers, including 9 skeletal and 1 soft issue region, with each region scored 0-3 based upon disease extent, and a cumulative consensus score generated. Optimal cut-points at diagnosis (Dx) and post-induction were determined using the Youden index, with outcomes determined. Curie scores from patients enrolled on COG A3973 at diagnosis (n= 280) and post-induction (n= 237) were used for comparison. **Results:** The optimal CS cut-points at Dx were 12 in SIOPEN-NB and 9 in COG A3973. There was a significant outcome difference by CS (≤ 12 vs > 12) at Dx [5-yr EFS: 43.0±5.7 vs 21.4±3.6%, p<0.0001] in the SIOPEN-NB cohort. By comparison, CS at Dx were not prognostic in COG A3973, with no outcome difference identified at any cut-point. The optimal CS cut-point post-induction was 2 in both SIOPEN-NB and COG A3973, with a post-induction CS > 2 associated with inferior outcomes (Table). A post-induction CS > 2 carried prognostic significance for both MYCN amplified and MYCN non-amplified tumors, in both COG A3973 and SIOPEN-NB. The Curie score at Dx and post-induction maintained independent statistical significance in Cox models when compared to standard predictive covariates age and MYCN. **Conclusions:** The prognostic significance of post-induction Curie scores has now been validated in an independent cohort of patients, with a post-induction Curie score > 2 associated with inferior outcome in two cooperative group trials, SIOPEN-HR-NBL1 and COG A3973.

| | | Post-induction Curie score | | | | | |
|---|---|---|---|---|---|---|---|
| | | 5-year EFS (± SE) | | | 5-year OS (± SE) | | |
| | No. | CS ≤ 2 | CS > 2 | p | CS ≤ 2 | CS > 2 | p |
| SIOPEN | 330 | 39.2 ± 4.7 | 16.4 ± 4.2 | <0.001 | 48.0 ± 4.7 | 29.5 ± 5.1 | <0.001 |
| COG | 237 | 42.0 ± 5.8 | 10.5 ± 10.0 | <0.001 | 55.4 ± 6.3 | 26.7 ± 11.4 | 0.02 |

**10032 Poster Highlights Session (Board #333), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**A phase 2 study of vincristine and irinotecan in metastatic diffuse anaplastic Wilms tumor: Results from the Children's Oncology Group AREN0321 study.** *Presenting Author: Najat C. Daw, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Patients with metastatic diffuse anaplastic histology Wilms tumor (DAWT) had an unacceptably low 4-year event-free survival (EFS) and overall survival of 33% on the National Wilms Tumor Study-5. Preclinical and clinical data showed promising antitumor activity of the camptothecins in Wilms tumor. **Methods:** AREN0321 evaluated the activity of vincristine (Vinc) and irinotecan (Irino) in a phase 2 window in newly-diagnosed patients with Stage IV DAWT. Patients received Vinc (1.5 mg/m$^2$/day) intravenously (IV) on days 1 and 8, and Irino (20 mg/m$^2$/day) IV on days 1-5 and 8-12 of a 21-day cycle. In the absence of progressive disease (PD), a second cycle was administered. Tumor responses after 2 cycles of therapy were centrally reviewed and assessed using the RECIST criteria. Patients with partial response (PR) had Vinc/Irino incorporated into a chemotherapy regimen consisting of Vinc, doxorubicin, cyclophosphamide, carboplatin, and etoposide, plus local and whole lung radiation therapy. Patients with stable disease or PD did not receive additional cycles of Vinc/Irino. A 2-stage design was used with the aim to accrue 10 patients in the first stage and continue accrual if an adequate number of responses was observed. The window study closed after other strata of AREN0321 reached their accrual targets. **Results:** Twenty-four patients with stage IV DAWT were enrolled from June 2006 to December 2012. Five patients did not have measurable disease and were ineligible for window therapy. Nineteen had measurable disease, 14 of whom elected to participate in the window. Of these 14 patients, 11 (79%) had PR and 3 had PD. Two of the 3 non-responders also did not achieve complete response to the other agents in the chemotherapy regimen. The most common grade 3-4 toxicities during the window were diarrhea (n=3), hypoxia (n=2), elevation of aspartate aminotransferase (n=2), hypoalbuminemia (n=2), and hyperglycemia (n=2). **Conclusions:** The Vinc/Irino combination was well tolerated and produced a high response rate in patients with metastatic DAWT. Its incorporation into Wilms tumor treatment regimens deserves further evaluation. Clinical trial information: NCT00335556.

**10033 Poster Highlights Session (Board #334), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**Phase II study of $^{131}$I-MIBG with vincristine and 5 days of irinotecan for patients with relapsed or refractory neuroblastoma.** *Presenting Author: Steven G. DuBois, University of California, San Francisco, San Francisco, CA*

**Background:** $^{131}$I-metaiodobenzylguanidine (MIBG) is a targeted radiopharmaceutical active in neuroblastoma. A previous study demonstrated that MIBG (18 mCi/kg) could be combined with vincristine and irinotecan (20 mg/m$^2$/dose for 5 days/week x 2 weeks) as a radiation sensitizer. However, 25% of courses were associated with grade 3 diarrhea. To reduce the incidence of diarrhea, the current study evaluated MIBG together with vincristine and 5 days of higher-dose irinotecan, a standard schedule in recent pediatric trials. This report describes the experience with this regimen at maximum tolerated MIBG dose of 18 mCi/kg. **Methods:** Patients $<$ 30 with relapsed or refractory MIBG-avid neuroblastoma were eligible for this multicenter trial (NCT01313936). Prior MIBG therapy was allowed if $>$ 6 months from prior MIBG and $<$ 18 mCi/kg cumulative prior dose. Patients received cefixime on days -1 to +6, irinotecan (50 mg/m$^2$/dose IV) on days 0-4, and vincristine (2 mg/m$^2$) on day 0. MIBG (18 mCi/kg) was given on day 1 and peripheral blood stem cells on day 13. Up to two courses of therapy were allowed. Response was assessed at day 42 and was the primary endpoint of this phase II portion. Consenting patients provided germline DNA for *UGT1A1* genotyping. **Results:** 26 patients received 37 courses of therapy. Myelosuppression was the most common toxicity, with 55% of patients with grade 4 thrombocytopenia and 65% of patients with grade 4 neutropenia in course 1. No patients had failure to engraft. Only 4.5% of first courses were associated with grade 3 diarrhea. Correlation of *UGT1A1* genotype with toxicity is ongoing. Centrally reviewed best response after course 1 is available for 17 patients at the time of this submission. Of these, the overall response rate was 23.5% (2 CR and 2 PR). The response rate by MIBG scan was 37.5%, including 4 CR. **Conclusions:** MIBG at doses of 18 mCi/kg with vincristine and 5 days of irinotecan is tolerable and active. This regimen is now being compared to single-agent MIBG in a randomized phase II trial. Clinical trial information: NCT01313936.

**10034 Poster Highlights Session (Board #335), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**Historical gold standard for time-to-progression (TTP) and progression-free survival (PFS) from relapsed/refractory neuroblastoma modern era (2002-2014) patients.** *Presenting Author: Wendy B. London, Dana-Farber Cancer Institute/Boston Children's Hospital, Boston, MA*

**Background:** Early phase trials of investigational agents in pediatric patients (pts) with relapsed neuroblastoma (NB) historically used "response" per RECIST as the primary endpoint; response rate determined whether to test agents in Phase 3. Response assessment is challenging because NB in bone and bone marrow is not 'measureable'. TTP and PFS endpoints are better suited to measure potential therapeutic benefit in NB, especially for targeted biologic agents and immunotherapies. Historical data on PFS or TTP exist only in small potentially biased NB cohorts. Herein, we study the largest cohort to date of relapsed/refractory NB pts, treated with modern era frontline and relapse therapy. We determined PFS, OS, & TTP, for use as historical comparators in future Phase 2 studies. **Methods:** 489 NB enrollments (consecutive 11/2002-1/2014), from 384 distinct pts, on 36 Phase 1 (27) or 2 (9) Children's Oncology Group trials were analyzed for PFS (relapse, progression, death from disease), overall survival (OS) (death- any cause), & TTP, starting from Phase 1,2 trial enrollment. If pts were on multiple trials, enrollments were analyzed as if they were independent. For PFS, non-disease deaths were censored. Using RECIST, only 2 Phase 2 trials met the prospective response rate bar for success. For high-risk pts, planned frontline therapy included HSCT; 11.6% received ch14.18 antibody. **Results:** From relapse study enrollment: 1-year & 4-year PFS were 19±2% & 8±3%, respectively; 56±3% & 14±4% for OS; median TTP was 63 days (95% CI: 56,79). Median follow-up time in pts without progression was 9.7 mos. Risk factors at diagnosis were known in pt subsets: 88% of 230 - INSS stage 4; 92% of 230 - ≥18 mos old; 18% of 189 - *MYCN* amplified; 49% of 180 - diploid; 94% of 172 - unfavorable histology. Only *MYCN* amplification was prognostic of worse PFS after relapse study enrollment ($p<0.001$). Median time from diagnosis to first relapse/progression was 22 mos (95% CI: 19,25) (n=214). **Conclusions:** PFS/TTP/OS from this representative comprehensive historical COG early-phase trial NB cohort should be used in Phase 2 trials as the gold standard comparator to identify promising new agents for NB.

**10035 Poster Highlights Session (Board #336), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**Clinical application of comprehensive next-generation sequencing-based genomic profiling for identification of actionable genomic alterations in pediatric solid tumors and hematolymphoid malignancies: The Foundation Medicine pediatric experience.** *Presenting Author: Matthew J. Hawryluk, Foundation Medicine, Inc., Cambridge, MA*

**Background:** Oncology is undergoing a paradigm shift with the advent and increasingly successful utilization of targeted therapies. Unfortunately, many pediatric tumors lack approved targeted therapies, and routine genomic profiling of pediatric tumors has yet to be broadly applied. Comprehensive testing platforms are required to determine the landscape of genomic alterations in pediatric solid tumors and thereby broaden therapeutic options. We have developed a next-generation sequencing-based test, optimized for routine clinical FFPE specimens, and report here on over 340 pediatric patients' tumors analyzed to date in our CLIA-certified, CAP-accredited laboratory. **Methods:** Hybridization capture of 3,320 exons from 182 cancer-related genes and 37 introns of 14 genes commonly rearranged in cancer (previous version of the test) or 3,769 exons from 236 cancer-related genes and 47 introns of 19 genes commonly rearranged in cancer (current version of the test) was applied to ≥ 50ng of DNA extracted from over 340 pediatric tumors. Genomic alterations were identified and reported for these patient samples. **Results:** Successful profiles were generated from 343 pediatric patient specimens from individuals ≤21 years old at the time of sample procurement. The pediatric clinical experience consists of: adrenal and soft tissue neuroblastomas (n=83), sarcomas (n=53), brain (n=42), bone sarcomas (n=26), leukemias (n=30), rhabdomyosarcomas (n=17), liver (n=16), kidney (n=14), lung (n=13), lymphomas (n=7), and other tumors (n=42). **Conclusions:** Comprehensive NGS-based genomic profiling identified alterations in a majority of 343 unselected pediatric cancer clinical cases and more than half of these patients were found to have at least one alteration targeted by a therapeutic on the market or in clinical trials. Widespread deployment of this approach may provide treatment options for pediatric cancer patients requiring systemic approaches.

**10036 Poster Highlights Session (Board #337), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**Molecular analysis of solid tumors (MAST): A protocol for comprehensive preclinical evaluation of pediatric solid tumors.** *Presenting Author: Sara Michele Federico, St. Jude Children's Research Hospital, Memphis, TN*

**Background:** The genomic landscape of pediatric solid tumors is actively being investigated and to date, few recurrent actionable mutations have been identified. Using orthotopic xenografts, we developed MAST to better characterize the genetic lesions of these tumors as well as investigate the correlations between drug sensitivity, gene expression and genomic and epigenetic findings. **Methods:** We obtained tumor samples from 24 pediatric solid malignancies including neuroblastoma (n=5), rhabdomyosarcoma (n=7), osteosarcoma (n=9), Ewing sarcoma (n=1) and high grade sarcoma NOS (n=2). Fresh tumor samples were extensively analyzed including histology, electron microscopy, gene expression profiling, single nucleotide polymorphism (SNP) microarrays, whole genome sequencing, exome sequencing, RNA-seq and DNA methylation. Orthotopic xenografts were developed, characterized and compared to the original patient tumors. High-throughput screening of primary cultures derived from the xenografts was performed to test drug sensitivity. Clonal evolution, for tumors with banked tissue from diagnosis, was studied in tumor samples obtained at the time of disease recurrence. **Results:** Our analysis demonstrated that the xenografts closely recapitulate the molecular features of their primary tumors. Drug screening demonstrated that there was little, if any, correlation between the identified genetic lesions, molecular markers and drug hits. Clonal analysis of recurrent tumors identified variability of major and minor clones present at the time of diagnosis and recurrence and specific to the site(s) of disease. **Conclusions:** Through the MAST protocol we developed a diverse panel of pediatric solid tumors for preclinical testing.Our data suggests that up front genetic profiling of tumor tissue may not be predictive of response to targeted therapies for many patients with pediatric solid tumors. Further studies on clonal evolution are necessary as mutations present at diagnosis may differ from those present at recurrence. The MAST model sets a new standard for preclinical testing in which we will use cell biology studies combined with genomic analysis to identify new therapies.

**10037 Poster Highlights Session (Board #338), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**Molecular profiling of 267 pediatric cancers to identify potential clinically relevant targets.** *Presenting Author: Todd Maney, Caris Life Sciences, Phoenix, AZ*

**Background:** Even though only 1% of cancers occur in children, it is the 2nd leading cause of death in children. Survival rates depend on the type of cancer, the majority of which arise from the central nervous system, bone, or neuroblasts. **Methods:** 267 cases referred to Caris Life Sciences were tested per physician request, including sequencing (Sanger, next generation [NGS]), protein expression (immunohistochemistry [IHC]), gene amplification (CISH or FISH), and/or MGMT methylation. Diagnoses were collected from referring physicians at intake; for this analysis, cases were initially grouped into carcinomas (CA), n=40, sarcomas (SA), n=117, neuroendocrine (NET), n=12, germ line (GL), n=11, or central nervous system (CNS), n=37. Within those groups the specific diagnoses were further delineated. **Results:** In this pediatric cohort, biomarker alterations included higher AR protein expression in CA and SA, higher ER expression in CA, GL, and NET, and EGFR amplification in all but GL. MGMT loss was highest in CNS, PTEN loss was highest in GL and both were lowest in CA. PGP was expressed at less than 15% in CNS and SA and 68% in CA. No HER2 protein overexpression, amplification, or gene mutations were seen. TP53 mutations were lowest in SA (9%) and varied between 25 and 50% in the others. Of the gene panel tested, CTNNB1 was mutated in 1 patient in CA and SA, while AKT1, CSFIR, and MPL were mutated in 1 patient each in GL. KRAS was mutated at least once in all but CNS. All other mutations (MT) were exclusive to the CNS group, and included PTEN, SMO, VEGF, ERBB4, EGFR, ALK, and APC. These were specific to the astrocytomas, which also had the only MGMT methylation event, except for ALK MT (neuroblastoma) PTEN MT (medulloblastoma), and EGFR MT (ganglioglioma). **Conclusions:** The mutations in the CNS group suggest MEK and mTOR pathway involvement. Biomarker profiling to identify therapeutic targets has potential in pediatric patients and warrants further investigation. Comparison to adult onset of these types of cancers may yield different molecular profiles for a subset of these cancers. Because children typically respond well to chemotherapy, targeting specific molecular alterations identified in childhood cancer could prove very effective.

**10038 Poster Highlights Session (Board #339), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**Association of genetic variants involved in drug metabolism and transport with efficacy and toxicity of chemotherapeutic treatment in osteosarcoma patients.** *Presenting Author: Hanneke I. Vos, Laboratory of Pediatric Oncology, Radboud University Medical Center, Nijmegen, Netherlands*

**Background:** Despite multiagent chemotherapeutic treatment, osteosarcoma patients relapse frequently and survival has reached a plateau in the past decades. A poor response to chemotherapy seems to be the predominant risk factor for an unfavorable outcome. We have previously identified several genetic polymorphisms in genes in the metabolic pathways of cisplatin and doxorubicin which might be used for risk stratification of patients in relation to treatment response. However, as the complex metabolism of drugs used in the treatment of osteosarcoma involves a broader range of genes, we have performed a DMET analysis including 1,936 genetic variants in 231 genes known to be involved in drug metabolism and transport. **Methods:** We used a two-stage design, including 135 osteosarcoma patients in the discovery stage. Germline DNA was genotyped using the DMET Plus array. Associations between the presence of genetic variants and histological response (HR) to preoperative cisplatin and doxorubicin based chemotherapy, 5-year Disease Free Survival (DFS) and ototoxicity (SIOP grade 1-3) were assessed by logistic regression models in PLINK. In the replication cohort 185 osteosarcoma patients will be included. **Results:** 734 markers and 131 patients passed quality control (call rates $> 0.9$, minor allele frequency $> 0.01$) in the discovery cohort. A total of 21 markers showed association ($p < 0.05$) with HR and 20 markers with 5-year DFS, with overlap of associated markers in the transporter *SLCO4A1* and Phase I enzyme *CYP8B1* genes. In addition, 21 markers were significantly associated with ototoxicity, the majority was located in cytochrome p450 genes. **Conclusions:** To the best of our knowledge, the present pharmacogenetic study is the first in osteosarcoma patients using the DMET analysis. Significant associations of treatment response and ototoxicity with genes previously unknown to impact cisplatin and doxorubicin metabolism and transport were explored. Following replication and validation in functional studies and in larger prospective studies, these markers are of potential interest for the development of new treatment strategies and optimizing current therapy.

**10039 Poster Highlights Session (Board #340), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**Subsequent neoplasms in the fifth and sixth decades of life in the Childhood Cancer Survivor Study cohort.** *Presenting Author: Lucie Marie Turcotte, University of Minnesota, Minneapolis, MN*

**Background:** The risk of subsequent neoplasms (SN) in childhood cancer survivors increases over time, but only limited data exist on risk beyond 40 years of age. **Methods:** Occurrence of SN was evaluated in 3171 5-year adult survivors of childhood cancer ≥40 years of age (median 44 years, range 40-58) following cancer diagnosed <21 years of age, between 1970-1986. Cumulative incidence and standardized incidence ratio (SIR), with corresponding 95% confidence intervals (CI) were used to evaluate risk of SN and subsequent invasive malignant neoplasm (SMN), respectively. SIR were calculated using age-, sex- and calendar year-specific incidence from the NCI Surveillance, Epidemiology and End Results program. Survivors with a history of SN prior to age 40 ($SN_{pos}$) were also compared to those without previous SN ($SN_{neg}$). **Results:** A total of 371 SN were diagnosed ≥40 years of age, including 136 SMN (SIR=2.2, CI 1.9-2.5), 191 non-melanoma skin cancers (NMSC), and 44 meningiomas and other non-invasive neoplasms. Cumulative incidence of a new SN after age 40 was 34.6% (CI 28.7-40.6) at age 55, with $SN_{pos}$ having a higher incidence compared to $SN_{neg}$ 57.6% (CI 46.7-68.6) versus 30.4% (CI 23.8-37). While cumulative incidence of new SMN at age 55 was similar for $SN_{neg}$ and $SN_{pos}$ (15.4% (CI 10.2-20.5) vs. 20.8% (CI 12.5-29.1)), $SN_{pos}$ experienced more NMSC compared to $SN_{neg}$ (cumulative incidence 16.2% (CI 10.8-21.6) vs. 38.2% (CI 27.9-48.5)). Compared to the U.S. population, risk of a SMN was elevated for both $SN_{neg}$ and $SN_{pos}$ (SIR=2.0, CI 1.7-2.4 vs. SIR=3.0, CI 2.2-4.0). Breast cancer was the most common SMN beyond age 40, and also carried the largest risk (SIR=5.5, CI 4.5-6.7). Significantly elevated risks were also seen for renal cancer (SIR=3.9, CI 2.0-7.5), soft tissue sarcoma (SIR=2.6, CI 1.5-4.4) and thyroid carcinoma (SIR=1.9, CI 1.0-3.5). Hodgkin lymphoma (SIR=3.6, CI 3.0-4.4) and radiation therapy (SIR=2.6, CI 2.2-3.1) were associated with high risk of SMN although the magnitude of risk for $SN_{neg}$ and $SN_{pos}$did not differ substantially. **Conclusions:** Risk of SN remains significantly elevated after age 40. These data have important implications for screening and should inform anticipatory guidance provided to childhood cancer survivors.

**10040 Poster Highlights Session (Board #341), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**Influence of polymorphisms discovered in cell-based model of cytarabine sensitivity on outcome in pediatric AML: A Children's Oncology Group Study.** *Presenting Author: Christine L. Phillips, Cincinnati Children's Hospital Medical Center, Cincinnati, OH*

**Background**: Genetic variability of patients with AML contributes to the success and tolerability of cytarabine-based therapy. **Methods**: We investigated 120 genetic polymorphisms (SNPs) associated with cytarabine sensitivity ($p<0.0001$) that were discovered in a previous cell-based genome wide association study using Hap Map lymphoblastoid cell lines. We tested these variants for impact on outcome in 412 children with de novo AML treated on Children's Oncology Group protocols, CCG 2941 and 2961. Therapy consisted of intensive cytarabine based induction and a randomization to consolidation with different cumulative doses of cytarabine; IDA-DCTER (3200 mg/m$^2$) or IDA-FLAG (9190 mg/m$^2$) in 2961. **Results**: The homozygous variant genotypes of rs 2025501 and rs 6661575 had increased in vitro cytarabine sensitivity and were also associated with increased treatment related mortality (TRM). TRM was most markedly increased in children randomized to the high dose cytarabine arm IDA-FLAG (rs 2025501: TRM 29 ± 7 % AA vs. 8 ± 3% GA, 17 ± 6% GG, p= 0.007 and rs 6661575: TRM 60 ± 20% T/T vs. 14 ± 5% C/T, 14 ± 4% CC, p=0.011) compared to the IDA-DCTER arm where no significant differences were observed. Improvement in three-year cumulative incidence of relapse was not statistically significant for either variant genotype. These SNPs are intragenic, but search in relevant databases indicate they are eQTLs with influence on expression of other genes. **Conclusions:** These findings warrant further exploration and validation in an independent dataset, but suggest cytarabine sensitivity genotypes may predict treatment related mortality and could be used to stratify to standard vs. high dose cytarabine regimens.

| rs 2025501 | 1-year cumulative incidence of TRM | TRM randomized to IDA-FLAG arm | 3-year relapse rate (RR) |
|---|---|---|---|
| | % deaths ± 1 SE | % deaths ± 1 SE | RR ± 1 SE |
| =G/G | 21 ± 5 % | 17 ± 6 % | 43 ± 5 % |
| G/A | 11 ± 3 % | 8 ± 3 % | 39 ± 4 % |
| A/A | 23 ± 5 % | 29 ± 7 % | 28 ± 5 % |
| p value | 0.048 | 0.007 | 0.184 |

| rs 6661575 | 1-year cumulative incidence of TRM | TRM randomized to IDA-FLAG arm | 3-year (RR) |
|---|---|---|---|
| | % deaths ± 1 SE | % deaths ± 1 SE | RR ± 1 SE |
| C/C | 15 ± 3 % | 14 ± 4 % | 38 ± 3 % |
| C/T | 19 ± 4 % | 14 ± 5 % | 38 ± 6 % |
| T/T | 50 ± 20 % | 60 ± 26 % | 12 ± 13 % |
| p value | 0.011 | 0.011 | 0.482 |

**10041 Poster Highlights Session (Board #342), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**Treatment and outcome of patients with relapsed clear cell sarcoma of the kidney (CCSK): A combined SIOP and AIEOP study.** *Presenting Author: Saskia L Gooskens, Department of Pediatric Hematology and Oncology, Erasmus MC - Sophia Children's Hospital, Rotterdam, Netherlands*

**Background:** Clear Cell Sarcoma of the Kidney (CCSK) is an uncommon pediatric renal tumor. Relapses occur in about 15% of the patients. Detailed clinical information on relapsed CCSK is scarce. The current study aims to describe outcome of patients with relapsed CCSK treated according to recent European protocols, in order to find a rational for creating future international CCSK relapse treatment protocols. **Methods:** We analysed prospectively collected data of all CCSK patients who developed a relapse after complete response to initial therapy, entered onto International Society of Pediatric Oncology (SIOP) and Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) trials between 1992 and 2012. **Results:** Thirty-seven of 237 CCSK patients (16%) treated according to SIOP and AIEOP protocols developed a relapse. Median time from initial diagnosis to relapse was 17 months (range, 5.5 months - 6.6 years). 35/37 relapses (95%) were metastatic; the most common sites of relapse were brain (n = 13), lungs (n = 7) and bone (n = 5). Relapse treatment consisted of chemotherapy (n = 30), surgery (n = 19) and/or radiotherapy (n = 18), followed by high dose chemotherapy and autologous bone marrow transplantation (ABMT) in 14 patients. 22/37 patients (59%) achieved a second complete remission (CR); 15 of whom (68%) developed a second relapse. Five-year event-free survival (EFS) after relapse was 18% (95% CI: 4-32%) and 5-year overall survival (OS) was 26% (95% CI: 10-42%). **Conclusions:** In this largest series of relapsed CCSK patients ever described, overall outcome is poor. Relapses tend to occur late, so extensive follow-up is desirable. Most relapses are metastatic and brain relapses are more common than previously recognized. Intensive treatment aiming for local control, followed by high dose chemotherapy and ABMT, seems to be of benefit to enhance survival. Novel development of targeted therapy is urgently required.

**10042 Poster Highlights Session (Board #343), Mon, 8:00 AM-11:45 AM and 11:30 AM-12:45 PM**

**Increased risk of second malignant neoplasms (SMN) in young children with embryonal rhabdomyosarcoma (ERMS): Evidence for a cancer predisposition syndrome?** *Presenting Author: Renata Parada Amorim, Faculdade de Ciências Médicas da Santa Casa de São Paulo, Sao Paulo, Brazil*

**Background:** Germline TP53 mutations have been recently described in children with anaplastic EMRS, suggesting a possible association with Li-Fraumeni syndrome (LFS). In this population-based study we aimed to assess the risk of SMN according to distinct rhabdomyosarcoma (RMS) subtypes and age groups that could identify high-risk individuals who warrant close surveillance. **Methods:** Data from SEER-9 (1973-2010) from children ages 0-19 with RMS were analyzed. Standardized incidence ratios (SIR) and corresponding 95% confidence intervals (95% CI) were calculated using SEERStat 8.1.2. **Results:** 1,151 children (median age=7 years) with RMS were included. Histologies were embryonal (58.2%), alveolar (24.8%), not otherwise specified (NOS) (14.3%), mixed (1.4%), and pleomorphic (1.3%).Twenty-nine SMN were identified, resulting in five-fold increased risk (SIR= 5.69, 95% CI 3.81-8.17). The increase in risk was attributable to second solid tumors, which were consistent with the LFS spectrum, and it was higher for pleomorphic type (SIR=15.77, 95% CI 1.91-56.96). Risk of SMN was higher among those treated at a younger age [children < 2 yrs at diagnosis (SIR=13.38, 95% CI 4.34-31.22) vs. children > 10 yrs (SIR=3.35, 95% CI 1.53-6.35)]. Among children < 2 yrs, those with ERMS histology were at greatest risk (SIR=14.72, 95% CI 4.01–37.70), and it increased when embryonal and NOS histologies were combined (SIR=19.08, 95% CI 6.20-44.54). Among children ages 5-9, the risk was the highest for children 5-9 yrs with pleomorphic type (SIR=314.95, 95% CI 7.91-1,754.80). The risk of SMN was independent of the use of radiation (RT) to the primary (RT: SIR=6.50, 95% CI 3.97–10.03 vs. no RT SIR=4.57, 95% CI 2.09-8.68,). Patients < 5 years receiving RT had higher risk than older patients (SIR=10.52, 95% CI 4.23-21.68 vs. SIR=3.07, 95% CI 1.46-8.65 for > 10 years, respectively). **Conclusions:** Children with RMS are at high risk of developing SMN. This risk is particularly higher for a subgroup of young children with embryonal or pleomorphic histology, and is independent of the use of RT, suggesting a constitutional predisposition.

**10043 General Poster Session (Board #344), Mon, 8:00 AM-11:45 AM**

**Correlation of childhood acute lymphoblastic leukemia subclones carrying intragenic *IKZF1* deletions with relapse.** *Presenting Author: Peter Hoogerbrugge, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands*

**Background:** Relapse is the major cause of treatment failure in childhood acute lymphoblastic leukemia (ALL), and further improvement of risk stratification is essential for obtaining better cure rates. We and others demonstrated that the presence at diagnosis of deletions in *IKZF1*, the gene encoding the lymphoid transcription factor IKAROS, is a strong risk factor for relapse. Furthermore, preliminary results show that these deletions can be present at subclonal levels, often undetectable by routine methodologies. These findings are in line with recent studies, which have shown a complex, dynamic architecture of clonal diversity in ALL, both at diagnosis and at relapse. This multiclonal diversity likely contributes to the selective outgrowth of therapy-resistant leukemic cells during or after chemotherapy treatment, resulting in relapse. Whether subclonal deletions in *IKZF1* are also associated with relapse has not been thoroughly investigated. **Methods:** Several recurrent intragenic deletions in *IKZF1* show clustering of their genomic breakpoints, which allows efficient detection of subclonal deletions by sensitive semi-quantitative breakpoint-spanning PCR. Using this method, we screened a cohort of 331 B-cell precursor ALL patients, treated according to the DCOG-ALL9 and ALL10 protocols, for the presence of subclonal exon 4-7 *IKZF1* deletions (*IKZF1*Δ4-7) at diagnosis. The cohort was slightly enriched for relapsed cases (36.6%). **Results:** A total of 34 *IKZF1*Δ4-7 deletions were found, of which 17 were not detected by routine MLPA. All deletions carried unique breakpoints and TdT-mediated non-templated sequences. The 17 MLPA-negative cases had an allelic burden of the *IKZF1*Δ4-7 deletion varying from 28% to <1%. Whereas 12 cases with full clonal *IKZF1*Δ4-7 deletions eventually relapsed, only 6 cases with subclonal *IKZF1*Δ4-7 deletions developed a relapse. Remarkably, in none of the cases for which material was available for testing (n=4), these subclonal lesions were detected in the relapsed clone. **Conclusions:** Our data suggest that, in contrast to clonal *IKZF1*Δ4-7 deletions, subclonal deletions of *IKZF1*Δ4-7 rarely contribute to relapse development in ALL.

**10044 General Poster Session (Board #345), Mon, 8:00 AM-11:45 AM**

**A comprehensive safety trial of chimeric antibody 14.18 (ch14.18) with GM-CSF, IL-2, and isotretinoin in high-risk neuroblastoma patients following myeloablative therapy: A Children's Oncology Group study.** *Presenting Author: Mehmet Fevzi Ozkaynak, New York Medical College, Valhalla, NY*

**Background:** In a Phase 3 randomized study (COG ANBL0032), we demonstrated that the addition of ImmRx to standard therapy isotretinoin for high-risk neuroblastoma (NB) patients in CR or VGPR after intensive induction and consolidation significantly improved outcome (Yu*, NEJM*, 2010). ANBL0931 study was designed to collect FDA-required comprehensive safety/toxicity data for ImmRx to support a new Biological License Application. Efficacy data were collected as a secondary endpoint. **Methods:** Newly diagnosed high-risk NB patients who achieved ≥PR to induction therapy and received myeloablative consolidation with stem cell rescue then received isotretinoin x 6 with 5 concomitant cycles of ch14.18 combined with GM-CSF (cycles 1,3,5) or IL2 (cycles 2,4). Ch14.18 infusion time was 10 hrs. which was prolonged compared to 5.75 hrs for the initial 245 patients on ANBL0032. Toxicity data were collected. **Results:** Of105 patients enrolled (none ineligible), five patients developed protocol-defined unacceptable toxicities and came off study (four grade 4 allergic reactions, one sudden death - sudden onset of abdominal pain and arrest). The most common grade 3 or higher non-hematologic toxicities of ImmRx were neuropathic pain (cycles 1, 2, 3, 4, 5 were 30.9%, 22%, 13.3%, 20%, 17%, respectively), hypotension (9.6%, 17%, 3.1%, 12.2%, 5.7%), allergic reactions (2.9%, 9%, 3%, 6.6%, 2.2%), capillary leak syndrome (1%, 4%, 0, 2.2%, 0), fever (21%, 58%, 6.1%, 31.1%, 4.5%). Toxicities occurred more frequently during IL-2 cycles compared to GM-CSF cycles. Dose modifications were reported in 73 patients (69%) most of which are thought to be prolongation of the ch14.18 infusion time beyond 10 hrs. The 2-year EFS and OS were 74±6% and 84±5%, respectively (n=105). **Conclusions:** This study has confirmed the significant, but manageable treatment-related toxicities of the ImmRx including pain, allergic reactions, hypotension and capillary leak syndrome. Decreased toxicity compared to ANBL0032 may be due to the 10 hr minimum ch14.18 infusion time for all patients in this study. EFS and OS appear similar to that observed on ANBL0032.

**10045 General Poster Session (Board #346), Mon, 8:00 AM-11:45 AM**

**IGF-1R inhibition effect on a yes/SFK bypass resistance pathway: Rational basis for cotargeting IGF-1R and yes/SFK kinase in rhabdomyosarcoma.** *Presenting Author: Xiaolin Wan, Pediatric Oncology, CCR, NCI, NIH, Bethesda, MD*

**Background:** The insulin-like growth factor 1 receptor (IGF-1R) has surfaced as a significant target in multiple solid cancers due to its fundamental roles in pro-survival and anti-apoptotic signaling. However, development of resistance to IGF-1R blockade represents a significant hindrance and limits treatment efficacy in the clinic. Thus, identifying the mechanisms of acquired resistance to IGF-1R blockade is a major goal. The aim of this study was to identify the molecular mechanisms responsible for acquired resistance to IGF-1R targeted therapy in rhabdomyosarcoma. **Methods:** Expression profiles of IGF components and Src family kinases (SFKs) were analyzed by cDNA microarray. Antiproliferative effects of anti-IGF-1R agents and SFK inhibitors alone or in combination were tested in vitro in multiple rhabdomyosarcoma (RMS) cell lines and in vivousing xenografts. Western blot and immunoprecipitation were performed to identify protential resistance mechanisms to IGF-1R inhibition. **Results:** We identified acquired resistance to IGF-1R blockade with R1507, an antibody against IGF-1R, and with BMS-754807, a small molecular inhibitor against IGF-1R/IR. In both cases, resistance was associated with increased activation of Yes/SFK in RMS. Combining anti-IGF-1R agents with SFK inhibitors resulted in blockade of IGF-1R inhibition induced activation of Yes/SFK and displayed enhanced antitumor activity in vitro and in vivo. **Conclusions:** Our data provide evidence that IGF-1R blockade results in activation of the Yes/Src family kinases (SFKs) by-pass resistance pathway in vitro and in vivo, and that co-targeting both IGF-IR and SFK shows advantageous antitumor activity in vitro and in vivo. Our preclinical data support consideration of clinical trials to test this combination in pediatric sarcomas.

**10046 General Poster Session (Board #347), Mon, 8:00 AM-11:45 AM**

**Identification of PDGFR-$\beta$ activation as a potential bypass resistance pathway in a rhabdomyosarcoma (RMS) model of acquired resistance to IGF-1 receptor blockade.** *Presenting Author: Christine Heske, National Cancer Institute, National Institutes of Health, Bethesda, MD*

**Background:** IGF-1R and its ligands have been shown to be potentially important therapeutic targets for sarcomas. Phase II sarcoma trials using IGF-1R blockade yielded clinically meaningful responses in unselected patients with pediatric type sarcomas. However, most responses were short-lived with rapid onset of resistance. Similarly, data from mouse xenograft RMS models showed initial response with subsequent resistance. Evaluation of tumor samples from treated mice showed persistently down-regulated IGF-1R, but rebound AKT phosphorylation, suggesting that resistance was not from loss of antibody activity against IGF-1R, but rather the result of a bypass pathway. We therefore sought to model acquired resistance in human RMS cells. **Methods:** Human RMS cell lines resistant to IGF-1R blockade were generated in xenografts from a highly sensitive parent cell line. Additional cell lines were selected for in vitro resistance. Parental and resistant lines were screened with a receptor phosphotyrosine array. Differences in expression were confirmed with Western Blot analysis and electrochemiluminescence detection. Cell growth under dual pathway inhibition was tested in vitro using IGF-1R antibody and several kinase inhibitors. **Results:** Screening of parental and resistant lines revealed increased phosphorylation of PDGFR-$\beta$ in resistant cells. PDGFR-$\beta$ and IGF-1R share several signaling pathways (PI3K, MAPK/ERK), suggesting that PDGFR-$\beta$ activation may act as a bypass mechanism to activate AKT. Target inhibition of PDGFR-$\beta$ in resistant cells was achieved with pazopanib. Proliferation assays have shown that dual inhibition of IGF-1R and PDGFR-$\beta$ in resistant clones enhances cell growth inhibition in vitro. Similar studies are ongoing using xenografted tumors. **Conclusions:** Activation of PDGFR-$\beta$ may be responsible for resistance to IGF-1R blockade in some RMS. This mechanism may also explain the rapid onset of resistance seen in clinical trials using IGF-1R blockade. Therapy targeting both IGF-1R and PDGFR-$\beta$ may be a rational combination to treat RMS and prevent onset of resistance in some patients.

**10047 General Poster Session (Board #348), Mon, 8:00 AM-11:45 AM**

**Preclinical evidence of craniofacial adverse effect of zoledronic acid in newborn mice: Potential consequences in pediatric osteosarcoma and Ewing's sarcoma patients.** *Presenting Author: Francoise Redini, INSERM UMR957, Nantes, France*

**Background**: Oncologic doses of zoledronic acid (ZOL) are currently evaluated in phase III clinical trials in Europe for the treatment of malignant primary bone tumors in children and adolescents. The impact of such an intensive treatment on the craniofacial skeleton growth is a critical question in the context of patients with actively growing skeleton. **Methods**: Two protocols adapted from pediatric treatments were developed for newborn mice (5 or 10 injections of ZOL 50 $\mu$g/kg every two days). Their impact on skull bones and teeth growth was analyzed by micro-CT and histology up to 3 months after the last injection. In parallel, panoramic radiographs of pediatric patients from the French OS2006 trial (chemotherapy +/- zoledronic acid) were analyzed for potential orofacial consequences. **Results**: In mouse, ZOL administrations induced a transient delay of skull bone growth and an irreversible delay in incisor, first molar eruption and root elongation. Root histogenesis was severely impacted for all molars and massive odontogenic tumor-like structures were observed in lower incisors. Panoramic radiograph analysis of 23 pediatric patients treated by chemotherapy + zoledronic acid in the OS2006 protocol showed not significant increase of tooth eruption delay comparatively to 21 patients treated by chemotherapy alone. **Conclusions**: In mouse, oncologic doses of ZOL irreversibly disturbed teeth eruption and elongation, and delayed skull bone formation. In human, ZOL treatment may impact the permanent teeth eruption. These observations are crucial for the follow-up of pediatric patients with bone tumors (osteosarcoma, Ewing's sarcoma) treated with zoledronic acid in several European and American protocols. Clinical trial information: NTC00470223.

**10048 General Poster Session (Board #349), Mon, 8:00 AM-11:45 AM**

**Preclinical evidence of positive effect of I-MTP-PE alone or combined with zoledronic acid in osteosarcoma.** *Presenting Author: Francoise Redini, INSERM UMR957, Nantes, France*

**Background**: Zoledronic Acid (ZA), a potent inhibitor of bone resorption is currently evaluated in phase III clinical trials in Europe for the treatment of malignant primary bone tumors. The beneficial effect of the liposomal form of MuramylTriPeptide-Phosphatidyl Ethanolamine (MTP-PE, mifamurtide), activating the macrophage population in tumors, has also proved its efficacy in osteosarcoma. The objective of our study was to evaluate the safety of the combination of zoledronic acid and liposomal mifamurtide in pre-clinical models of osteosarcoma before transfer to patients. **Methods**: Two protocols were developed in mouse syngenic models of osteosarcoma: (1) 1 or 2.5 mg/kg mifamurtide alone in primary tumor progression and pulmonary metastasis dissemination (experimental model induced by paratibial injection of murine osteosrcoma cells), (2) the potential interference of mifamurtide on ZA induced effect on osteosarcoma. These effects were evaluated at clinical, radiological (bone microarchitecture by microCT analysis), biological and histological levels. **Results**: Mifamurtide alone induced slight but not significant inhibitory effect on primary osteosarcoma growth. However, it significantly inhibits spontaneous (lung metastasis dissemination from primary bone tumor) and experimental (lung colonization after intraveinous injection of osteosarcoma cells) metastases at pulmonary site. Combinatory studies of mifamurtide associated with zoledronic acid showed no significant interference on specific effect on primary bone tumor growth, but rather synergism. **Conclusions**: In mouse, mifamurtide alone has a potent inhibitory effect on lung metastasis development, probably due to high macrophage infiltration in the lung parenchyma. Preliminary data did not evidence any interference of mifamurtide with ZA potential therapeutic activity in preclinical models of osteosarcoma.

**10049 General Poster Session (Board #350), Mon, 8:00 AM-11:45 AM**

**Regorafenib antitumor activity alone and in combination with radio or chemotherapy in preclinical models of pediatric solid tumors.** *Presenting Author: Estelle Daudigeos-Dubus, Institut Gustave Roussy, Villejuif, France*

**Background:** Angiogenesis plays a pivotal role in tumor growth and metastatic spread in children. High VEGF expression is correlated with invasion, metastases and risk for recurrence. In several pediatric tumors, angiogenesis is further driven by PDGFR and FGFR signaling. We evaluated the novel potent oral multikinase inhibitor regorafenib (BAY-73-4506) against pediatric cell lines and xenografts. **Methods:** Inhibition of cell proliferation and migration was explored in vitro against the Innovative Therapies for Children with Cancer (ITCC) cell line panel by MTS assay and against neuroblastoma cells by phase-contrast with Incucyte. In vivo, athymic mice bearing subcutaneous PDGFRA gene amplified IGRG93 glioma (derived from an adult patient) and IGRM57 medulloblastoma, and orthotopic IGR-N91-Luc neuroblastoma xenografts were treated with regorafenib at 10 or 30 mg/kg orally during at least 21 days alone or in combination with irradiation or irinotecan. **Results:** Regorafenib inhibited cell proliferation in vitro at GI50s of 1.85 – 31.8 $\mu$M in pediatric cell lines. It exhibited a dose-dependent effect on proliferation and migration of IMR-32-Luc and IGR-N91-Luc neuroblastoma cells with IC50s of 0.8 $\mu$M and 2.6 $\mu$M respectively. In IGR-N91-Luc neuroblastoma, IGRG93 glioma and IGRM57 medulloblastoma xenografts, regorafenib at 10 or 30 mg/kg resulted in significant tumor growth inhibition associated with decreased tumor vascularisation. In IGRG93 glioma, regorafenib resulted in significant tumor growth delay and 100% tumor regression (3/10 complete responses (CR) and 7/10 partial responses (PR) at 10 mg/kg; 5/11 CR and 6/11 PR at 30 mg/kg) when combined with irradiation which alone resulted in 3 PR in 11 tumors. Equivalent effects were observed against IGRM57 medulloblastoma when regorafenib was combined with irinotecan (5/7 CR and 2/7 PR versus 2/7 CR and 5/7 PR respectively). Inhibition of angiogenesis was associated with induction of tumor cell death, particularly in the combination strategies. **Conclusions:** Regorafenib exhibits significant antitumor activity alone and increased effects when combined with standard of care treatments.

**10050 General Poster Session (Board #351), Mon, 8:00 AM-11:45 AM**

**Molecular screening for cancer treatment optimization (MOSCATO 01) in pediatric patients: First feasibility results of a prospective molecular stratification trial.** *Presenting Author: Birgit Geoerger, Institut Gustave Roussy, Villejuif, France*

**Background:** This feasibility study intends to characterize genomic alterations in recurrent tumors of an individual pediatric patient in order to select a targeted therapy approach. **Methods:** Pediatric patients with recurrent or refractory solid tumor were proposed to undergo on-purpose tumor biopsy or surgical resection for molecular characterization. Biopsies were obtained using 18G needles under ultrasound, CT or MRI control from primary tumor or metastatic sites. DNA extracted from fresh samples was analyzed by CGHarray 180K (if $\geq$ 50% tumor cells in the sample) and by sequencing for 74 target genes (if $\geq$ 30% tumor cells). A panel of scientists and clinicians reviewed results to determine biological signification of the alteration and match patients to the most relevant targeted therapy available (mainly in early clinical trials). **Results:** From December 2012 to January 2014, 12 patients were consented; 3 were screening failures. Nine enrolled patients with a median age of 7 years (range, 3-18) and a median of 3 previous treatment lines underwent dedicated intervention. Six patients (rhabdomyosarcoma (2), osteosarcoma, angiosarcoma, cervical clear cell adenocarcinoma, high-grade glioma) had biopsy, two (medulloblastoma, PNET) underwent neurosurgical resection; one with leukemic Burkitt lymphoma had blood sample for analysis. Percentage of tumor cells per sample ranged between 50 and 90% in 8 out of 9 patients. Median time between biopsy/surgery and molecular results was 21 days (14-46). At least one actionable target was identified in 6 patients (75%). Genetic alterations encompassed *CDK4, EGFR, MYCN, MDM2, AR* amplification, *ERBB4, FGF, FGFR2, TCR* gain, *PTEN* loss, *PI3K* and *TP53*mutation/deletion. Two patients received an adapted targeted therapy; the others could not be treated with a matched therapy due to rapid tumor progression (1) or lack of a pediatric trial (3). **Conclusions:** High throughput molecular analysis of recurrent/refractory malignancies in pediatric patients is feasible. Presence of multiple alterations and limited access to targeted agents within pediatric clinical trials remain the main limiting factors. Clinical trial information: NCT01566019.

**10051 General Poster Session (Board #352), Mon, 8:00 AM-11:45 AM**

**Phase I study of proteasome inhibitor bortezomib in combination with irinotecan in patients with relapsed/refractory neuroblatoma.** *Presenting Author: Rajen Mody, University of Michigan Medical Center, Ann Arbor, MI*

**Background:** Despite recent progress in neuroblastoma (NBL) therapy, prognosis for relapsed/ refractory NBL remains poor. Bortezomib, a proteasome inhibitor has been shown to be effective by our group and others, against NBL in vitro and in vivo, either as a single agent or in combination with cytotoxic agents including irinotecan. **Methods:** Eligible patients high risk NBL, with primary refractory (n=8) or relapsed (n=10) disease. Bortezomib (1.2 mg/m2/day) was administered on days 1, 4, 8 and 11 intravenously (IV), with irinotecan 35, 40, or 45 mg/m2/day (Dose Level (DL) 1,2, and 3 respectively) administered IV days 1-5 of each 21day course. The maximum tolerated dose (MTD), dose limiting toxicity (DLT), and response were examined. **Results:** Eighteen patients with relapsed/ refractory, high risk NBL were treated, of which17 were evaluable. Three patients were treated at DL-1, 9 patients at DL-2 and 6 patients at DL-3. A total of 149 courses were delivered (mean of 8.2 and median of 2) with 2 patients receiving $>$ 40 courses of therapy. Therapy was very well tolerated and MTD was not reached. Two dose limiting toxicities (DLT) were reported, including grade 3 thrombocytopenia (n=1) and grade 3 irritability (n=1), at dose levels 2 and 3 respectively. Other grade 3 toxicities included neuropathy (n=1) after 34 cycles of therapy, and reversible hematologic toxicities (n=9). None of the patients experienced serious infection. DL-3 is the recommended dose for Phase-II studies. Two out of seventeen (12%) evaluable patients showed sustained objective responses lasting $>$ 40 courses, including 1 partial remission (PR) and 1 complete remission (CR). Four additional patients (23%) had prolonged stable disease (SD) lasting 6 courses or more with a total of 35% patients having prolonged SD or better. **Conclusions:** The combination of bortezomib with irinotecan was extremely well tolerated by patients with relapsed/ refractory NBL and exhibited very favorable toxicity profile. It showed promising clinical activity with 35% patients experiencing prolonged clinical benefit and merits further testing in Phase-II studies. Clinical trial information: NCT00644696.

**10052 General Poster Session (Board #353), Mon, 8:00 AM-11:45 AM**

**Phase 1 study of sorafenib and irinotecan in pediatric patients with relapsed or refractory solid tumors.** *Presenting Author: Holly Jane Meany, Children's National Medical Center, Washington, DC*

**Background:** Sorafenib, an orally bioavailable, multi-target tyrosine kinase inhibitor, and irinotecan, a topoisomerase I inhibitor, have demonstrated single agent activity in various malignancies. This study was designed to determine the maximum tolerated dose of sorafenib in combination with irinotecan and assess the feasibility of incorporating patient reported outcome (PRO) measures into a phase I trial in children with relapsed or refractory solid tumors. **Methods:** Sorafenib was administered orally twice daily, continuously, beginning at 150 mg/m$^2$/dose with irinotecan, 70 mg/m$^2$/dose orally, once daily for 5 days to complete a 21-day cycle (dose level 1). Sorafenib was escalated to 200 mg/m$^2$/dose (dose level 2) followed by escalation of irinotecan to 90 mg/m$^2$/dose (dose level 3). Three patients enrolled initially at each dose level. Secondary aims included evaluating PRO measures as an adjunct to traditional phase 1 endpoints and determining the pharmacokinetic profile of sorafenib and irinotecan in children. **Results:** Twelve evaluable patients [6 male, 6 female; median age 13 years (range 4.6-19.8)] with Wilms tumor (n= 4), osteosarcoma (n=3), neuroblastoma (n=1), CNS tumor (n=1), desmoplastic small round cell tumor (n=1), soft tissue sarcoma (n=1) and germ cell tumor (n=1) have enrolled to date. No dose limiting toxicities (DLT) were seen at dose level 1 (n=3). Two of 3 patients at dose level 2 experienced DLT (grade 3 diarrhea with dehydration, grade 3 hyponatremia). Dose level 1 was expanded to evaluate up to 12 patients. Of 9 patients who have completed therapy at this dose level, one patient had DLT, grade 4 thrombocytopenia. Three patients received ≥6 cycles with stable disease prior to disease progression. Two additional patients were removed from protocol therapy after experiencing responses that rendered them eligible for surgical resection. All eligible patients (n=4) completed PRO measures. **Conclusions:** The recommended dose for children is anticipated to be sorafenib 150 mg/m$^2$/dose, twice daily, continuously with irinotecan 70 mg/m$^2$/dose, once daily for 5 days, repeated every 21 days. This convenient, oral outpatient regimen is well tolerated in pediatric patients. Clinical trial information: NCT01518413.

**10053 General Poster Session (Board #354), Mon, 8:00 AM-11:45 AM**

**Prospective assessment of renal function using cystatin C and functional MRI in children with newly diagnosed renal tumors.** *Presenting Author: Elizabeth Fox, The Children's Hospital of Philadelphia, Philadelphia, PA*

**Background:** Serum creatinine (sCr) is an imprecise renal function marker in children. Serum cystatin C (cysC) is a more sensitive marker to estimate glomerular filtration rate (GFR). Functional MRI (*f*MRI) measures the contribution of each kidney to overall renal function. **Methods:** Renal function was serially evaluated in children with renal tumors. sCr, cysC and contrast enhanced *f*MRI were obtained at baseline and during therapy in children [n=11,median (range) age 3y (0.5-7.8y)] with newly diagnosed renal tumors. Three children had a tumor predisposition syndrome, one had horseshoe kidney. Diagnoses were Wilms tumor [unilateral (n=5), multifocal/bilateral (n=4)] metanephric stromal tumor (n=1) and no tumor (n=1). Therapy included unilateral total nephrectomy (n=5), partial nephrectomy (n=3), bilateral partial nephrectomy (n=2), chemotherapy (n=9), flank/abdomen radiation (n=4). GFR was estimated using the Schwartz formula ($GFR_{Cr}$) and cysC ($GFR_{cycC}$). **Results:** At baseline, median (range) $GFR_{Cr}$ was 138 (81-198)$_2$ mL/min/1.73m$^2$ including 3 patients with $GFR_{Cr}$ <100 ml/min/1.73m$^2$ and one had progressive acute kidney injury during therapy; $GFR_{cycC}$ was 108 (77-136) mL/min/1.73m$^2$. Pre- vs post-surgery (n=8), median $GFR_{Cr}$ was 142 vs 104 mL/min/1.73m$^2$ (P=0.04), $GFR_{cycC}$ was 114 vs 88 mL/min/1.73m$^2$ (P=0.01). At end of therapy, median (range) percent change from baseline in $GFR_{Cr}$ was -23% (-64 to +23%), $GFR_{cycC}$ was -25% (-60 to +24%). *f*MRI analysis was completed in 26/27 scans. Using *f*MRI, median (range) percent of total renal function contributed by the involved kidney at diagnosis was 35% (23-48%) and the percent change in total parenchymal volume pre- and post-surgery was -50% (-17 to +63%) after unilateral nephrectomy (n=3) and -9% (-40 to +5%) after partial nephrectomy (n=4). **Conclusions:** Some children with Wilms tumor have decreased GFR at diagnosis. At end of therapy, median decrease in GFR was 25%. $GFR_{cysC}$ may be more sensitive to changes in renal function after complete or partial nephrectomy. *f*MRI is feasible and quantifies the contribution of tumor-involved kidney to overall renal function. Partial nephrectomy spared 90% of renal parenchymal volume in this small cohort of children.

**10054 General Poster Session (Board #355), Mon, 8:00 AM-11:45 AM**

**Effect of nerve growth factor administered as eye-drop on visual function in children with optic glioma-associated visual impairement: A controlled, cross-over clinical trial.** *Presenting Author: Riccardo Riccardi, Department of Pediatric Oncology, Catholic University of Sacred Heart, Rome, Italy*

**Background:** To date, no specific therapy is available for visual dysfunction associated with optic pathway glioma (OPG). The aim of this study was to evaluate the effects on visual function of murine nerve growth factor (NGF) administered as eye drop in children with OPG and visual impairment. **Methods:** A controlled randomized double-blind study (EudraCT 2011-003030) was conducted in 18 pts (age range 2-23 yrs , median age 10 yrs) with OPG, off-therapy with stable disease, and visual impairment. NGF eye-drop was prepared with standards required for human use by Policlinico Gemelli Pharmacy. A single 10-day course of 1 mg topical murine NGF or placebo was administered. Assessment included visual acuity, visual field, optical coherence tomography, Ganzfeld electroretinogram photopic negative response (PhNR), and visual evoked potentials (VEPs) at baseline and 15, 30, 90 and 180 days post treatment. Brain MRI was performed at baseline and at 180 days post-treatment. Following the double-blind trial, a cross-over treatment with NGF was also performed, in open label, for patients originally receiving placebo. **Results:** Ten pts received placebo and eight NGF. Drug was always well tolerated. In treated pts there was an improvement of visual field by 50% (p=0.02) and 40% (p=0.05), compared to a 14% and 5% increase in the placebo group, at 30 and at 90 days post-treatment, respectively. There was a median VEP amplitude increase from baseline, compared to placebo group, at 30 days ($p < 0.05$). In the cross-over testing, following NGF treatment, visual field and VEP amplitudes improved from either baseline or from the values recorded after placebo . The overall NGF response rate in all 18 patients was 75% (95% CI : 65-80 % ) for visual field improvement. **Conclusions:** NGF administration appears to be an effective and safe treatment in patients with OPG-associated visual impairment. Clinical trial information: 2011-003030.

**10055 General Poster Session (Board #356), Mon, 8:00 AM-11:45 AM**

**A combination chemotherapy, temozolomide (TMZ) with etoposide (VP), in relapsed or refractory pediatric solid cancer: Preliminary report of randomized phase II study of two different outpatient setting regimens (rPII).** *Presenting Author: Atsushi Ogawa, Niigata Cancer Center Hospital, Niigata, Japan*

**Background:** Each of TMZ and VP has been shown its own anti-cancer activity and they have oral formulation. Although there are established active combinations comprising alkylating agent and topoisomerase inhibitor, TMZ and VP combination (TE), has never been evaluated in pediatric solid cancer. We report efficacy, safety, feasibility of outpatient setting of TE in advance of final analysis of rPII. **Methods:** This multicenter rpII included children and young adults with recurrent or refractory pediatric solid cancer, who received disease-specific standard chemotherapies. The study design has been reported in ASCO2010 (TPS328). TMZ (150 mg/m2) and VP (50 mg/m2) were administered orally on d1-5 and d1-12 respectively every 28 days, repetitively. The main efficacy endpoint, DSMC approved to be published, was response rate. Response was evaluated according to RECIST 1.1 and toxicity was assessed by CTCAE v4.0. **Results:** Thirty-four patients(pts) from 13 centers, median age 14 years (range 3-30), received TE: 8 neuroblastoma (NB), 5 rhabdomyosarcoma, 6 Ewing sarcoma family tumor, 8 osteosarcoma (OS), 3 CNS tumors and 4 others. Overall 114 cycles were administered (median 3 per patient; range 1-20). Seventeen pts experienced grade 3-4 neutropenia, but none developed febrile neutropenia. Eight pts had grade 3-4 thrombocytopenia and twelve pts developed grade 3-4 anemia. No grade 4 non-hematological toxicity occurred. Hospitalization was required only in two pts due to VZV infection and grade 2 fever episode, respectively. Response rate (RR) was 14.7% with CR 1 and PR4. Disease control rate (CR+PR+ more than two courses stable disease (SD)) was 38.2% with eight SD. Clinical benefit ratio (CBR, CR+PR+long SD) was 29.4% with five long SD (stable disease during more than 4 course). In NB, CBR was 62.5% with 1 CR, 1 PR and 3 long SD. In OS, RR was 40.7% with 3 PR/7 (one who terminated therapy first 2-3 days due to tumor hemorrhage was excluded). **Conclusions:** TE is a promising regimen for heavily pretreated recurrent pediatric solid cancer, especially in NB and OS, with acceptable toxicities in outpatient setting. Clinical trial information: 000003002.

**10056 General Poster Session (Board #357), Mon, 8:00 AM-11:45 AM**

**Complete radiographic responses in pediatric patients with *BRAF*$^{V600}$-positive tumors including high-grade gliomas: Preliminary results of an ongoing phase 1/2a safety and pharmacokinetics (PK) study of dabrafenib.** *Presenting Author: Mark W. Kieran, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Dabrafenib is a selective inhibitor of V600 mutant BRAF kinase activity with a mechanism of action consistent with adenosine triphosphate-competitive inhibition. Dabrafenib has demonstrated anti-tumor efficacy in adult patients (pts) with *BRAF*$^{V600}$ mutant tumors, including melanoma, papillary thyroid cancer (PTC), and non-small cell lung cancer. **Methods:** This 2-part study was designed to identify phase 2 recommended dose, safety, PK, and clinical activity in pediatric pts who have had ≥1 previous therapy. Part 1 is a PK-driven dose escalation. Part 2 is an expansion study to evaluate the safety and activity of dabrafenib in pediatric pts with 1 of 4 pre-specified tumor types. Pts are treated with dabrafenib orally twice daily, using capsules or a powder for oral suspension. Serial PK samples are obtained on days 1 and 15. Imaging is performed every 2 cycles, and responses require confirmation on a follow-up scan at least 4 weeks later. **Results:** From May 2013 to Jan 2014, 8 pts (median age, 11 y; range 3-17 y) with recurrent/refractory *BRAF*$^{V600}$ mutant solid tumors including 6 high grade glioma (HGG), 1 each of Langerhans cell histiocytosis (LCH), and PTC were enrolled at dose levels 3mg/kg (n=3) and 3.75mg/kg (n=5). Radiographic responses for the HGG pts included 3 complete responses (2 confirmed and maintained at the 6 month assessment [both anaplastic astrocytoma], 1 unconfirmed [pleomorphic xanthoastrocytoma]), and 2 progressive disease. The LCH pt continues to exhibit stable disease at week 16. Data are not yet available for a PTC pt and 1 HGG pt. There were no DLTs or drug-related grade 3/4 toxicities in these 8 pts. No dose reductions have been required, and PK data analysis and dose escalation continues. Two pts (1 in each cohort) achieved plasma dabrafenib concentrations associated with clinical efficacy in adults. **Conclusions:** Dabrafenib shows encouraging initial clinical activity in this small number of evaluable pediatric pts with *BRAF*$^{V600}$ mutant solid tumors, including primary brain tumors. The preliminary safety profile in pediatric pts is consistent with that in adults. Clinical trial information: NCT01677741.

**10057 General Poster Session (Board #358), Mon, 8:00 AM-11:45 AM**

**Heat-shock protein 90 inhibition in pediatric sarcomas.** *Presenting Author: Fernanda Irene Arnaldez, Pediatric Oncology Branch, National Cancer Institute, Bethesda, MD*

**Background:** Hsp90 is a molecular chaperone that regulates post-translational folding, stability, and function of many client proteins, which play critical roles in key signal transduction pathways implicated in cell growth, differentiation, and survival. Several relevant oncogenic proteins are described as clients, such as IGF1R, AKT/PKB, and Src-family kinases. Signaling through these molecules is critical in the biology of rhabdomyosarcoma (RMS) and Ewing's sarcoma (ES). Novel therapies for these tumors are clearly needed since patients with relapsed and metastatic disease continue to have poor outcomes. Ganetespib (Synta Pharmaceuticals) is a small molecule Hsp90 inhibitor that binds to the ATP pocket in the N-terminus of Hsp90, leading to down-regulation of Hsp90 client protein levels. **Methods:** We sought to evaluate the preclinical activity of ganetespib in a panel of ES and RMS cell lines. We evaluated in vitro activity of ganetespib in ES cell lines (TC71, TC32, EW8, RDES) and in RMScell lines (RD, RH30) using kinetic proliferation assays and MTS. **Results:** In all cases, a marked inhibition of cell growth was achieved in a dose-dependent manner with drug concentrations in the low nanomolar range (3-6 nM). We found that ganetespib exposure is associated with induction of apoptosis using caspase 3/7 assay; as well as alterations in cell cycle progression. In addition to upregulation of Hsp70, which is considered a biomarker of Hsp90 inhibition, ganetespib treatment was associated with loss of expression of IGF1R-beta as well as downregulation of key signaling pathways such as mammalian target of rapamycin (mTOR), pAKT, and Src-family kinases, particularly YES1, a kinase we identified as critical in RMS biology. Moreover, we observed a cooperative effect between Hsp90 inhibition and IGF1R blockade with R1507, a monoclonal antibody targeting this receptor (Hoffman-La Roche). Furthermore, a synergistic effect was seen when ganetespib treatment was combined with SFK inhibition using dasatinib. **Conclusions:** Ganetespib exhibited activity alone and in combination in ES and RMS cell lines and is an attractive strategy to explore in the therapy of pediatric sarcomas; possibly in combination with other targeted therapies.

**10058 General Poster Session (Board #359), Mon, 8:00 AM-11:45 AM**

**Adolescent and young adult oncology (AYAO) patient enrollments onto National Cancer Institute (NCI)-supported trials from 2000 to 2010.** *Presenting Author: Nita Seibel, Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD*

**Background:** Lack of participation in clinical trials has been proposed as a key explanation for the survival deficit of AYAO patients. We compared the proportion of newly diagnosed AYAO patients (out of all patients) enrolled on NCI-sponsored cooperative group therapeutic trials from 2000 to 2010 to the proportion that would be expected based on SEER incidence data. Location of care was also assessed. **Methods:** We studied AYAO accrual to all open trials by evaluating two age groups (15-19 and 20-39 years) and two time periods (2000-2005 and 2006-2010). For each cancer type, the observed proportion of AYAO patients was calculated by dividing the total number of AYAO participants accrued by the total number of trial participants. This was compared to SEER 17 data by calculating the same proportion using the cancer specific incidence for the same age and year groupings. The proportion of community based (CCOP) accrual to non-CCOP accrual was compared for the AYAO patients. **Results:** Of 116,665 patients enrolled from 294 NCI-sponsored studies with eighteen cancer types, 12,392 were aged 15-39 years. For both time periods, the observed proportion of 15 - 19 year olds was greater than the SEER data for ALL, AML, CNS, Hodgkins, and bone cancers while the clinical trial proportion of 20-39 year olds exceeded the SEER data for AML, colon, NHL, and breast cancer. Among CCOPs, the proportion of AYAO accrual was greater for younger than older patients in ALL, bone cancer, Hodgkin, and STS. **Conclusions:** For many cancer types, both adolescent and young adult patient enrollments onto NCI studies exceed what would be expected based on SEER incidence data. Although AYAO patients are represented on clinical trials, recruiting and ensuring trials are available for this age group should remain a priority.

**10059 General Poster Session (Board #360), Mon, 8:00 AM-11:45 AM**

**Evaluation of ciclopirox efficacy in rhabdomyosarcoma.** *Presenting Author: Alaa Altahan, St. Jude Children's Research Hospital, Memphis, TN*

**Background:** Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in the pediatric age group. Despite current multimodal treatment, a significant portion of patients still have poor outcomes. Recent studies have shown that ciclopirox (CPX), an antifungal agent, has antitumor activity in some types of cancers like leukemia and breast cancer. The aim of this study is to evaluate the therapeutic efficacy of ciclopirox in treating rhabdomyosarcoma both in-vitro and in-vivo. **Methods:** The effect of ciclopirox on RMS in-vitro was evaluated by performing dose and time response curves in 4 RMS cell lines (Rh30, Rh41 alveolar and Rh18, RD embryonal). Flow cytometry was used to evaluate cell cycle status and degree of apoptosis. Western blotting was used to evaluate protein changes. Levels of N-MYC and C-MYC in RMS were analyzed using R2: microarray analysis and visualization platform (http://r2.amc.nl). The efficacy of CPX in-vivowas tested in a subcutaneous RMS xenograft model in SCID mice. Once tumors were established, mice were randomized to treatment or control groups. **Results:** In-vitro studies showed high sensitivity of all the RMS cell lines to CPX with IC50 = 0.5-2.5uM. In contrast, normal human fibroblasts were minimally affected in this dose range. Cell cycle and apoptosis analysis showed different responses to CPX in different cell lines. Interestingly, western blot analysis showed a significant reduction of N-MYC and C-MYC levels with CPX treatment. Analysis of public data sets showed increased expression of N-MYC and C-MYC in RMS compared to normal muscle. In-vivoresults showed that CPX treatment leads to significant delay in tumor growth, with 47% reduction in tumor volume after 26 days of starting treatment (p-value 0.005), compared to the control group. **Conclusions:** Our results show that ciclopirox is effective at inhibiting rhabdomyosarcoma cell proliferation. Interestingly, we found that CPX significantly reduces N-MYC and C-MYC expression. Further studies are being done to better understand the mechanism behind this change. Finally, in-vivo results demonstrated therapeutic efficacy of CPX in treating RMS tumors. Results of our study suggest a potential therapeutic role for ciclopirox in the treatment of rhabdomyosarcoma.

**10060 General Poster Session (Board #361), Mon, 8:00 AM-11:45 AM**

**IVADo treatment of type II and type III pleuropulmonary blastoma (PPB): A report from the International PPB Registry.** *Presenting Author: Leslie Ann Doros, Children's National Medical Center, Washington, DC*

**Background:** Pleuropulmonary blastoma (PPB) is a rare malignancy of the lung presenting in young children. The International PPB Registry (IPBBR) has pathologically confirmed more than 400 cases of PPB. Three pathologic subtypes correlate with age and outcome: Type I, a purely cystic lesion often cured by surgery alone; Type II, a combined cystic and solid lesion; and Type III, a purely solid high-grade sarcoma. Previously reported five-year survival rates for Types II and III PPB are 67% and 51%, respectively. Historically, treatment for Types II and III PPB has not been uniform. The IPPBR conducted the first prospective treatment study to evaluate the response of Type II and III PPB to a standardized chemotherapy regimen. **Methods:** Treatment records were obtained forpatients with Type II and III PPB who enrolled on the IPBBR Treatment and Biology registry. A regimen of 36 weeks of ifosfamide, vincristine, actinomycin and doxorubicin (IVADo) was recommended. Sixty-two patients were treated on the IVADo regimen; 42 completed 3 or more cycles of induction IVADo and were considered fully assessable for analyses. The IVADo group was compared as a group to 200 historical IPPBR confirmed PPB patients who received regimens other than IVADo for both event-free survival (EFS) and overall survival (OS). **Results:** Of the 42 patients, 25 (60%) were males and 17 (40%) females; median age at diagnosis was 35 months (range 19-83). There were 24 (57%) Type II; 4 (10%) Type II/III, and 14 (33%) Type III. At a median follow-up of 28 months (range 2-71), 10 (24%) relapsed; 6 (14%) died at 12-24 months. Compared to the historical group, the IVADo group had better EFS (Log-rank test, p=0.008) and better OS (p=0.04). At 5 years, IVADo had better EFS: 70.8% (95% CI 55.3-86.3%) vs. 44.7% (95% CI 37.1-52.4%), and better OS 79.2% (64.1-94.2%) vs. 60.1% (52.3-67.9%). **Conclusions:** To date, the IPPBR treatment study represents the only cohort of patients with Type II and Type III PPB that have been treated uniformly. The standardized use of IVADo showed improvement in EFS and OS compared to the historical group. Importantly, the follow-up of the IVADo cohort is shorter, and there are late events and deaths in the historical group, limiting our conclusion. Clinical trial information: NCT01464606.

**10061 General Poster Session (Board #362), Mon, 8:00 AM-11:45 AM**

**A phase I study of panobinostat in pediatric patients with refractory solid tumors, including CNS tumors.** *Presenting Author: Paul James Wood, Monash Health, Children's Cancer Centre, Melbourne, Australia*

**Background:** Deregulated acetylation of histones plays a key role in the pathogenesis of haematological and solid tumors by changing the transcription of genes involved in cell cycle control, differentiation or apoptosis. Thus, there is considerable interest in HDAC inhibition as a potential therapeutic modality in the treatment of hematological and solid tumor malignancies, including pediatric malignancies. **Methods:** This is an open label, Phase I, multi-centre study evaluating panobinostat in pediatric patients with refractory solid tumours. Primary endpoints were to define and describe associated toxicities, and to characterize its pharmacokinetics (PK). Secondary endpoints included assessing the anti-tumour activity of panobinostat, and also to assess its biologic activity by measuring the histone acetylation status in peripheral blood mononuclear cells (PBMNC). **Results:** Nine patients were enrolled and treated with intravenous panobinostat at a dosing level of 15mg/m$^2$. Three patients were removed from study prior to completion of course one due to tumour progression. A dose of 15mg/m$^2$ was tolerated with one dose limiting toxicity (DLT) observed in the six patients evaluated for DLT. Two (22%) patients experienced grade 3-4 thrombocytopenia, 1 (11%) experienced grade 3 anemia, and 2 (22%) experienced grade 3 neutropenia. Grade 4 drug related pain occurred in 2 (22%) of patients studied. Vomiting (44%), nausea (33%) and hypokalaemia (22%) were also common adverse events. Two (22%) of patients experienced a Grade II QTcF change (0.478 +/- 0.006 msec). One cardiac DLT (T wave changes) was reported. PK values for 15mg/m$^2$ (n=9) dosing were: Tmax 0.8 hours, Cmax 235.2 ng/ml, $AUC_{0\text{-}t}$ 346.8h.ng/ml and $t_{1/2}$ 7.3 hours. Pooled flow cytometry results of all nine patient samples confirm that panobinostat significantly induced acetylation of histone H3 and H4 at 6 hours ($p< 0.001$), 24 hours ($P<0.01$) and 28-70 hours ($p<0.05$) post dose. **Conclusions:** A significant, sustained, biological effect of panobinostat, as measured by acetylation status of histone H3 and H4, was achieved at a dosing level of 15mg/m$^2$. PK data and drug tolerability at 15mg/m$^2$ was very similar to that seen in adults at an equivalent dosing level. Clinical trial information: ACTRN12609000978268.

**10062 General Poster Session (Board #363), Mon, 8:00 AM-11:45 AM**

**Similar exposure and pharmacokinetics of bevacizumab in pediatric and adult cancer patients: Analysis of individual data of 152 pediatric patients.** *Presenting Author: Kelong Han, Genentech, Inc., South San Francisco, CA*

**Background:** Bevacizumab (BEV) is approved for various cancers. BEV pharmacokinetics (PK) is well established by a population PK (PPK) model in adults, but has not been comprehensively evaluated in children. Four pediatric studies have been conducted to assess BEV exposure (EXP) and PK in children, to explore the influence of patient variables on BEV PK and to compare BEV EXP and PK between pediatric and adult patients. **Methods:** BEV was administered at 5, 7.5, 10 or 15 mg/kg (Q2W or Q3W) with chemotherapy to children with primary CNS tumor (n=76), metastatic soft tissue sarcoma (n=39), osteosarcoma (n=27), or other refractory solid tumors (n=10). A nonlinear mixed effects PK model was fitted to BEV serum concentrations (Cs). Pediatric BEV EXP (trough Cs) were simulated by the pediatric PPK model under the same BSA-based or WT-based dose, and compared to adult EXP simulated by the adult PPK model. **Results:** Totally 1,464 BEV Cs from 152 patients between 6 months and 21 years old (median 10.8) were analyzed, with 9 patients under the age of 3 years. Body weight (WT) ranged from 5.9 to 125 kg (median 43.8 kg). Typical BEV clearance (CL), central volume of distribution (V1) and half life for a 75 kg individual are 9.47 mL/h, 2.98 L and 18 days in children (vs. 9.31 mL/h, 2.91 L and 20 days in adults based on the adult PPK model). In pediatric patients, CL and V1 increase with WT and are lower in females and primary CNS tumor, and CL decreases with albumin. Age is not correlated with WT-normalized CL or V1. BEV EXP in children decreases with decreasing WT given the same mg/kg dose. BEV EXP under BSA-based dose (mg/m$^2$) and WT-based dose both generally fall within the 90% predictive interval of adult EXP across pediatric age and WT range. **Conclusions:** A robust BEV PPK model for children that can be used to perform simulations was developed based on this large pediatric population with a wide range of age (0.5~21 years) and WT (5.9~125 kg). BEV PK is similar across pediatric age range when corrected for WT. BEV PK and factors correlated with BEV PK are similar in pediatric and adult patients. Pediatric BEV EXP is similar to adult EXP across pediatric WT range. BSA-based dose offers no substantial advantage over WT-based dose.

**10063 General Poster Session (Board #364), Mon, 8:00 AM-11:45 AM**

**Protein network mapping of retinoblastomas for the identification of therapeutic targets.** *Presenting Author: Elisa Baldelli, George Mason University, Manassas, VA*

**Background:** Retinoblastoma is the most common ocular tumor of childhood. Diagnosis times differ across the word, with diagnosis occurring significantly earlier in developed countries. Necrosis and invasion of the optic nerve are usually associated with poor prognosis and higher incidence of recurrence and metastases. Treatment options include surgery, radiotherapy, and chemotherapy while targeted therapies are still not available. The aim of this study was to investigate the protein signaling architecture of retinoblastomas to identify new druggable targets for personalized therapy. **Methods:** Six paraffin embedded retinoblastomas collected at the Bugando Medical Center (Mwanza, Tanzania) were analyzed in this feasibility study. Samples were collected from patients aged 2 to 10. Two tumors presented invasion of the optic nerve, 2 were free of invasion, and 2 tumors were unclassified. Four tumors were necrotic, while 2 displayed no signs of necrosis. Samples were subjected to laser capture microdissection to isolate the cancer cells from the surrounding microenvironment and analyzed by Reverse Phase Protein Microarray to evaluate the activation status of 52 drug targets and downstream effectors. **Results:** Unsupervised hierarchical clustering analysis identified 2 major clusters, one with high and one with low activation of the drug targets. Stratification based on age, invasion of the optic nerve, and necrosis showed no clustering based on the signaling network. A clear distinction between the 2 groups was detected for the activation of ErbB family members, IGF-1R, Mek and c-Met. The activation of PDGFR$\alpha$, PDGFR$\beta$ and VEGFR2 was more heterogeneous across all samples and revealed high activation only in a small portion of patients. **Conclusions:** Based on these preliminary results there is an indication that retinoblastoma has several sub-populations that exhibit different activation of drug targets. Patients whose tumors present with high activation levels for these proteins may benefit from a more targeted and specific treatment. Further analysis is needed to explore the underlying architecture and robustness of these two groups to provide evidence for the use of more targeted therapies in retinoblastoma.

**10064 General Poster Session (Board #365), Mon, 8:00 AM-11:45 AM**

**First-in-pediatrics phase I study of crenolanib besylate (CP-868,596-26) administered during and after radiation therapy (RT) in newly diagnosed diffuse intrinsic pontine glioma (DIPG) and recurrent high-grade glioma (HGG).** *Presenting Author: Cynthia Wetmore, St. Jude Children's Research Hospital, Memphis, TN*

**Background:** Children diagnosed with DIPG have a median survival of less than one year despite RT, the primary modality of therapy. PDGF pathway activation has been noted in tumor analyzed from approximately 70 % of pediatric DIPG and 50% of HGG patients, suggesting inhibition of this pathway may be of clinical benefit. Crenolanib is a highly selective and potent antagonist of the PDGF pathway with in vitro $IC_{50}$of 35- and 185-fold lower than observed with dasatanib and imatinib, respectively. **Methods:** We used a rolling-6 design to study the MTD of once-daily crenolanib administered during and after local RT in children with newly diagnosed DIPG (Stratum A), and in recurrent/progressive HGG, including DIPG (Stratum B). We have completed accrual of 55 patients, 29 and 20 evaluable in Stratum A and B, respectively. Serum pharmacokinetic analyses were performed using non-compartmental techniques on all patients for samples collected on days 1 and 28 of course 1. Pharmacodynamic and mutational analyses of peripheral blood mononuclear cells and tumor tissue are ongoing. **Results:** Forty-nine evaluable patients have been enrolled to the following dose levels: 100, 130, 170 and 220 mg/m$^2$. Dose limiting toxicities (DLTs) were primarily elevated liver enzymes in both strata, and the most common Grade 3 toxicity seen on Stratum A was leukopenia that resolved with drug interruption. Mild (Grade 2) elevation in liver enzymes was observed in fewer than 15% of patients. The maximum tolerated dose (MTD) of 170 mg/m$^2$ has been established in each stratum. On day 1, median crenolanib non-compartmental $AUC_{0-\infty}$ values for 170 mg/m$^2$dosage on Stratum A was 13,942 nM*hr (6,314-24,369), which was comparable to adult Phase I data at the 280mg flat dose. **Conclusions:** We have established an MTD in pediatric patients. The PK and current preliminary toxicity data indicate that crenolanib is well tolerated in children at doses slightly higher than the established MTD from Phase I trial in adults (280 mg/day). The spectrum of toxicities observed in children is similar to those observed in adults, though leukopenia is a novel toxicity. Clinical trial information: NCT01393912.

**10065 General Poster Session (Board #366), Mon, 8:00 AM-11:45 AM**

**A phase 1 study of AZD6244 in children with recurrent or refractory low-grade gliomas: A Pediatric Brain Tumor Consortium report.** *Presenting Author: Anuradha Banerjee, University of California, San Francisco, San Francisco, CA*

**Background:** Pathway activating genetic aberrations of the Ras-MAP kinase signaling pathway have been observed in pediatric low grade glioma (LGG), most commonly a fusion gene, BRAF-KIAA1549 or a mutation of BRAFV600E. MEK is a downstream target of BRAF; thus, MEK inhibition may represent a promising treatment strategy for patients with LGGs. **Methods:** AZD6244 was administered orally BID to children $\geq$ 3yrs and $\leq$21 years with refractory or recurrent LGG. The starting dose was 33 mg/m$^2$/day BID and continual reassessment method was used for dose finding. Pre-treatment tissue was assessed for BRAF aberrations by FISH and IHC. Serial PK studies were obtained on day 1 cycle 1. **Results:** Thirty eight eligible patients were enrolled. Initially, only patients $>$12 and $\leq$21 years were eligible. Dose levels 1 and 2 (33 and 43 mg/m$^2$/dose, BID) were deemed intolerable with dose limiting toxicities (DLTs) of headache, rash and mucositis. Following de-escalation to dose level 0 (25mg/m$^2$/dose BID), eligibility was extended to patients $<$12 years. Among the 24 patients treated at dose level 0, no patient $<$12 years and 3 of 12 patients $\geq$12 years experienced DLTs of elevated amylase/lipase, rash and mucositis. The MTD/RP2D for both cohorts was 25 mg/m$^2$/dose BID. Non-compartmental pharmacokinetic analysis in 23 patients at 25 mg/m2/dose BID indicated the median (range) $AUC_{0-\infty}$ and CL/F were 3,855 ng*hr/mL(1,780 to 7,250 ng$\times$hr/mL) and 6.5 L$\times$hr$^{-1}\times$m$^{-2}$ (3.4 to 14.0 L$\times$hr$^{-1}\times$m$^{-2}$), respectively. Similar plasma exposures of AZD6244 are known to inhibit ERK phosphorylation in peripheral blood cells. Nineteen patients had sufficient tissue for BRAF studies. Eleven patients had KIAA1549:BRAF fusion products, 3 had BRAF-V600E mutations; and 1 patient had both. ERK1/2 phosphorylation immunohistochemical staining was noted in all 19 cases studied. There were 8/38 sustained responses (1 complete and 7 partial). Of these, 5 had biology data: 3 had BRAF fusion, 1 had BRAFV600E mutation and 1 was negative for both. **Conclusions:** The RP2D of AZD6244 in children with recurrent LGG is 25 mg/m$^2$/dose BID, with the most common toxicity being rash. This study suggests promising activity in pediatric LGG. A Phase II study is currently ongoing. Clinical trial information: NCT01089101.

**10066 General Poster Session (Board #367), Mon, 8:00 AM-11:45 AM**

**Phase II trial of cixutumumab in combination with temsirolimus in pediatric patients with recurrent or refractory sarcoma: A report from the Children's Oncology Group.** *Presenting Author: Lars M. Wagner, University of Kentucky, Lexington, KY*

**Background:** The combined inhibition of insulin-growth factor type 1 receptor (IGF-1R) and the mammalian target of rapamycin (mTOR) has shown activity in preclinical models of pediatric sarcoma and in adult sarcoma patients. We evaluated the activity of the anti-IGF-1R antibody cixutumumab with the mTOR inhibitor temsirolimus in patients with relapsed Ewing sarcoma, osteosarcoma, rhabdomyosarcoma, and other soft tissue sarcoma. **Methods:** Cixutumumab 6 mg/kg and temsirolimus 8 mg/m$^2$ were administered intravenously once weekly in 4-week cycles to patients $<$ 30 years of age with recurrent or refractory sarcoma. Temsirolimus was escalated to 10 mg/m$^2$ for subsequent cycles in patients who did not experience unacceptable first-cycle toxicity. A two-stage enrollment design was used to identify a response rate of $<$ 10% or $>$ 35%, with expansion of a tumor-specific cohort only if 2 or more complete or partial responses were seen in the first 11 patients. Tumor tissue was analyzed by immunohistochemistry for potential biomarkers of response. **Results:** Forty-three evaluable patients (median age 17 years, range 1-27) received a median of 2 cycles (range, 1-7). No objective responses were observed; 7 (16%) patients were progression-free at 12 weeks. Dose-limiting toxicity occurred in 15 (16%) of 92 cycles. The most common toxicities were mucositis, electrolyte disturbances, and myelosuppression. The lack of objective responses precluded correlation with tissue biomarkers. **Conclusions:** Despite encouraging preclinical data, the combination of cixutumumab and temsirolimus did not result in objective responses in this Phase II trial of pediatric sarcoma patients with recurrent or refractory disease. Clinical trial information: NCT01614795.

**10067 General Poster Session (Board #368), Mon, 8:00 AM-11:45 AM**

**Characterization of *KIAA1549:BRAF* fusion in young pilocytic astrocytoma patients through fluorescence in situ hybridization.** *Presenting Author: Marileila Varella-Garcia, University of Colorado School of Medicine, Aurora, CO*

**Background:** Pilocytic astrocytoma (PA) often arises in young patients and may be related to type 1 neurofibromatosis (NF1). Although the 5-year survival is high, up to 10% of cases progress poorly. Alterations of *BRAF* mainly through gene fusions are key genetic events in this tumor type, and are reported to influence patient outcome. Our aim was to assess *BRAF* molecular changes in PAs for both p.V600E mutation and *KIAA1549:BRAF (K:B)* fusion and correlate with clinicopathological features in retrospective studies. **Methods:** Sanger sequencing was used to evaluate *BRAF* V600E mutation. *K:B* fusion was evaluated by a customized dual-target, dual-color fluorescence in situ hybridization (FISH) probe set in samples in tissue microarray format. The designed *K:B*FISH probe was validated in Agilent 8x60K aCGH and RT-PCR assays in 5 cases. **Results:** A total of 75 samples were evaluated from 69 patients (1.2 M/F), mean age of 11.6 years and long-term follow-up (7-196 months). Cerebellum was the main location (53.6%). Five patients had confirmed diagnosis of NF1 (7.2%) and 5 patients showed growing residual lesions in this series. There was only one *BRAF* mutated case. Complete concordance was seen between methodologies in the validation set, in which samples exhibiting gains at 7q34 were also positive for *K:B* by RT-PCR and FISH. Overall, we evaluated 69/75 samples by FISH, and observed that 38/64 (59.4%) of primary lesions displayed *K:B* fusion, with a strong positive correlation with cerebellar lesions ($p<0.001$) and negative with NF1 ($p=0.009$). No statistical difference was seen between age groups ($p=0.467$), and the Kaplan-Meier curve showed that presence of *K:B* fusion was significantly associated with better survival ($p=0.009$). Interestingly, in the subset of patients that recur, two specimens that demonstrated *K:B* fusion in the primary tumor, exhibited loss of the gene fusion in the recurrence. **Conclusions:** This study confirms the pivotal role of *K:B* fusion in PAs biology and its clinical impact, defining a subset of patients with better outcome. Moreover, we showed the feasibility of a custom FISH assay as a reliable method for detection of this alteration in routine-based neuropathology laboratory.

**10068 General Poster Session (Board #369), Mon, 8:00 AM-11:45 AM**

**The role of MEK inhibition in neuroblastoma tumor cells.** *Presenting Author: Peter E. Zage, Baylor College of Medicine, Houston, TX*

**Background:** Neuroblastoma is the most common extracranial solid tumor of childhood. High-risk cases of neuroblastoma have extremely poor long-term survival rates, and novel therapies are needed. The RAS/MAPK pathway has been shown to be involved in neuroblastoma tumorigenesis. We hypothesized that RAS/MAPK pathway inhibition via MEK inhibition with MEK162 would be effective against neuroblastoma tumor cells. **Methods:** We evaluated expression and activity of MEK and ERK in a panel of neuroblastoma tumor cells using Western blots and neuroblastoma tumor cell viability after treatment with MEK162 using MTT assays. Expression of NF1 protein was determined by Western blot. Analyses were performed for changes in RAS/MAPK pathway activity after MEK162 treatment. **Results:** Neuroblastoma tumor cell lines displayed differential responses to MEK162, with some cell lines being very sensitive and others being resistant. IC50 values for sensitive cell lines ranged from <10nM to 5mM, while resistant cells did not demonstrate any reduction in cell viability at doses exceeding 20mM. NF1 expression correlated with responses to MEK162. MEK162 treatment resulted in reduced ERK phosphorylation in sensitive neuroblastoma cells, while increased levels of MEK phosphorylation were seen in resistant cells. **Conclusions:** Treatment of neuroblastoma tumor cells with MEK162 inhibits RAS/MAPK pathway activity, resulting in cell death in sensitive cell lines. Resistant neuroblastoma tumor cell lines displayed increased MEK phosphorylation in response to MEK162, suggesting a possible feedback loop leading to treatment resistance. Inhibition of MEK represents a potential new therapeutic strategy for neuroblastoma, and further preclinical studies of MEK162 are warranted.

**10069 General Poster Session (Board #370), Mon, 8:00 AM-11:45 AM**

**Evaluation of resources used during care of children with high-risk neuroblastoma (HR NBL) via merging of cooperative group trial data and administrative data.** *Presenting Author: Rochelle Bagatell, The Children's Hospital of Philadelphia, Philadelphia, PA*

**Background:** Cooperative group trials have improved outcomes for children with HR NBL. Trial data provide reliable information regarding patient characteristics, treatment, and response but do not include information regarding resource utilization. Merging of trial and administrative data would facilitate comparative effectiveness studies. **Methods:** Data from the Children's Oncology Group (COG) and the Pediatric Health Information Systems (PHIS) were merged for patients (pts) enrolled on Phase 3 COG trials for HR NBL (A3973 and ANBL0032) at 43 PHIS centers. A3973 included induction chemotherapy, surgery, stem cell transplant, and radiation. Responders were eligible for ANBL0032, a randomized trial of chimeric antibody, cytokine and isotretinoin vs isotretinoin alone. Inpatient resource utilization summary statistics were tabulated based on PHIS data. **Results:** Of 323 enrollments on A3973 and/or ANBL0032 at PHIS centers, matching was successful and resource utilization data were available for 223 pts. The median age of newly diagnosed pts was 3.19 years (range 0.3-16.09) and 163 (88%) children had Stage 4 disease. Sixty-six (36%) had *MYCN* amplified tumors, 145 (87%) had unfavorable histology. Pts treated on A3973 for whom complete data were available (n=192) were hospitalized for a median of 100 days (d). Of these, 75 (39%) required intensive care resources; these services were delivered for a median of 4d per pt. Median cumulative duration of antibiotic use was 72d per pt. Ototoxic antibiotics were administered to 44% of pts; these were delivered for a median of 6d in total (range 1-93). **Conclusions:** Pts enrolled on cooperative group HR NBL studies can be successfully identified and resource utilization data can be collected across trials using an administrative dataset. Characteristics of pts in this cohort are consistent with those of pts on recent HR NBL studies. Information regarding length of stay and supportive care required for treatment of children with HR NBL will be used in comparative effectiveness studies and will aid in patient/family education. A larger cohort, created by adding pts from future trials, will permit additional analyses.

**10070 General Poster Session (Board #371), Mon, 8:00 AM-11:45 AM**

**Phase 1 trial of decitabine and CT antigen-specific vaccine in relapsed pediatric solid tumors.** *Presenting Author: Rani George, Dana-Farber Cancer Institute, Boston, MA*

**Background:** The Cancer/Testis (CT) antigens MAGE-A1, MAGE-A3 and NY-ESO-1 are selectively expressed at varying levels on many pediatric solid tumor cells, including neuroblastoma (NB), and thus have the potential to be targeted for immune therapy by antigen-specific T cells. We have shown that the DNA methylating agent decitabine (DAC) upregulates CT antigen expression in a range of tumor types, leading us to evaluate the feasibility of combining DAC with a CT antigen-targeted dendritic cell (DC) vaccine in patients with relapsed solid tumors. **Methods:** In this two-institution trial, eligible patients had PBMCs collected by apheresis and transported to the lead center for vaccine preparation. The treatment regimen included 4 cycles of therapy: DAC 10mg/m$^2$/day for 5 days, followed by 2 weekly vaccinations of autologous DC pulsed with overlapping peptide mixes derived from full-length CT antigen sequences. The toll-like receptor agonist imiquimod was used at vaccination sites to facilitate immune response. Peripheral blood was collected weekly and analyzed for CT antigen-specific antibodies and CD137$^+$antigen-specific T cells by flow cytometry. **Results:** Fifteen patients have been enrolled (median age, 8.5 yrs); 10 with NB, 2 each with Ewing sarcoma and osteosarcoma, and 1 with rhabdomyosarcoma. DC vaccine preparation was successful for all 15 patients. Five patients did not receive vaccine due to disease progression. Of the 10 patients who received therapy, 3 completed all 4 cycles, and two, 3 cycles. Five patients received $\leq$ 2 cycles only, 4 due to disease progression and one due to a vaccine reaction. The major toxicity was neutropenia requiring growth factor support. Three of 7 NB patients in whom antigen-specific immune response was assessed had an increase in the number of CT antigen-specific CD8$^+$CD137$^+$ and/or CD4$^+$CD137$^+$T cells, while one had an antibody response to all three CT antigens. **Conclusions:** DAC followed by DC/CT antigen-targeted vaccine is well tolerated and highly feasible in heavily pretreated children with relapsed solid tumors, warranting further investigation in larger trials. Clinical trial information: NCT01241162.

**10071 General Poster Session (Board #372), Mon, 8:00 AM-11:45 AM**

**Fenretinide (4-HPR)/Lym-X-Sorb (LXS) oral powder plus ketoconazole in patients with high-risk (HR) recurrent or resistant neuroblastoma: A New Approach to Neuroblastoma Therapy (NANT) Consortium trial.** *Presenting Author: Barry James Maurer, Texas Tech University Health Sciences Center, Lubbock, TX*

**Background:** Fenretinide (4-HPR), a cytotoxic retinoid with preclinical activity in neuroblastoma (NB), formulated as 4-HPR/LXS oral powder increased plasma levels over a capsule formulation but exhibited a PK plateau at higher doses (Pediatr Blood Cancer 60:1801, 2013). Two expansion cohorts were undertaken to assess effects on 4-HPR plasma levels of: 1) removing dietary restrictions, 2) adding ketoconazole, an inhibitor of 4-HPR metabolism. **Methods:** Eligible patients had high-risk NB with recurrent or refractory disease, including in complete response (CR) after relapse (Cohort One-only). Treatment in Cohort One was 4-HPR at 1500 mg/m$^2$/day, divided TID, given on Days 1-7, every 3 weeks, with an unrestricted diet. In Cohort Two, concurrent oral ketoconazole (6 mg/kg/day) was given on Days 1-7. **Results:** Cohort One accrued 23 patients (3 not treated) with 15 eligible for PK analysis; Cohort Two accrued 22 patients, with 16 eligible for PK analysis (3 too early). There were no Course 1 DLT's. Grade 3 toxicities included rash, elevated triglycerides, lymphopenia, diarrhea, and transient transaminase elevation. Overall, patients received a median of 3 (range: <1-27) courses. In Courses 1 and 2, the mean (95% confidence interval) Day 7, 4-HPR peak plasma level ($\mu$M) at 4-6 hours post-morning dose for Cohort One was 11.7 (8.3, 15.1) and for Cohort 2 was 18.4 (14.6, 22.1). Ketoconazole significantly increased peak 4-HPR plasma levels ($p$=0.005, mixed effects ANOVA). Of 16 patients in Cohort One and 18 patients in Cohort Two with evaluable disease at study entry, there were 2 complete responses, 1 partial response, 1 mixed response (MIBG CR), 14 stable disease, and 12 progressive disease; 4 patients did not complete 1$^{st}$ course. For the 34 patients with evaluable disease, the median progression-free survival (PFS) is 4.1 (1.35-36.9+) months. **Conclusions:** 4-HPR/LXS + ketoconazole was tolerated and increased 4-HPR plasma levels. Objective responses and encouraging PFS in this heavily pre-treated patient population support evaluation of 4-HPR/LXS with ketoconazole in future trials of high-risk neuroblastoma. Clinical trial information: NCT00295919.

**10072 General Poster Session (Board #373), Mon, 8:00 AM-11:45 AM**

**Discrepancies in treatment of osteosarcoma according to insurance coverage: A review of the National Cancer Data Base.** *Presenting Author: Mimi Longo, Creighton University School of Medicine, Omaha, NE*

**Background:** Osteosarcoma is the most common primary bone malignancy in children and adolescents. It is an aggressive tumor with a tendency to metastasize to the lungs. It is believed that at the time of diagnosis, all patients have micrometastases. Therefore, neoadjuvant and adjuvant chemotherapy in addition to surgical removal of the tumors became the gold standard of care in the 1990s. The authors sought to learn if patients in the National Cancer Database from 2000-2011 received surgery and chemotherapy as their first course treatment. **Methods:** The National Cancer Data Base contains cases of cancer diagnoses from 1,404 American College of Surgeons-Accredited hospitals. There are 5,501 cases of osteosarcoma from 2000-2011 in the database, and these cases were used for analysis. **Results:** The authors found that 46.6% of patients with no insurance received surgery and chemotherapy, but 63.8% of patients with private/managed insurance received surgery and chemotherapy as their first course treatment (p-value $<0.01$). Only 21.20% of patients who had Medicare got surgery and chemotherapy as their first course treatment. Furthermore, a significant number of patients with no insurance received no therapy (14.8%) as compared to 3.7% of patients who had private/managed insurance ($p<0.001$). **Conclusions:** Patients with no insurance were less likely to receive chemotherapy and surgery for their disease, and they were much more likely to receive no treatment. Lack of insurance prevented patients from receiving life-saving treatments. Thirty-four percent of patients with no insurance were under age 20. Although only 21.20% of patients who had Medicare got surgery and chemotherapy as their first course treatment, 79% of the patients who had Medicare and got osteosarcoma were age 60 and older, so they may have had comorbidities that prevented them from getting surgery and chemotherapy. This is the largest review of osteosarcoma treatments according to insurance status to date.

**10073 General Poster Session (Board #374), Mon, 8:00 AM-11:45 AM**

**Preclinical evaluation of PARP inhibitors in combination with DNA-damaging agents in a Ewing sarcoma orthotopic xenograft model.** *Presenting Author: Elizabeth Stewart, St. Jude Children's Research Hospital, Memphis, TN*

**Background:** Ewing sarcoma (EWS) is an aggressive malignancy of childhood with a dismal prognosis in patients with metastatic or recurrent disease. Previous research demonstrated EWS cell lines with the EWS-FLI1 translocation be sensitive to Poly (ADP ribose) polymerase inhibitors (PARPi). Although phase 1 clinical trials have failed to demonstrate significant single agent efficacy for EWS, preclinical studies suggest increased efficacy with the addition of DNA damaging agents to PARPi. We examined the PARPi BMN 673, olaparib, and veliparib in combination with irinotecan and temozolomide (TMZ) in a clinically relevant EWS orthotopic xenograft model. **Methods:** EWS orthotopic xenografts were created by injecting EW-8 luciferase labeled cells into the femur of CD-1 nude mice. Mice were randomized to the following treatment groups (see Table.) Allometric doses were administered on a clinically relevant schedule for two cycles. Complete response (CR), stable disease (SD), and progressive disease (PD) were determined using bioluminescence. **Results:** The addition of TMZ and irinotecan to BMN 673 and olaparib (Groups 1, 2) showed significant disease response in comparison to irinotecan and TMZ alone (Group 4). Mice that received BMN 673 had the best response with 100% achieving CR. Mice that received olaparib (Group 2) had a 50% CR and 50% SD. Groups 3, 4, and 5 all had 80% PD and 20% SD. **Conclusions:** The addition of the PARP inhibitors BMN 673 and olaparib to irinotecan and TMZ provides significant disease response and stabilization in an orthotopic xenograft model of EWS. These drug combinations may be effective in the treatment of pediatric patients with EWS. Ongoing pharmacokinetic and preclinical studies will be performed to determine if efficacy is likely to be achieved within the therapeutic window of this patient population.

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|---|---|
| **Group 1 (n = 5)** | Irinotecan + TMZ + BMN 673 |
| **Group 2 (n = 4)** | Irinotecan + TMZ + Olaparib |
| **Group 3 (n = 5)** | Irinotecan + TMZ + Veliparib |
| **Group 4 (n = 5)** | Irinotecan + TMZ |
| **Group 5 (n = 5)** | Placebo |

**10074 General Poster Session (Board #375), Mon, 8:00 AM-11:45 AM**

**Postrecurrence survival for pediatric extracranial malignant germ cell tumors: A report from the Malignant Germ Cell Tumors International Collaborative (MaGIC) Group.** *Presenting Author: Furqan Shaikh, Hospital For Sick Children, Toronto, ON, Canada*

**Background:** Post-recurrence survival (PRS) of children and adolescents with malignant germ cell tumors (MGCTs) has not previously been described, due to the limited sample size of relapsed patients in clinical trials. **Methods:** Data from 7 pediatric extracranial GCT trials conducted by the Children's Oncology Group (COG, United States) or the Children's Cancer and Leukemia Group (CCLG, United Kingdom) between 1985-2009 were merged. The COG and CCLG trials differed mainly in the type of platinum agent used for upfront treatment (cisplatin or carboplatin, respectively), and event-free survival after either treatment were not significantly different, as previously reported. Kaplan-Meier survival curves and Cox regression were used to analyze the effects of potential predictor variables on PRS. **Results:** Among 1,107 children in the pooled dataset, 700 MGCT patients received treatment with platinum-based chemotherapy. 72 of these patients experienced a relapse or refractory disease. For these 72 patients, the 5-year PRS was 38% (95% confidence interval (CI) 26% - 49%). The 5-year PRS was significantly higher for 29 children who had been treated upfront with carboplatin regimens (51% , CI 31% - 67%) compared to 43 children treated upfront with cisplatin regimens (28%, CI 15% - 43%; log-rank $p=0.046$). PRS was not significantly associated with age at diagnosis, tumor site, stage, initial AFP, or time to relapse. In a multivariable model where the known prognostic factors for upfront pediatric GCT (age, stage, and site) were added, the effect of chemotherapy regimen remained significant (hazard ratio 2.06, CI 1.03 - 4.10; $p=0.041$). Data on post-recurrence treatment regimens were not available. **Conclusions:** Though limited by the lack of data on type of salvage therapy, we observed a significantly higher PRS after upfront carboplatin regimens compared to upfront cisplatin regimens. This observation should be explicitly tested in a prospective trial. This finding also suggests that overall survival, rather than relapse-free survival, should be utilized as the primary end-point in reduction-of-therapy trials for treatments with differences in PRS.

**10075 General Poster Session (Board #376), Mon, 8:00 AM-11:45 AM**

**Metastatic melanoma presenting during childhood: NCI Pediatric Oncology Branch experience.** *Presenting Author: Melinda S. Merchant, National Cancer Institute at the National Institutes of Health, Bethesda, MD*

**Background:** Childhood melanoma is rare with an incidence of ~300 cases/yr in the United States. Stage IV disease is detected in 1-10% of reported pediatric melanomas. The treatment of this chemoresistant disease in pediatric patients can be quite challenging, even with access to recently approved therapies for melanoma. Limited numbers have made it difficult to determine if the presentation and characteristics of pediatric metastatic melanoma are similar to the disease seen in adults. **Methods:** In a retrospective chart review, we identified sixteen pediatric patients with metastatic melanoma who were referred to the Pediatric Oncology Branch. Molecular status of tumors was determined by CLIA certified tests. Patient overall survival data was collected while patients were treated with ongoing immunotherapy protocols or with treatment using approved agents. **Results:** A total of 16 patients aged 2-21yo were evaluated from January 2009 to January 2014. Fifteen patients had cutaneous melanoma and one teen had mucosal melanoma. Eleven patients (68%) had a head and neck primary, including 8 patients with the scalp identified as the primary site. One teenager presented with widely metastatic disease from an unknown primary. In addition to common sites of metastases in lymph node, liver, and lung, pediatric patients also developed brain metastases ($n=8$ patients) and ocular metastases ($n=1$ patient). Five of the 12 tumors (42%) tested at diagnosis were found to harbor the BRAF V600E mutation. An NRAS mutation was identified in two melanomas. No ckit mutations were identified. Despite multiple treatment strategies, all patients experienced progressive or relapsed disease. The median survival of this cohort was 6 months following diagnosis of metastatic melanoma. **Conclusions:** Metastatic melanoma in the pediatric population is an aggressive disease with widespread pattern of metastasis. Head and neck primaries had a higher incidence in this series than has been identified in pediatric or adult melanoma of all stages. It is unclear if this increase is due to delayed detection or differences in biology. Further advances in pediatric melanoma will be aided by in-depth genomic analysis and collaborative study of these rare cases.

**10076 General Poster Session (Board #377), Mon, 8:00 AM-11:45 AM**

**Proton radiation for treatment of infratentorial brain tumors in infants and very young children.** *Presenting Author: Christine E. Hill-Kayser, Hospital of the University of Pennsylvania, Philadelphia, PA*

**Background:** Radiation therapy (RT) has historically been delayed for infants with brain tumors due to data suggesting unacceptable toxicity after photon RT. Proton therapy allows definite sparing of normal brain, and may allow improved outcomes. **Methods:** 21 consecutive subjects age 3y or less with infratentorial brain tumors requiring RT were enrolled on a prospective registry from 6/2010 – 10/2013. All underwent maximal safe tumor resection. Eight received pre-radiation chemotherapy (ChT) based on diagnosis and tumor-specific treatment plan, but radiation was not delayed due to age. Focal RT was planned after CT simulation and fusion of pre and post-operative MRI scans. The tumor bed, clinical target volume (1 cm expansion), and organs at risk were contoured with Eclipse planning software. Doses are reported in radiobiologic-equivalent-weighted absorbed dose (cGyRBE). Brainstem planning constraints included maximum dose 6,000 and 95% ≤ 5,400. **Results:** The patient population at the time of RT ranged from 11 – 47m, and 13 (62%) were male. Diagnoses included ependymoma (13), medulloblastoma (5), ATRT (2), and Ewing sarcoma (1); the non-ependymoma patients received ChT pre RT. Median RT dose was 5,400 (R 5,040-5,940), and median days for RT course was 44 (R 40-50). RT was delivered using passive scattered proton beams for 20 patients, and pencil beam scanning for 1. All patients received daily general anesthesia. No patient experienced greater than grade 1 (CTCAEv4) acute toxicity. Grade 1 toxicities included fatigue (2), nausea (5), anorexia (4), constipation (2), dermatitis (15). With maximum follow-up of 35 months (range 1.4-35, mean 15 months), 19 patients are alive, no evidence of disease, 1 patient is LTFU, and one is dead of disease. No patient has experienced serious (grade 3-4) long-term toxicity related to radiation. **Conclusions:** With 3 years of follow-up, proton RT for infratentorial brain tumors appears to be well-tolerated by very young children, resulting in minimal acute toxicity and no serious long-term toxicity, with excellent disease control. Increasing use of RT for very young children supports more sophisticated toxicity evaluation prospectively, which is currently being performed at our center.

**10077 General Poster Session (Board #378), Mon, 8:00 AM-11:45 AM**

**Outcomes after proton radiotherapy for localized childhood ependymoma (EP).** *Presenting Author: Christine E. Hill-Kayser, Hospital of the University of Pennsylvania, Philadelphia, PA*

**Background:** Radiotherapy (RT) results in excellent local control and outcomes for resected EP. Proton RT may reduce acute and late RT-related toxicity by reduced exposure of normal brain and other organs at risk (OAR). **Methods:** From 2010-13, 23 subjects with newly diagnosed EP were enrolled on a prospective registry. All subjects underwent maximal safe resection; none had dissemination. Focal RT was planned after CT simulation and fusion of pre and post-operative MRI scans. The tumor bed, clinical target volume (1 cm expansion), and OAR were contoured using Eclipse treatment planning software. Doses are reported in radiobiologic-equivalent-weighted absorbed dose (cGyRBE). Brainstem planning constraints included maximum dose 6,000 and 95% less than 5,400. Neurocognitive (NC) testing was planned for all subjects prior to start of RT. **Results:** The median age at start of RT was 4yr (range 1-15) and 70% were male. Disease characteristics included infratentorial in 18, (78%), supratentorial in 5 (22%) [occipital (2), parietal (2), frontal (1)], and anaplastic histology in 11. Baseline NC testing was performed in 13 subjects, with overall pre-RT NC abilities ranging from low average to superior (median IQ=105, range 88-127). In subjects with non-anaplastic histology, average RT dose was 5,565 (range 5,400-5,940). For anaplastic disease, average dose was 5,900 (range 5,580-5,940). Median duration of RT was 44 days (range 37-50). RT was delivered using passive scattered proton beams for 20 subjects, and pencil beam scanning for 3. Toxicities during treatment (CTAEv4) included fatigue (G1, n = 3) headache (G1, n = 3), dermatitis (G1, n = 12; G2, n = 2), nausea (G1, n = 5), vomiting (G1, n = 2), anorexia (G1, n = 2), dysphagia (G1, n = 1). Post-RT chemotherapy was given to 2 subjects. With a maximum follow-up of 43 months (range 1-43, mean 17), 18 subjects are alive without disease, 2-dead of disease, 3-AWD. None have experienced grade 3 or 4 late RT-related toxicity. At 1 yr post-RT, overall IQ was 96-118 (n=5); at 2 years, 99-121 (n = 3). **Conclusions:** With over 3 years of follow-up, proton RT for pediatric EP appears well-tolerated, resulting in minimal acute toxicity and no serious late toxicity, with excellent disease control.

**10078 General Poster Session (Board #379), Mon, 8:00 AM-11:45 AM**

**A phase I study of cabozantinib (XL184) in children and adolescents with recurrent or refractory solid tumors, including CNS tumors: A Children's Oncology Group phase I consortium trial.** *Presenting Author: Meredith K. Chuk, Pediatric Oncology Branch, National Cancer Institute, Bethesda, MD*

**Background**: Cabozantinib, an oral inhibitor of tyrosine kinases including MET, VEGFR2 and RET, is approved for adults with progressive, metastatic medullary thyroid carcinoma (MTC). We conducted a phase I and pharmacokinetic (PK) trial of cabozantinib in children with refractory solid tumors. **Methods**: Cabozantinib was administered daily (28 day cycles) using the rolling 6 design; 3 dose levels were evaluated. If a cohort was filled, patients (pts) with MTC could be enrolled at the previous lower dose. PK and pharmacodynamic (PD) studies were conducted in all patients, including an expanded cohort at the recommended phase 2 dose (RP2D). **Results**: 29 eligible (25 evaluable) pts, median age 14 yr (range, 4-18) [CNS tumor (n=6), MTC (n=3), hepatocellular carcinoma (HCC, n=2), Ewing sarcoma (EWS, n=2), other sarcomas (n=8), or other (n=8)] have received a median of 3 (range, 1-10) cycles, with 6 pts still on study. During the dose escalation phase dose-limiting toxicities (DLT) occurred in 0/6 pts at 30 and 40 mg/m$^2$ and 1/6 pts at 55 mg/m$^2$ [Gr3 fatigue and headache]. Other first cycle DLTs in expansion cohorts included: Gr 2 palmar plantar erythrodysesthesia (PPE) and oral mucositis (n=1; 40 mg/m$^2$); Gr3 proteinuria and Gr2 hypertension (HTN) (n=1; 55 mg/m$^2$); and Gr3 HTN and reversible posterior leukoencephalopathy syndrome (n=1; 55mg/m$^2$). Later cycle DLTs in 10 pts include: Gr3 weight loss (n=2), Gr3 PPE (n=2), Gr3 and 4 lipase increase (n=1 each), Gr4 neutropenia (n=1), Gr2 fatigue (n=1), Gr2 arthralgia (n=1) and Gr3 anorexia, dyspnea, skin ulcer (n=1). Cabozantinib exposure was not dose proportional. The mean ± SD steady state $AUC_{0\text{-}24h}$ at 30 mg/m$^2$ (n=6), 40 mg/m$^2$ (n=6) and 55 mg/m$^2$(n=6) was 31.9 ± 7.8, 33.3 ± 11.3 and 33.7 ± 15 $\mu$g·h/mL, respectively. The median accumulation index was 3.0 (0.5-8.7). Responses will be reported. **Conclusions**: Based on DLTs observed in later cycles, the recommended dose of cabozantinib in children with solid tumors is 40 mg/m$^2$ (adult fixed dose ≈72 mg). Enrollment is ongoing to further assess PK and PD at the RP2D. A phase II trial is planned. Clinical trial information: NCT01709435.

**10079 General Poster Session (Board #380), Mon, 8:00 AM-11:45 AM**

**Risk of subsequent malignant neoplasms in long-term retinoblastoma survivors following chemotherapy and radiotherapy.** *Presenting Author: Jeannette R Wong, National Cancer Institute, Rockville, MD*

**Background:** Hereditary retinoblastoma (Rb) survivors have increased risk for developing subsequent malignant neoplasms (SMN). Previous studies report elevated SMN risks related to radiotherapy (RT), but less is known about chemotherapy-related risks. Patients and **Methods:** In a long-term follow-up study of 906 five-year hereditary Rb survivors diagnosed 1914-1996 and followed through 2009, risks were quantified using cumulative incidence analyses and compared by type of Rb treatment using hazard ratios (HRs) and 95% confidence intervals (CIs) derived from multivariate Cox proportional hazards regression models. **Results:** Nearly 90% of Rb survivors were treated with RT and almost 40% received alkylating-agent (AA)-containing chemotherapy. Overall SMN risk was elevated among survivors receiving AA+RT compared to RT (without chemotherapy; HR 1.27, 95%CI 0.99-1.63). AA-related risks were significantly increased for subsequent bone (HR 1.30, 95%CI 1.03-2.49) and leiomyosarcoma (HR 2.67, 95%CI 1.22-5.85), but not melanoma (HR=0.74, 95%CI 0.36-1.55). Leiomyosarcoma risk was higher for survivors who received AAs at <1 year of age (HR 5.17, 95%CI 1.76-15.17) versus ≥1 (HR 1.75, 95%CI 0.68-4.51). Development of leiomyosarcoma was significantly more common among survivors who were treated with AA+RT versus RT (8.7% versus 6.3% at age 50 years, p=0.02). **Conclusions:** This first comprehensive quantification of SMN risk after chemotherapy and RT among hereditary Rb survivors demonstrates the contribution of AAs to SMN risk. This effect was driven by Rb survivors who were treated with triethylene melamine (64%). Although no longer prescribed, our findings warrant further follow-up to investigate potential SMN risks associated with current chemotherapies used for Rb.

**10080 General Poster Session (Board #381), Mon, 8:00 AM-11:45 AM**

**Individual risk prediction of major cardiovascular events after cancer: A Childhood Cancer Survivor Study report.** *Presenting Author: Eric Jessen Chow, Fred Hutchinson Cancer Research Center, Seattle Children's Hospital, Seattle, WA*

**Background:** Childhood cancer survivors are at increased risk of cardiovascular (CV) events. Models that combine information on cancer treatment exposures and conventional CV risk factors to estimate an individual's probability of developing major CV events would be clinically important. **Methods:** Cohort study of 10,521 five-year survivors of childhood cancer diagnosed 1970-86, free of CV disease at initial baseline survey, and who were followed with longitudinal surveys. Poisson regression models estimated the risk of the developing severe, life-threatening, or fatal CV events: 1) congestive heart failure (CHF), 2) coronary heart disease (CHD), 3) stroke, and 4) any CV-related death. Models accounted for sex, age at cancer diagnosis, and select chemo- and radiotherapy exposures. Secondary models accounted for late relapse and second cancers occurring beyond 5 years, and the effect of conventional CV risk factors (current smoking, alcohol use, physical activity, obesity, and any treatment for hypertension, dyslipidemia, or diabetes). Model prediction and discrimination were assessed via area under the curve (AUC) and the concordance (C) index. **Results:** After a median follow-up period of 25.8 years (range 7.4-39.2) since cancer diagnosis, the cohort experienced 182 (1.7%) CHF, 186 (1.8%) CHD, 159 (1.5%) stroke, and 66 (0.6%) deaths related to CV events. Models based on primary cancer treatment exposures predicted CHF, CHD, stroke, and CV death risk at/through age 40 with AUC and C-statistics ranging from 0.71-0.77. Adjusting for late relapse/second cancers and conventional CV risk factors further improved prediction (AUC/C-statistics 0.73-0.78; improvement in model prediction, $p=0.01$ to 0.07). The predictive weights assigned to hypertension and diabetes were similar to those assigned to high-level anthracycline or chest radiotherapy exposures. **Conclusions:** The predictive models we generated offer the potential for individual risk assessment of serious CV diseases at/through age 40. Once validated in other cohorts, these models may become important clinical tools in helping care for long-term childhood cancer survivors.

**10081 General Poster Session (Board #382), Mon, 8:00 AM-11:45 AM**

**Myocardial strain for detection of treatment-related cardiac dysfunction in adult survivors of childhood cancer: Results from the St. Jude lifetime cohort study.** *Presenting Author: Gregory T. Armstrong, St. Jude Children's Research Hospital, Memphis, TN*

**Background:** Ejection fraction (EF) by echocardiography (echo) is the recommended screening modality for treatment-related cardiac dysfunction in survivors of childhood cancer. Because decreased EF occurs late in its natural history more sensitive detection methods are needed. We hypothesized that myocardial strain would improve identification of survivors with reduced exercise capacity. **Methods:** Analysis included 1,107 >10 yr survivors of childhood cancer (median age 32 yrs, range 18-59; 593 anthracycline-no chest radiation [RT], 206 chest RT-no anthracycline, and 308 anthracycline + chest RT). Echo included systolic (3D EF, abnormal defined as <50%) and diastolic function (grades 1-3 abnormal), and global longitudinal (>-18.9) and circumferential (>-22.1) myocardial strain. Exercise capacity was assessed with a 6-minute walk (<490 meters abnormal). Associations between echo measures and exercise capacity were assessed using logistic regression adjusted for age, weight, height, pulmonary function, muscle strength, diastolic function, hypertension and diabetes to calculate odds ratios (ORs) and 95% confidence intervals (CI). **Results:** Systolic dysfunction was detected in 5%, diastolic dysfunction in 12%, and abnormal longitudinal and circumferential strain in 47% and 57%. Longitudinal strain was the only echo measure associated with reduced exercise capacity (OR 1.7, CI 1.1-2.6) with no association for 3D EF (OR 0.6, CI 0.2-1.8), diastolic function (OR 1.1, CI 0.6-1.9), or circumferential strain (OR 1.0, CI 0.7-1.6). Abnormal longitudinal strain was associated with older age, male sex and dose of chest RT. Among survivors with normal EF, abnormal longitudinal strain was significantly associated with detection of survivors with reduced exercise capacity (OR 1.7, CI 1.0-2.7). **Conclusions:** Among adult survivors of childhood cancer, abnormal global longitudinal strain is prevalent, associated with chest-directed RT exposure, and is the only echo measure independently associated with reduced exercise capacity. Longitudinal strain identifies at-risk survivors who should be targeted for potential clinical interventions.

**10082 General Poster Session (Board #383), Mon, 8:00 AM-11:45 AM**

**Breast cancer following spinal radiotherapy for a childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS).** *Presenting Author: Chaya S. Moskowitz, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Small dosimetry-based studies suggest females treated with spinal radiotherapy (RT) for a pediatric malignancy may have an increased risk of subsequent breast cancer (BC) due to scatter radiation to breast tissue. However, BC risk in this population has not been assessed in well-characterized survivor cohorts with long-term follow-up. **Methods:** In the CCSS cohort, we estimated BC incidence in 363 5-yr survivors of leukemia ($n=195$) and central nervous system (CNS) tumors ($n=168$) diagnosed 1970-86 prior to age 21 and treated with spinal RT. The median delivered dose of spinal RT for leukemia survivors was 1800 cGy (range 150-4175 cGy) and for CNS tumor survivors was 3453 cGy (range 475-6500 cGy). BC risk compared with the general population was evaluated with standardized incidence ratios (SIRs) estimated using the Surveillance, Epidemiology, and End Results (SEER) Program. Cumulative incidence was estimated treating death as a competing risk. **Results:** With a median follow-up time of 27.5 yrs (range 9-38) and a median attained age of 35 yrs (range 10-53), 3 women were diagnosed with BC at ages 31, 41 and 41 yrs. All were leukemia survivors with spinal RT doses of 1800, 2000, and 2588 cGy; none had a known family history of BC (1 was adopted). BC cumulative incidence by age 40 was 0.5% (95% confidence interval (CI) 0-2.5%). The SIR was 1.2 (95% CI 0.8-7.8) for all survivors treated with spinal RT, 3.9 (95% CI 1.3-12.1) for leukemia survivors, and 0 for CNS tumor survivors. **Conclusions:** We did not find convincing evidence that spinal RT for a childhood cancer is associated with an increased BC risk. The increased risk in leukemia survivors who were treated with lower doses of RT relative to CNS tumor survivors may be due to other factors including a genetic predisposition.

**10083 General Poster Session (Board #384), Mon, 8:00 AM-11:45 AM**

**Plasma microRNAs: Novel markers of cardiotoxicity in children undergoing anthracycline chemotherapy.** *Presenting Author: Kasey Joanne Leger, The University of Texas Southwestern Medical Center, Dallas, TX*

**Background:** Early detection of anthracycline cardiotoxicity may allow cardioprotective intervention(s) prior to irreversible damage. microRNA (miRNA) modulation in anthracycline cardiotoxicity has been identified in animal models, however there are no data regarding circulating miR expression following anthracycline-induced cardiac injury in humans. **Methods:** Plasma miRNA profiling was performed in 25 children before and after a cycle of anthracycline (AC, $n=18$) or non-cardiotoxic chemotherapy (CTRL, $n=7$). Samples were screened by qRT-PCR for 25 candidate miRNAs, including miRs -1, 133a/b, 145, 146, 195, 208a/b, 21, 210, 214, 215, 216, 23a, 29a/b/c, 30a, 34c, 423-3p/5p, 361, 367, 499, and let-7g. Candidates were selected based on their established roles in cardiovascular disease or pathways associated with cardiotoxicity. Relative quantification of each miRNA between the pre and post-cycle timepoints (6, 12, and 24 hours) was determined within each group. miRNAs with significant dysregulation from baseline were identified utilizing the paired t-test function within RealTime StatMiner (Integromics). Differences in miRNA regulation over time were compared between groups (AC vs. CTRL) using a mixed effects linear regression model. **Results:** Three miRNAs were upregulated post-anthracycline therapy, while unchanged after non-cardiotoxic chemotherapy. miR-1 was up by 7 and 5.6-fold at 6 and 12 hours post-anthracycline, respectively ($p<0.05$). Six hours post-anthracycline, miRs-29b and -499 were up by 10-fold ($p<0.01$) and 5.1-fold ($p=0.04$), respectively. In contrast, miRs-1, -29b, and -499 were unchanged at all timepoints after non-cardiotoxic chemotherapy. The difference in post-chemo miRNA dysregulation from baseline was significantly different between AC and CTRL groups at 6 hours for miRs-1, 29b, and 499 ($p<0.01$) and 12 and 24 hours for miR-499 ($p<0.01$); Thus it appears this miRNA upregulation is specifically anthracycline-induced. **Conclusions:** Plasma miR-1, -29b, and -499 are specifically upregulated following anthracycline chemotherapy and may herald acute cardiac injury. Further work is ongoing to evaluate these miRs as early markers of anthracycline-induced cardiotoxicity.

**10084 General Poster Session (Board #385), Mon, 8:00 AM-11:45 AM**

**Risk of second thyroid cancer (STC) among survivors of childhood cancer.** *Presenting Author: Rafaela Naves, Faculdade de Ciências Médicas da Santa Casa de São Paulo, Sao Paulo, Brazil*

**Background**: Thyroid carcinomas account for almost 10% of all second malignant neoplasms. The aim of our study was to assess the risk factors for second thyroid cancer (STC) among childhood cancer survivors (CCS), using population-based data. **Methods**: Using SEER-9 we identified 40,876 individuals with ages 0-19 diagnosed with any malignancy in the period 1973-2010. Standardized incidence ratios (SIR) and corresponding 95% confidence intervals (95% CI) for STC were calculated using SEERStat 8.1.2. **Results**: 131 STC were observed (SIR=5.10, 95% CI 4.26-6.05). The risk of STC was higher for males than females (SIR=8.93, 95% CI, 6.38-12.15, *vs.* SIR=4.29, 95% CI 3.45-5.27, respectively) and for blacks compared to whites (SIR= 10.96, 95% CI 5.26-20.15 *vs.* SIR=4.86, 95% CI 4.01-5.85). Patients < 10 years at diagnosis had a higher risk than patients diagnosed at an older age. (< 10 yrs SIR=8.73, 95% CI 6.50-11.48 vs.> 10 yrs SIR=4.03, 95% CI 3.20-5.02, respectively). Radiation therapy (RT) was associated with a higher risk of STC; risk associated with RT varied by race (blacks: SIR=15.85, 95% CI 5.15-37.00 vs. whites: SIR=7.21, 95% CI 5.54-9.22) and gender (males: SIR=15.23, 95% CI 9.95-22.31 vs. females: SIR=5.76, 95% CI 4.20-7.71). Black children <10 yrs who received RT had the highest risk of STC (SIR=42.67, 95% CI 11.63-109.24). However, an elevated risk was seen for STC even among children who did not receive RT [leukemia (No RT: SIR=6.57, 95% CI 3.59-11.03; RT: SIR=9.30, 95% CI 4.80-16.24) lymphoma (No RT: SIR=7.99, 95% CI 4.65-12.79; RT: SIR=9.71, 95% CI 6.68-13.64)]. The increased risk for CNS (SIR: 8.43; 95%CI, 4.66 – 14.31) and renal tumors (SIR: 8.54; 95% CI, 1.03 – 30.84) and for neuroblastoma (SIR: 21.83; 95%CI, 5.95 – 55.90) was only observed for individuals who had received RT. The increased risk of STC for bone tumors was not associated with RT (SIR=5.02, 95% CI 1.63-11.71). **Conclusions:** Risk for STC is higher for males and blacks, as compared to primary thyroid cancers that occur more commonly in whites and females. The risk of STC is elevated among those who received RT, but even CCS who did not receive RT are at risk. Surveillance of all CCS is recommended, particularly those treated at a younger age, and more exploration of non-RT risk factors is warranted.

**10085 General Poster Session (Board #386), Mon, 8:00 AM-11:45 AM**

**Extracting predictor variables for late effects of childhood cancer treatments from clinical notes.** *Presenting Author: Robert M Johnson, Innovation Center for Biomedical Informatics, Georgetown University, Washington, DC*

**Background:** Today almost 80% of children and adolescents diagnosed with cancer will be long term survivors. As a result of their treatment/cancer, research studies on childhood cancer survivors from the 1970s-1990s show that 75% of the survivors have at least one chronic health condition thirty years after diagnosis. Our goal was to develop a model that predicts late effects of cancer treatment given a set of drugs and diagnoses, which were extracted from clinical notes. Such late effects data could inform current treatments to minimize the incidence of late effects, and help clinicians monitor potential health outcomes for follow up care. **Methods:** We processed 27,533 clinical notes from 245 patients using cTAKES to extract disease/disorder, sign/symptom, and medication mentions. Patients were automatically diagnosed from clinical notes by filtering these extractions to a list of 26 known pediatric cancer diagnoses. Explicitly extracting drug mentions in text was not always reliable. Sometimes only protocols were mentioned (e.g. "COG protocol AALL0434") which infers a set of drugs. Machine learning was used to extract protocols from text and mapped to data from clinicaltrials.gov to obtain a list of drugs. **Results:** 1,785 unique sign/symptom, 1,866 unique disease/disorder, and 417 unique medication mentions were extracted by cTAKES for 245 pediatric cancer patients. Our protocol extraction algorithm performed with precision and recall of 0.86 and 0.83 respectively and inferred 54 drugs with 26 of them never being mentioned in text. Curated diagnoses for 237 patients revealed our diagnoses technique resulted in a precision of 0.68 and recall of 0.95. **Conclusions:** Our next steps are to automatically filter disease/disorder and sign/symptom mentions to extract legitimate late effects related to treatment for particular cancers, using a similar technique as how we diagnosed patients. Given the uncertainties associated with our extractions, we plan to use a Bayesian Network for our prediction model.

**10086 General Poster Session (Board #387), Mon, 8:00 AM-11:45 AM**

**Young and uninsured: Insurance patterns of recently diagnosed adolescent and young adult cancer survivors in the AYA HOPE study.** *Presenting Author: Helen M. Parsons, The University of Texas Health Science Center at San Antonio, San Antonio, TX*

**Background:** Young adults have historically been the least likely to have health insurance in the United States. Previous studies of childhood cancer survivors found lower rates of insurance and less access to medical care compared to siblings; however, no studies have examined continuity of insurance after cancer diagnosis in adolescents and young adults (AYAs). **Methods:** Using the AYA Health Outcomes and Patient Experience study, a cohort of 465 15-39 year-olds from participating Surveillance, Epidemiology and End Results registries, we evaluated changes in and sponsors of health insurance coverage after diagnosis, coverage of doctor-recommended tests, and factors associated with lack of insurance post-diagnosis using chi-square tests and multivariable logistic regression. **Results:** Over 25% (n=118) of AYA cancer survivors experienced some period without insurance up to 35 months post-diagnosis. Insurance rates were high in the initial year after diagnosis (6-14 months; 93.3%) but decreased substantially at follow-up (15-35 months; 85.2%). The most common sponsor of health insurance was employer/school-coverage (43.7%). Multivariable analysis indicated that older survivors (25-39 vs. 15-19; Odds Ratio (OR): 3.35, p<0.01) and those with less education (high school or less vs. college graduate; OR: 2.80, p<0.01) were more likely to experience a period without insurance after diagnosis. Furthermore, >20% of survivors indicated there were doctor-recommended tests/treatments not covered by insurance, but >80% received them regardless of coverage. **Conclusions:** Insurance rates decrease with time since diagnosis in AYA cancer survivors. Future studies should examine how new policies under the Affordable Care Act extend access and insurance coverage beyond initial treatment.

**10087 General Poster Session (Board #388), Mon, 8:00 AM-11:45 AM**

**Investigating the effectiveness of the cognitive remediation and cognitive behavior therapy skills training program (CRCST).** *Presenting Author: Jun Zhao, Children's Blood and Cancer Center/ Dell Children's Hospital, Austin, TX*

**Background**: Improvements in cancer treatments over the past forty years have led to a significant increase in the number of pediatric oncology survivors. With this feat, also emerges the ongoing risk for the development of long-term cognitive impairments and corresponding emotional distress. In particular, neurocognitive late effects from treatment include deficits in attention, memory, and processing speed. Promising research has demonstrated cognitive remediation using a computerized exercise program can produce improvements in this area. Additionally, therapeutic skills from cognitive behavior therapy have shown to effectively reduce emotional vulnerability. The aim of this program was to improve difficulties with working memory, attention, and executive functioning as well as enhance emotional well being using a unique intervention program. **Methods**: Twenty-four patients, ages 8 to 18 years old, who have undergone radiation and/or chemotherapy treatment and displayed neurocognitive and/or psychological late effects indicated by neuropsychological testing participated. The program consisted of 9 group sessions in clinic and completion of 45 twenty-minute computer training sessions at home. Participants and parents completed self-report measures of the Behavior Rating Inventory of Executive Function and the Behavior Assessment System, 2nd Edition. **Results**: A paired sample t-test using the SPSS was conducted. A significant improvement was noted from pre-testing to post-testing for working memory [t(23)= 2.6., p<.05], attention [t(23) = 4.7, p<.05], executive functioning [t (23) = 2.1, p<.05], and emotional well being with improvement in internalization [t(23) = 2.6., p <.05]. **Conclusions:** These results suggest that a combined program with computerized cognitive exercises and cognitive strategies can effectively improve late-effects from treatment.

**10088 General Poster Session (Board #389), Mon, 8:00 AM-11:45 AM**

**Transitioning childhood cancer survivors to adult care: A survey of pediatric oncologists.** *Presenting Author: Lisa Brazzamano Kenney, Dana-Farber Boston Children's Cancer and Blood Disorders Center, Boston, MA*

**Background:** Pediatric oncologists are responsible for facilitating the transition of childhood cancer survivors to risk based adult focused care. This study describes transition practices, perceived barriers to transfer to adult care, and identifies areas for potential intervention. **Methods:** An electronic survey of U.S. members of the Children's Oncology Group; 492/1449 responded (34%) and 347/492 (71%) met eligibility (pediatric oncologist caring for outpatients > age 11 years). **Results:** Of the 347 respondents, 50% are male, median years in practice 10 (range 5-22), 82% are at an academic institution, 37% a free standing children's hospital, and 5% are board certified in adult medicine. Almost all continue to care for patients up to age 21 years (96%), 42% report continuing to take care of adult patients over age 25 years, 16% over age 30 years, and only 8% over 40 years. While 66% of oncologists report providing transition education to their patients, the majority report also having other staff provide this education (89%). Compared to the 147 (42%) who care for adult patients older than 25 years, those who do not were more likely to endorse specific criteria for transfer including survivors' age (p=0. 006), pregnancy (p=0.014), marriage (p=0.010), college graduation (p=0.006), and substance use (p=0.036). Most oncologists identified barriers to transfer to adult care including patients' attachment to provider (91%), parents' attachment to provider (90%), lack of knowledgeable adult providers (86%), cognitive delay (81%), and unstable social situation (80%). However, oncologists who continue to care for patients older than 25 years are more likely to perceive parents' attachment to provider (p=0.037) and patients' unstable social situation as barriers to transfer (p=0.044). **Conclusions:** Most pediatric oncologists report transferring adult childhood cancer survivors to adult care and providing transition education to their patients. Those who continue to care for survivors as adults are more likely to perceive psychosocial needs as barriers to transfer. Transition practices that address developmental and psychosocial challenges might facilitate successful transfer of childhood cancer survivors to adult care.

**10089 General Poster Session (Board #390), Mon, 8:00 AM-11:45 AM**

**Contraceptive recommendations for young women during cancer treatment: Examining contraceptive knowledge of pediatric oncology clinicians.** *Presenting Author: Sloane L. York, Rush University Medical Center, Chicago, IL*

**Background:** Adolescent and young adult women with cancer have specific reproductive health needs and may seek guidance from oncology clinicians. This study examined oncology clinicians' reported contraceptive recommendations and contraceptive knowledge. **Methods:** Oncology clinicians caring for women aged 13-45 completed an online survey. This secondary analysis reports on pediatric clinicians' contraceptive knowledge by identifying typical failure rates of 10 contraceptives and safety of 4 hormonal contraceptives using case scenarios. Knowledge score was determined by averaging the percent correct on safety and efficacy questions. **Results:** 518 respondents were included. Most were practicing pediatric oncologists (52.3%) or advanced practice clinicians (42.5%). Participants practiced a mean of 12.5 years and most (64.1%) saw 3-10 reproductive-aged female patients per month. Most (82.0%) reported regularly recommending a woman use contraception during treatment. Over half (53.2%) stated they were comfortable with contraceptive counseling, 69.9% provided contraception in the past year, and 67.1% wanted more information on contraception. Almost half (47.3%) stated they do not discuss pregnancy planning and 233 (45.0%) had cared for at least one pregnant cancer patient. Total knowledge score was 47.4% (95% CI: 45.8, 49.0). Participants identified 61.9% of contraceptives' safety (95% CI: 60.0, 64.2). 87.1% identified combined oral contraceptives as unsafe after pulmonary embolism. For a nulliparous woman with AML, 30.4% correctly identified the safety of the levonorgestrel intrauterine device (IUD) and 28.9% for the copper IUD. Participants identified 32.6% (95% CI: 31.0, 34.2) of 10 contraceptives' efficacy. 19.4% correctly identified condoms' efficacy, 12% for oral contraceptive pills, and 34.8% for depot-medroxyprogesterone acetate. Almost half correctly identified the failure rate of IUDs (46.1%). Most over-estimated the effectiveness of contraceptives. **Conclusions:** Pediatric oncology clinicians report recommending contraception during cancer treatment, but may lack comprehensive knowledge for counseling their patients.

**10090 General Poster Session (Board #391), Mon, 8:00 AM-11:45 AM**

**Knowledge, attitudes, and beliefs of parents toward whole-genome sequencing in pediatric cancer.** *Presenting Author: Jenny Ruiz, Columbia University College of Physicians and Surgeons, New York, NY*

**Background:** Introducing whole genome sequencing (WGS) in pediatric cancer patients at diagnosis poses a unique set of issues. We investigated parental knowledge, attitudes and beliefs about the role of genetics and WGS in the care of children with cancer and towards the return of secondary findings. **Methods:** Focus groups with parents/caretakers of children with cancer and semi-structured interviews with parents of healthy children were conducted. Participants were recruited from the outpatient pediatric oncology clinic and in-patient units, respectively, at Columbia University Medical Center. The topic guides included questions on genetic research, WGS, secondary findings, and timing of the consent process. All focus groups and interviews were audio recorded, transcribed and analyzed using thematic analysis. **Results:** 4 focus groups (16 participants (11 females, 5 males; 4 Hispanic, 4 African American, 1 Asian, 10 White)), and 8 semi structured interviews (7 females, 2 males; 4 Hispanic, 3 African American, and 3 White) ranging from high school to graduate school education were conducted. A wide range of knowledge about genetic testing existed among participants; few participants had prior knowledge about WGS. Participants expected that WGS research was more likely to benefit future children rather than their own child. Most participants said they would participate in WGS if there were no additional immediate risks to their child; they wanted to be told about secondary findings but worried about the potential psychosocial burden of those results. There was close to universal opinion that they would not be offering informed consent if asked to participate in WGS at diagnosis and preferred the idea of a two-step consent process. **Conclusions:** At baseline, parents have very limited knowledge about WGS, regardless of gender, ethnicity or attained education. Parents felt their current level of understanding and perceived level of stress at the time of a cancer diagnosis in their child would hamper the ability to give informed consent. Additional research is required to optimize patient education and timing of the informed consent discussion for WGS.

**10091 General Poster Session (Board #392), Mon, 8:00 AM-11:45 AM**

**Effect of topical clonidine on the duration and severity of radiation-induced oral mucositis (OM) in a translational hamster model.** *Presenting Author: Pierre Attali, BioAlliance Pharma, Paris, France*

**Background:** There is currently no effective mechanistically-targeted intervention for radiation-induced OM. Clonidine, a a2 adrenergic agonist, has been shown to impact NF-kappaB with consequent inhibition of the expression and the release of the pro-inflammatory cytokines thought to be involved in OM's pathogenesis. We assessed the efficacy of a topical formulation of clonidine to mitigate radiation-induced OM in an established translational hamster model. **Methods:** Two independent studies were performed in which 32 male Syrian Golden hamsters were randomly assigned to four equally-sized groups in each. OM in a saline-treated control was compared to three groups which received clonidine in different concentrations and/or dosing frequency. Study drug was administered topically from the day before radiation (Day -1) until day 20. On study day 0, hamsters were irradiated with a single 40 Gy dose directed to the left buccal cheek pouch. Beginning on day 6 images of the left cheek pouch mucosa were obtained every other day and blindly scored for OM severity using a validated 6-point scale. The number of days of ulcerative OM with scores of $\geq 3$ was assessed (Chi-2 test). The individual daily group scores were evaluated (rank sum test). In Study 1 (S1), clonidine was given topically once daily at doses of 30, 100 and 300 $\mu$g/kg. In Study 2 (S2), clonidine was given QD at 100 $\mu$g/kg and QID at 12.5 and 25 $\mu$g/kg. **Results:** Clonidine consistently reduced the duration and severity of OM. In S1, clonidine dose dependently reduced the % days of score $\geq 3$ from 46.9% in controls to 41.7%, (p=0.35), 29.2% (p<0.001) and 30.2% (p<0.001) in clonidine 30, 100 and 300 $\mu$g/kg treated animals. In S2, % days was reduced from 35.4% in controls to 21.9% (100 $\mu$g/kg, p=0.003), 28.1% (12.5 $\mu$g/kg, p=0.12) and 26% (25 $\mu$g/kg, p=0.04). OM severity was significantly reduced compared to controls in the clonidine 100 and 300 $\mu$g/kg QD groups in S1, and in the clonidine 100 $\mu$g/kg QD, 12.5 and 25 $\mu$g/kg qid in S2. Clonidine was not shown toxic. **Conclusions:** Topically administered clonidine mitigated radiation-induced OM in hamsters in a dose-dependent manner. QD administration was as effective as QID dosing. The optimal dose in this model was 100 $\mu$g/kg QD.

**10092 General Poster Session (Board #393), Mon, 8:00 AM-11:45 AM**

**Mediating role of emotional symptoms on assessment of health-related quality of life of adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study.** *Presenting Author: I-Chan Huang, University of Florida College of Medicine, Gainesville, FL*

**Background:** Factors that may mediate or influence how cancer survivors endorse health-related quality of life (HRQOL) items are not well studied. This study compared HRQOL between adult survivors of childhood cancer and siblings by accounting for the mediating effect and measurement non-invariance related to emotional symptoms. **Methods:** 7,103 cancer survivors and 390 siblings in the Childhood Cancer Survivor Study completed the SF-36 measuring eight domains of HRQOL. Symptoms of anxiety, depression and somatization were measured using the Brief Symptom Inventory-18. Multiple Indicators & Multiple Causes model was used to identify measurement non-invariance related to emotional symptoms in the SF-36 items. Structural equation modeling was performed to test direct and indirect effects of cancer experience on HRQOL accounting for the mediating role of emotional symptoms. **Results:** 10, 12, and 14 items of the SF-36 were identified with measurement non-invariance related to anxiety, somatization and depression, respectively. Survivors reported poorer HRQOL in all domains than siblings did (all p's$<$0.05), except for pain (p$>$0.05). Poorer physical functioning was significantly explained by direct effect of cancer experience (p$<$0.05) and indirect effect of cancer experience through emotional symptoms (p$<$0.05). However, poorer HRQOL in other domains was greatly explained by the mediating role of emotional symptoms, indicating indirect effect (p$<$0.05) rather than direct effect (p$>$0.05). Indirect effects explained 40-70% of total effects in the association of cancer experience and HRQOL. Adjusting for measurement non-invariance for the SF-36 items did not change the association of cancer experience with HRQOL compared to not adjusting for non-invariance. **Conclusions:** Childhood cancer survivors reported poorer HRQOL than siblings. The differences appear due, in part, to measurement non-invariance related to emotional symptoms that influence perceptions of HRQOL, and the mediating effect of emotional symptoms on HRQOL. Evaluating emotional health is an important component in survivorship care toward improving their HRQOL.

**10093 General Poster Session (Board #394), Mon, 8:00 AM-11:45 AM**

**Cardiotoxicity and second malignant neoplasms associated with dexrazoxane in children and adolescents: A systematic review of randomized trials and nonrandomized studies.** *Presenting Author: Furqan Shaikh, Hospital For Sick Children, Toronto, ON, Canada*

**Background:** Several randomized controlled trials (RCTs) in breast cancer have demonstrated the efficacy of dexrazoxane (DRZ) in reducing anthracycline cardiotoxicity. However, research on DRZ in pediatric patients has been stalled by a recent report of increased second malignant neoplasms (SMN). The objective of this study was to systematically review the evidence for and against the use of DRZ in children. **Methods:** We searched Medline, Embase, Cochrane, and abstracts for all RCTs and non-randomized studies (NRSs) that compared DRZ to no cardioprotection among cancer patients $<$18 years of age receiving anthracyclines. **Results:** 23 articles reporting 5 RCTs (1,254 patients) and 11 NRSs (3,329 patients) were identified. Among 5 RCTs, there were 16/625 (2.5%) SMN with DRZ vs 6/619 (1.0%) SMN without DRZ (risk ratio (RR) 2.52, p=0.06, number needed to harm = 63). The types of SMN varied: two RCTs that used concurrent etoposide reported an increased risk of AML, while one RCT that used cranial radiation reported an increased risk of brain tumors. There was no significant difference in EFS (5 RCTs, p=0.93). Among 2 RCTs, DRZ was associated with an improved shortening fraction Z-score (mean difference (MD) 0.61, p=0.002) and thickness: dimension Z-score (MD 0.66, p$<$0.001). A significant effect on clinical cardiotoxicity could not be shown due to a very low cardiotoxic event rate (3 events among all RCT patients). Among NRSs, there were 6/860 (0.7%) SMN with DRZ vs 18/1,825 (1.0%) SMN without DRZ (p=0.58). DRZ was associated with a reduction in clinical cardiotoxicity (RR 0.29, p=0.001, NNT=14) and clinical+subclinical cardiotoxicity (RR 0.43, P$<$0.001, NNT=4). However, NRSs were subject to time-related bias, with control arms generally having longer follow-up. **Conclusions:** DRZ is associated with a significant reduction in cardiotoxicity in pediatric NRSs. Evidence of benefit from pediatric RCTs currently relates only to surrogate outcomes and is limited by a low clinical event rate. DRZ is associated with a statistically borderline increase in SMN, although an interaction with other carcinogenic treatments (radiation, etoposide) may be responsible.

**TPS10094 General Poster Session (Board #395A), Mon, 8:00 AM-11:45 AM**

**SIOPEL 6: A multicenter open-label randomized phase III trial of the efficacy of sodium thiosulphate (STS) in reducing ototoxicity in patients receiving cisplatin (Cis) monotherapy for standard-risk hepatoblastoma (SR-HB).** *Presenting Author: Rudolf Maibach, IBCSG Coordinating Center, Bern, Switzerland*

**Background:** The SIOPEL 3 trial of Cis monotherapy and surgery in SR-HB showed a 3yr OS of 95% at 5 years. SR-HB is defined as tumor extension limited to PRETEXT I, II or III, no involvement of portal or hepatic veins, no intra-abdominal extrahepatic disease, AFP $>$100ng/ml and no metastases. At commonly used doses and schedules, Cis can cause permanent bilateral high-frequency hearing loss. Several pre-clinical and clinical studies in adults and children (particularly from the Oregon group) suggest that STS may reduce the risk of ototoxicity. There are however concerns that STS could reduce the anti-tumor efficacy of Cis, hence the time separation of Cis and STS and the close monitoring of the trial. **Methods:** Newly diagnosed patients with SR-HB are treated with 4 chemotherapy courses every 2 weeks before surgery and 2 courses after surgery. Patients are randomly assigned to receive Cis alone or Cis followed by STS. Cis 80mg/m$^2$ is administered i.v. over 6 hrs. STS is administered i.v. exactly 6 hrs after stop of Cis over 15 minutes at 20g/m$^2$. Serum sodium is monitored 1 hr, 6 hrs and 18 hrs post STS. Tumor response is assessed after 2 and 4 cycles preoperatively with serum AFP and liver imaging. In case of lack of response after 2 cycles, STS is stopped and chemotherapy is changed to combination therapy with Cis and doxorubicin 60mg/m$^2$ continuous infusion over 48 hrs. A DNA sample for central analysis of ototoxicity predisposition factors and a tumor sample are requested. The primary endpoint of the trial is centrally reviewed absolute hearing threshold, at the age of $\geq$3.5 yrs, by pure tone audiometry. With a sample size of 102, the trial has 80% power to detect a reduction of the rate of hearing loss defined as Brock grade $\geq$ 1 from 60% under Cis alone to 35% under Cis and STS. In case of concerns of an adverse effect of STS on the efficacy of the Cis chemotherapy, the trial may be stopped early. Interim efficacy results on response to chemotherapy are evaluated after every 20 patients and submitted immediately to the IDMC. The IDMC has recommended continuing the trial after review of the results on 20, 40 and 60 pts. Clinical trial information: NCT00652132.

**TPS10095 General Poster Session (Board #395B), Mon, 8:00 AM-11:45 AM**

**Phase I/IIa multicenter trial for high-risk and recurrent neuroblastoma: Anti-GD2 antibody (ch14.18) immunotherapies using M-CSF or G-CSF.** *Presenting Author: Hiroshi Kawamoto, National Cancer Center Hospital, Tokyo, Japan*

**Background:** Anti-GD2 antibody, ch14.18, with GM-CSF or IL2, has significantly improved disease free survival in high-risk neuroblastoma. ch14.18 generally induces cell lysis through the process of antibody-dependent Cellular Cytotoxicity (ADCC) through PBMC (NK cell etc.) as effector cell. Concurrent use of GM-CSF with ch14.18 enhances the effect of both neutrophils and PBMC mediated ADCC. To maximize ADCC, this phase I/IIa study was planned to optimize dosing and feasibility, and to evaluate ADCC in using M-CSF (R1) and G-CSF (R2). **Methods:** Eligibility: Patients (pts) aged between 2 and 45 years with refractory or relapsed (phase I and phase IIa) and high risk (phase IIa) neuroblastoma. Other important requirements were as follows: good PS; normal organ function; appropriate interval from prior antitumor therapies; no history of allogeneic hematopoietic stem cell transplantation; No intracranial hemorrhagic episode within one month if central nervous system metastasis exits. Treatment plan: In R1, CSF regimen (ch14.18 10-20h div d4-7, M-CSF 2h div d1-14) and IL2 regimen (ch14.18 10-20h div d8-11, IL2 24h div d1-4, d8-11) are alternately performed every one month, up to 5 courses with starting from CSF regimen. In R2, G-CSF s.c. is replaced with M-CSF in CSF regimen. Endpoints: Primary endpoint is DLT of ch14.18, IL2, M-CSF, G-CSF (phase I) and proportion of completing 5 courses of R1 and R2 (phase IIa). Secondary endpoints include pharmacokinetics and dose-response for ch14.18 and IL2, ADCC activity and anti-chimera antibody response proportion. Study design: Multi-center, phase I/IIa design. In phase I, ch14.18, M-CSF, G-CSF, IL2 are all object for dose finding by 3+3 design, with starting dose 17.5mg/m2 (level1), 6 million IU/m2 (level1), 5 ug/kg (level1), 0.75 million IU/m2(1 week) and 1 million IU/m2(2 week) (level0). In phase IIa, sixteen pts are required to confirm feasibility of optimized R1 and R2 regimens in phase I with a threshold for five month PFS of 31% and one-sided alpha level 5%. Clinical trial information: UMIN000012001.

**10500 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Prognostic/predictive biomarkers in advanced soft tissue sarcomas (STS): Translational research associated to randomized phase II trial comparing trabectedin-doxorubicin versus doxorubicin—A GEIS study.** *Presenting Author: Javier Martin Broto, Hospital Son Espases, Palma de Mallorca, Spain*

**Background:** Nucleotide excision and homologous recombination DNA repair pathways are the most recognized antitumor mechanism of action of trabectedin in STS. Additionally, our group has shown the relevance of FAS and calcium signaling pathways in the efficacy of trabectedin in preclinical experiments with sarcoma cell lines. Thus, in vein with that, a prospective translational research focusing on DNA repair genes, calcium and FAS signaling pathways was designed accompanying a randomized phase II trial in STS. The trial comparing trabectedin-doxorubicin (TD) vs doxorubicin (D) as first line of advanced or metastatic STS patients was stopped for futility after enrolling 115 patients. **Methods:** Immunohistochemistry studies were performed for FASR, Bcl2, p53, PKC-$\alpha$ and PKC-$\beta$ and for RNA expression *FASR*, *FASL*, *CUL4A*, *ERCC1* and *ERCC5* were analyzed. Kaplan–Meier estimations were used for time-to-event variables and the log-rank test was used to compare groups. **Results:** With a median follow-up of 11 months, there were 95 events of recurrences and 63 of deaths. Regarding the entire series, p53+ had significant lower PFS (1.33m vs 6.53m, p= 0.002) and FASR+ showed a significant better OS (21.07m vs 8.33m, p= 0.002). Remarkably, combining FASR/p53 showed to be a strong prognostic factor for PFS (7.03m if FASR+ and p53-, 2.93m if FASR+ or p53 – and 0.50m if FASR- and p53 +; p < 0.001) and OS (26.9m if FASR+ and p53-, 13.5m if FASR+ or p53- and 4.5m if FASR- and p53 +; p=0.001). In TD arm, the following biomarkers showed significant better PFS: FASR+ (6.5m vs 2.9m; p= 0.033); p53- (6.53 m vs 1.33 m; p=0.02); CUL4A above median (8.1 m vs 1.7m; p= 0.015) and ERCC1 above median (8.23 m vs 2.93, p= 0.031). Those with a significant better OS were: FASR+ (21.07m vs 5.9 m; p=0.033) and CUL4A above median (21.83m vs 9.43m; p=0.041). In D arm no significant association was seen **Conclusions:** FASR and p53 have shown to be strong prognostic factors in advanced/metastatic STS while CUL4A seemed highly predictive to trabectedin. These biomarkers should be taken into account in future trials design focusing on this population of STS. Clinical trial information: NCT01104298.

**10501 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**ANGIOTAX-PLUS trial: A randomized phase II trial assessing the activity of weekly paclitaxel (WP) plus or minus bevacizumab (B) in advanced angiosarcoma (AS).** *Presenting Author: Nicolas Penel, Centre Oscar Lambret, Lille, France*

**Background:** Paclitaxel is an active agent in advanced AS. The objective of this study was to explore the activity and safety of adding B to WP in treatment of AS. **Methods:** We conducted a multicenter randomized (1/1) phase II trial for assessing both regimens. WP: 90 mg/m$^2$ d1,8 and 15 in 4-wks cycle for 6 cycles, +/- B 10 mg/kg d1,8 and 15 followed by maintenance therapy 15 mg/kg/3 wks until intolerance/progression. Stratification factors were: superficial vs visceral AS, de novo vs radiation-induced (RI) AS. Primary endpoint was 6-month progression-free rate (RECIST 1.1). Statistical assumptions were: P0=20%; P1=40%, $\alpha$=10% and $\beta$=20%. **Results:** From 09/2010 to 09/2013, 50 pts (26 in WP and 26 in WP-B arm) have been enrolled in 14 centers. There were 12 men and 38 women (median age 66, 24-82). Most common primaries were: breast (24, 49%) and skin (6, 12%). There was 17 (34%) visceral and 24 (49%) RI AS. PS was 0 in 24 (50%) and 1 in 23 (48%). 16 pts have previously received anthracyclines (32%); 32 pts (64%) were chemo-naive. 8/24 (33%) pts enrolled in WP-B arm have received B as maintenance therapy. Median follow-up was 14.5 months. Both regimens were considered active with a 6-mPFR of 57% (15/26) in WP arm and 57% (14/24) in WP+B arm. Median PFS was 6.8 vs 6.9 months. 1-year OS was 55 vs 58%. 4 pts experienced Gr5-AE: 1 in WP arm (hemorrhage) and 3 in WP-B arm (suicide, intestinal occlusion, general condition deterioration). We had observed arterial hypertension in both arms: WP (1 Gr2) and WP-B (1 Gr2/1 Gr3), hemorrhage in both arms: WP (2 Gr1/1 Gr5) and WP-B (2 Gr1/1 Gr2), thrombosis in both arms: WP (1 Gr1) and WP-B (1 Gr2/ 1 Gr4) and 1 case of Gr1 proteinuria in WP-B arm. There was no reported wound dehiscence and gastro-intestinal perforation. Hematological toxicity profile was similar in both arms. **Conclusions:** WP and WP-B are both active regimens of AS. B did not improve the outcome of AS pts. This study illustrates the importance of randomization in phase II trial. In the present trial, WP provides PFS (6.8 vs 4.0 months) and OS (>12 vs 8 months) significantly higher than previously reported in the AngioTax Study (Penel JCO 2008). Clinical trial information: 2009-017020-59.

**10502 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Randomized phase 2b trial comparing first-line treatment with aldoxorubicin versus doxorubicin in patients with advanced soft tissue sarcomas.** *Presenting Author: Sant P. Chawla, Sarcoma Oncology Center, Santa Monica, CA*

**Background:** Doxorubicin (D) is the only approved first line therapy for most advanced soft tissue sarcomas (STS). Aldoxorubicin (A) consists of doxorubicin attached to an acid-sensitive linker that binds covalently to serum albumin. We compared the efficacy and safety of A to D as first line treatment for patients with advanced STS. **Methods:** 31 site international trial; 123 patients ages 18-78 years with histologically confirmed metastatic, locally advanced or unresectable STS randomized 2:1 to receive either 350 mg/m$^2$ A (260 mg/m$^2$ D equivalents) or 75 mg/m$^2$D, every 3 weeks for a maximum of 6 cycles. Tumor response by CT was monitored every 6 weeks until completion of treatment, 2 months post treatment, then every 3 months to progression or withdrawal from study. Primary endpoint: progression-free survival (PFS). Secondary endpoints: overall response rate (ORR), PFS at 6 months and overall survival (OS). Both a blinded, independent review and an investigator site review were performed for each scan. **Results:** 83 patients were randomized to A and 40 to D. Groups were well-balanced for age, sex, race, performance status, and sarcoma pathology. Median (range) # of completed cycles: A = 6 (1-6); D = 4 (1-6). 30% of patients were from the U.S., 47% from Europe and 23% from Asia Pacific. Efficacy results are shown in the Table. Grade 3 or 4 adverse events that were increased in patients treated with A were neutropenia (28% vs 15%), nausea/vomiting (10% vs 0%), mucositis (12% vs 2 %), fatigue (5% vs 0%) and anorexia (4% vs 0%). LVEF < 50%: A = 0, D = 9.5%. Grade 3/4 pain was increased in the D arm (2% vs 8%). Grade 3/4 febrile neutropenia (17% vs 18%), anemia (17% vs 20%) thrombocytopenia (7% vs 5%) were similar for patients receiving A or D. **Conclusions:** Aldoxorubin is more efficacious than doxorubicin in the treatment of advanced STS with an acceptable safety profile. Clinical trial information: NCT01514188.

| Investigator review | | | |
|---|---|---|---|
| | A | D | p |
| PFS (months, median) | 8.4 | 4.7 | 0.0002 |
| HR (CI) | 0.370 (0.212-0.643) | | 0.0004 |
| PFS, 6 months | 67.1% | 36.1% | 0.008 |
| ORR (%) | 24.0 | 5.3 | |
| CR | 2.7 | 0 | |
| PR | 21.3 | 5.3 | |
| **Blinded independent review** | | | |
| PFS (months, median) | 5.7 | 2.8 | 0.018 |
| HR (CI) | 0.586 (0.358-0.960 | | 0.034 |
| PFS, 6 months | 46.8% | 23.7% | 0.038 |
| ORR (%) | 23 | 0 | |
| CR | 0 | 0 | |
| PR | 23 | 0 | |

**10503^ Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**A pilot study of PLX3397, a selective colony-stimulating factor 1 receptor (CSF1R) kinase inhibitor, in pigmented villonodular synovitis (PVNS).** *Presenting Author: William D. Tap, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** PLX3397 is a novel, oral small molecule that potently and selectively inhibits CSF1R, Kit, and Flt3 kinases. CSF1R and Kit regulate key components of both the tumor and its microenvironment (macrophages, osteoclasts, mast cells). PVNS is a rare proliferative neoplasm involving the synovium of joints or tendon sheaths. Tumors contain CSF1R-bearing macrophages recruited by local overexpression of CSF-1 due to a gene translocation. **Methods:** Patients (pts) with advanced PVNS were enrolled onto an expansion cohort of an ongoing single-arm, multicenter, clinical study. PLX3397 was given orally, 1000 mg daily (600 mg AM, 400 mg PM – 28 day cycles). MRI assessment by a central musculoskeletal radiologist blinded to chronology was performed every 2 cycles using a novel Tumor Volume Score (TVS) developed specifically for PVNS. Partial response (PR) was defined as ≥50% decrease in TVS compared to screening and progressive disease was ≥30% increase relative to lowest score. Patients remained on treatment until disease progression or intolerability. **Results:** 17 PVNS pts have been enrolled to date. Median exposure 166 days (range 23- 264). 59% pts were women; median age 46 yrs (range 22-80). Tumor locations: knees (12), ankles (2), feet (2), elbow (1). Of the 11 pts with evaluable MRI scans at this interim analysis, 7 pts (64%) achieved a PR and 4 pts (36%) had stable disease (SD). Mean tumor size reduction was 51% (range: -10% to -88%). Clinical improvements were seen in pain, stiffness, and overall function. Common AEs (>10%): fatigue, nausea, hair color changes, and diarrhea. Treatment-related AEs ≥Grade 3: anemia (1), hyponatremia (2), elevated ALT and AST (1), fatigue (1) and diarrhea (1). **Conclusions:** PLX3397 was well tolerated and demonstrated profound activity as measured by a novel response criterion in pts with advanced PVNS. PLX3397 warrants further study in a larger clinical trial. Clinical trial information: NCT01004861.

**Percent change in TVS compared to screening.**

| | Cycle | | | | |
|---|---|---|---|---|---|
| Patient | 3 | 5 | 7 | 9 | Best response |
| 1 | -64% | -40% | -68% | -64% | PR |
| 2 | -85% | -85% | -87% | -88% | PR |
| 3 | -50% | -50% | -50% | -58% | PR |
| 4 | -60% | -75% | - | -83% | PR |
| 5 | -13% | -13% | -13% | - | SD |
| 6 | -42% | -50% | -58% | - | PR |
| 7 | -5% | -10% | - | - | SD |
| 8 | -40% | - | - | - | SD |
| 9 | -43% | -57% | - | - | PR |
| 10 | -50% | - | - | - | PR |
| 11 | -39% | - | - | - | SD |

**10504^ Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Phase 1 study of RG7155, a novel anti-CSF1R antibody, in patients with locally advanced pigmented villonodular synovitis (PVNS).** *Presenting Author: Philippe Alexandre Cassier, Centre Léon Bérard, Lyon, France*

**Background:** PVNS, also known as tenosynovial giant cell tumor (TGCT), is a rare disease mainly affecting young adults. This neoplastic disease is driven in most cases by a t(1;2) translocation resulting in fusion of COL6A3 and M-CSF genes encoding for colony-stimulating factor 1 (CSF1). The bulk tumor mass consists of CSF1 receptor (CSF1R) positive cells. RG7155 is a monoclonal antibody that potently inhibits the dimerization of CSF1R. **Methods:** In this dose-escalation and −extension phase I study, we treated patients with locally advanced PVNS, who were not amenable to surgical treatment. Primary objectives were to assess safety, tolerability, pharmaco-kinetics and -dynamics. Clinical activity was evaluated using FDG-PET (at 4 weeks after treatment start; EORTC criteria) and MRI (at 6 weeks; RECIST 1.1). Pre- and on-treatment biopsies of tumor and surrogate skin tissue as well as peripheral blood PD markers were analyzed. **Results:** Between September 2012 and October 2013, 11 PVNS patients (median age 38 (range 18-64)) were treated at three French institutions at four different dose levels (q2w). Three patients had previously been treated with nilotinib and imatinib, respectively. Seven patients had undergone previous surgeries. RG7155 induced a sustained increase of CSF1 associated with a decrease of $CD14^{+}CD16^{+}$ monocytes in peripheral blood in all 10 evaluable patients. RG7155 led to striking reductions of $CSF1R^{+}$ and $CD163^{+}$ macrophages in tumor tissue associated with rapid onset of objective clinical responses in 7/9 patients (78%; partial metabolic response at 4 weeks; FDG-PET) and 7/10 patients (70%; PR at 6 weeks; MRI). All patients showed tumor shrinkage associated with symptomatic improvement. 9/10 patients remained clinically progression-free with a longest follow-up of 17 months. RG7155 was well tolerated with only two patients experiencing grade 3 adverse events (periorbital edema; mucositis). **Conclusions:** RG7155 treatment induced rapid clinical responses in the vast majority of PVNS patients associated with profound reduction of $CSF1R^{+}$ and $CD163^{+}$ macrophages in tumor tissue. Clinical trial information: NCT01494688. Clinical trial information: NCT01494688.

**10505 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Response to treatment with denosumab in patients with giant cell tumor of bone (GCTB): FDG PET results from two phase 2 trials.** *Presenting Author: Keith M. Skubitz, University of Minnesota, Minneapolis, MN*

**Background:** GCTB is a primary osteolytic tumor characterized by local invasiveness and limited non-surgical treatment options. Osteoclast-like giant cells expressing surface RANK, and stromal cells expressing RANK ligand (RANKL), are features of GCTB. Denosumab, a monoclonal antibody against RANKL, is approved in the US for treatment of GCTB that is unresectable or where surgery would be associated with severe morbidity. Here, we report sequential FDG-PET as a sensitive early indicator of GCTB response to denosumab from 2 phase 2 trials. **Methods:** Adult or skeletally mature patients with GCTB (N=360) received subcutaneous (SC) denosumab 120 mg on days 1, 8, and 15, and every 4 weeks thereafter. In some centers, combination FDG-PET and CT images were obtained sequentially as part of routine care. All evaluable scans were reviewed by central independent treatment-blinded reviewers. **Results:** Paired pre- and post-treatment FDG PET scans from 26 patients (144 scans) showed marked reductions in FDG-PET avidity and reductions in standardized uptake values (SUV) early in response to denosumab at the first post-treatment scan (median [Q1, Q3] 68.5 [50, 84] days from first dose). All paired samples showed a best EORTC response of >25% reduction in SUV uptake following initiation of denosumab treatment. Sequential PET imaging studies revealed a sustained and progressive SUVmax reduction in GCTB lesions with continued denosumab treatment. **Conclusions:** This study represents the largest GCTB FDG-PET imaging data set from an interventional clinical trial reported to date. It shows that FDG-PET is a sensitive early indicator of tumor response to denosumab, preceding both cytoreduction (RECIST) and new bone formation/calcification (HU density), and that this response is sustained in denosumab-treated GCTB. Clinical trial information: NCT00396279, NCT00680992.

| Tumor site (N patients) | Baseline SUVmax, median (range) | Best on-study SUVmax, median (range) | EORTC standard uptake, mean | Best SUVmax response (mean % change from baseline) |
|---|---|---|---|---|
| Appendecular skeleton (11) | 10.0 (6.4-21.6) | 4.0 (1.3-10.4) | 2.1 | -66 |
| Axial skeleton (11) | 9.2 (2.9-16.1) | 2.7 (1.1-5.1) | 1.7 | -64 |
| Lung (5) | 6.5 (3.6-11.0) | 1.8 (1.1-5.0) | 1.4 | -64 |
| All lesions (26) | 9.8 (2.9-21.6) | 2.7 (1.1-10.4) | 1.8 | -64 |

**10506 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**A phase 2 study of ponatinib in patients (pts) with advanced gastrointestinal stromal tumors (GIST) after failure of tyrosine kinase inhibitor (TKI) therapy: Initial report.** *Presenting Author: Michael C. Heinrich, OHSU Knight Cancer Institute and Portland VA Medical Center, Portland, OR*

**Background:** Ponatinib is an oral TKI that has potent preclinical activity against several mutant isoforms of KIT, including secondary exon 17 resistance mutants, and PDGFRA. Its preclinical activity against a broad spectrum of clinically-relevant resistance mutations suggests it may provide clinical benefit in pts with GIST resistant to standard approved TKI therapies. **Methods:** This phase 2 single arm trial evaluates efficacy and safety of ponatinib at 45 mg QD in advanced GIST pts after TKI failure. Cohorts are enrolled based on the presence (A) or absence (B) of primary mutations in *KIT* exon 11. Primary end point: clinical benefit rate (CBR=CR+PR+SD ≥16 wks) by modified RECIST 1.1 in Cohort A. Secondary end points include CBR in Cohort B, ORR, safety/tolerability. Enrollment of new pts is on hold due to safety observations in other ponatinib trials; enrollment criteria are being revised to include only pts with failure of all 3 TKIs approved for GIST. NCT01874665. **Results:** From June to Oct 2013, 35 of a planned 45 pts have been enrolled (24 in Cohort A). Baseline characteristics: median age 58 yrs; 46% 2 prior approved TKIs, 46% 3 prior approved TKIs. 74% of pts had ≥4 prior cancer regimens. The median time since diagnosis was 6 yrs. 17 pts discontinued (8 PD, 5 AE, 4 other). As of 6 Jan 2014, median follow-up: Cohort A 4 mos, Cohort B 3 mos. Cohort A CBR at ≥16 wks: 55% (11/20 pts) 1 PR and 10 SD. Cohort A ORR: 8% (2/24). All 5 Cohort A pts with matched PET scans (BL v. C1) had decreased FDG uptake in active lesions and remain on study with SD or better. Cohort B CBR: 22% (2/9); Cohort B ORR: 0%. Most common (≥30%) treatment-emergent AEs of any grade are: rash (54%), fatigue (46%), myalgia (46%), dry skin (40%), headache (40%), abdominal pain (34%), constipation (34%). Treatment-emergent serious AEs (SAEs) occurring in ≥2 pts are: abdominal pain (11%), nausea (6%), vomiting (6%), fatigue (6%). One pt had myocardial ischemia. There was 1 death (pneumonia) possibly ponatinib-related. **Conclusions:** Initial analysis of this ongoing trial suggests that ponatinib has activity in pts with advanced GIST after failure of prior TKI therapy. Clinical trial information: NCT01874665.

**10507 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Results of SARC 022, a phase II multicenter study of linsitinib in pediatric and adult wild-type (WT) gastrointestinal stromal tumors (GIST).** *Presenting Author: Margaret von Mehren, Fox Chase Cancer Center, Philadelphia, PA*

**Background:** Most GISTs have activating mutations of KIT/PDGFRA, with rare cases of B-RAF/RAS mutations. 15% of GIST in adults and 85% in children are WT and commonly have high expression of IGF1R likely due to loss of succinate dehydrogenase (SDH) function. We tested the clnical benefit of linsitinib (L), an oral TKI with in vitro efficacy against IGF1R in WT GIST patients (pts). **Methods:** A multi-center phase II trial of L using Clopper-Pearson two-stage design was conducted by SARC. All eligible pts signed consent, were >18 yo, had KIT/ PDGFRA WT GIST, RECIST1.1 measurable disease, ECOG PS of 0-2, and adequate organ function including: fasting glucose of < 150 mg/dL, hemoglobin A1c < 7%, and a QTcF interval of < 450 msec. The trial's primary endpoint was objective response rate (ORR) and secondary endpoints were clinical benefit rate (CBR): CR, PR and SD≥9 mos, and qualitative and quantitative FDG metabolic response (MR) at 8 weeks. **Results:** 20 pts were accrued to stage I of the study from 11/12-4/13 (Table). Treatment with L was well tolerated. Of the toxicities reported, 8.5% were grade 3/4. 36% were possibly related to L with nausea/vomiting (7.3%), fatigue (3.6%), and elevated LFTs (3.2%) being the most common. No objective responses were seen. Qualitative partial and stable MR were seen in 6/17 (35%) respectively. As of 1/5/2014, the average days on study was 231 (range 49-318+) with 5 patients remaining on L. CBR at 9 mos was 45% and MR was seen in 2/13 (15%); PFS and OS Kaplan Meier estimates at 9 months were 52% and 80% respectively. Correlative studies of SDHB immunohistochemistry and mutational testing, serum levels of insulin, IGF1R, its ligands and inhibitors at baseline, week 2, 4 and 8 on therapy will be presented. **Conclusions:** L is well tolerated in patients with WT GIST. While the CBR with L was 45% and PFS at 9 mos was 52%, no objective responses have been observed. Rapid accrual to this study demonstrates clinical studies in selected subtypes of GIST are feasible. Clinical trial information: NCT01560260.

| | |
|---|---|
| **Female** | 12 |
| **Male** | 8 |
| **Age** | 18-62, average 41 |
| **Performance status** | |
| **0/1/2** | 12/7/1 |
| **Primary site** | |
| **Stomach (gastroesophageal)** | 16 (1) |
| **Small bowel** | 2 |
| **Peritoneum** | 1 |
| **Metastatic sites** | |
| **Liver** | 17 |
| **Peritoneum** | 11 |
| **Lymph nodes** | 4 |
| **Prior therapies** | 1-7, median 3 |

**10508 Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

**Long-term disease control of advanced gastrointestinal stromal tumors (GIST) with imatinib (IM): 10-year outcomes from SWOG phase III intergroup trial S0033.** *Presenting Author: George D. Demetri, Dana-Farber Cancer Institute, Boston, MA*

**Background:** S0033 was designed to study the impact of IM, randomized between two doses, in patients (pts) with incurable GIST. **Methods:** Full accrual to this phase III trial occurred over 8 months, ending 01SEP2001. A study amendment allowed collection of additional clinical information on long-term survival outcomes and annotation of any therapies subsequent to IM. **Results:** Of 695 eligible patients, 180 (26%) survived 8 years or longer [94 on IM 400 mg/day arm and 86 on IM 800 mg/d arm). The 10-year estimate of overall survival (OS) across both study arms combined is 22% (95% confidence interval (CI)=19-26%). Additional therapy information was obtained for 137 long-term survivors: IM was the sole therapy, administered continuously, in 49%; fifty-four (39%) received subsequent systemic agents, including sunitinib (41) and sorafenib (16). Local therapies, includingsurgical resection of metastases, radiofrequency ablation, and radiation therapy were also utilized in subsets. Univariate analyses with long-term survival data show that pts whose tumors harbored a *KIT* exon 9 mutation had a significantly shorter OS than those with *KIT* exon 11 mutations (p=0.0013) or *KIT/PDGFRA*wild-type (WT) genotypes (0.047). **Conclusions:** A significant subset of pts with metastatic GIST achieved durable long-term overall survival with single-agent IM. Further investigation of what enables pts to live progression-free for more than a decade is warranted to optimize treatment approaches in this oncogene-driven disease, as well as to improve outcomes for more challenging molecular subsets, including *KIT* exon 9 or SDH-deficient (*KIT/PDGFRA* WT) GIST. Clinical trial information: NCT00009906.

**10509 Clinical Science Symposium, Mon, 1:15 PM-2:45 PM**

**Predictive biomarker profiling of > 1,900 sarcomas: Identification of potential novel treatment modalities.** *Presenting Author: Sujana Movva, Fox Chase Cancer Center, Philadelphia, PA*

**Background:** Sarcomas are a heterogeneous group of tumors with > 50 subtypes. First line chemotherapy such as doxorubicin and ifosfamide yields limited survival benefit. New therapeutic options for sarcomas are needed; multiplatform profiling may provide potential targeted therapies. **Methods:** 1922 sarcomas were profiled using multiplatform biomarker assessment (Caris Life Sciences, Phoenix, AZ), including DNA sequencing (Sanger and next generation (NGS), Illumina MiSeq), gene copy variations and protein expression by immunohistochemistry. **Results:** Overexpression of TOPO2 and TOPO1 were observed in > 50% of sarcomas of various histopathologic types. Low MGMT expression was observed in 75% of osteosarcomas. Absence or low thymidine synthase (TS) expression was seen in Kaposi sarcoma, leiomyosarcomas (LMS), hemangiopericytomas and liposarcoma. PTEN loss was observed in up to 80% of subtypes including angiosarcoma, Kaposi sarcoma, LMS, liposarcoma, rhabdomyosarcoma, Ewing sarcoma, osteosarcoma, chondrosarcoma and others. cMET was amplified in 17 % of LMS; increased EGFR gene copies were detected in > 30% of malignant fibrous histiocytomas and malignant peripheral nerve sheath tumors. Of 281 patients tested using NGS, 137 mutations were detected in 24 genes (37%). TP53 was the most common (40%) followed by PIK3CA, PTEN, APC, KRAS, RB and ATM. TP53 mutations were associated with TOPO2 overexpression in 80% ($p$=0.0003), with PTEN loss in 20% of patients ($p$=0.17) and with PIK3CA mutations in 2 patients (liposarcoma, LPS). **Conclusions:** Profiling of protein expression, gene copy variations and mutations identified clinically relevant alterations in 99% of sarcomas. Given the overexpression of TOPO2 in approximately 50% of sarcomas, its utility as a biomarker of sensitivity to anthracyclines should be studied, especially in relation to TP53 status in a tumor. Trials of agents like mTOR and PI3K inhibitors could benefit from designs in which patient selection is based on PTEN loss or PIK3CA mutations instead of sarcoma histology. The prognostic implications of the co-existence of TP53 mutations and PTEN loss in sarcomas is yet to be elucidated.

**10510 Clinical Science Symposium, Mon, 1:15 PM-2:45 PM**

**Preliminary analysis of the mutational landscape of non-rhabdomyosarcoma soft tissue sarcoma: A Children's Oncology Group study.** *Presenting Author: Raphael Asher Wilson, The University of Texas Southwestern Medical Center, Dallas, TX*

**Background:** Pediatric non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) represent a histologically diverse group of more than 20 tumor subtypes, including synovial sarcoma, liposarcoma, and malignant peripheral nerve sheath tumors. Unlike children with rhabdomyosarcoma, systemic chemotherapy has failed to improve survival for those with NRSTS. Of the nearly 50% with intermediate or high-risk disease, only 50% and 15%, respectively, are expected to survive. **Methods:** To determine more effective, targeted therapies, we analyzed 55 archived formalin-fixed paraffin-embedded (FFPE) cases of NRSTS using Sequenom's MassARRAY system to interrogate 296 unique "actionable" mutations (mutations that can be targeted by currently available drugs) in 33 oncogenes and tumor suppressor genes. We also analyzed 15 of the samples for copy-number variation and 74 additional "actionable" mutations in 9 cancer-associated genes using the Affymetrix OncoScan platform. **Results:** Using MassARRAY, we found 11 mutations in 8 NRSTS subtypes. Interestingly, about half of these mutations are in genes involved in the Ras signaling pathway. We found an additional 33 potential mutations in 15 NRSTS subtypes, 28 of which are involved in Ras signaling; these mutations were detected at around 10% of the alleles present in a sample, the detection limit for MassARRAY, so they cannot be distinguished from background with certainty. Using OncoScan, we found that 67% and 73% of the samples contained mutations in EGFR and TP53, respectively, and 53% contained mutations in NRAS. 6 of the 15 samples contained between 1 and 5 large chromosomal gains or losses, while 2 of the samples had more than 10 large gains or losses. 3 recurrent gains were found in several of the samples, while 10 of the samples contained gains or losses in at least one gene. **Conclusions:** The rarity of the individual NRSTS subtypes has made it nearly impossible to determine the mutational profiles and optimal treatment for this group of tumors. With the ability to extract information from FFPE material using new genomic platforms, we have successfully grouped tumor subtypes and have identified actionable mutations guiding future directions.

**10511 Clinical Science Symposium, Mon, 1:15 PM-2:45 PM**

**The driver landscape of angiosarcoma.** *Presenting Author: Sam Behjati, Wellcome Trust Sanger Institute, Cambridge, United Kingdom*

**Background:** Angiosarcoma is an aggressive tumour of presumed vascular endothelial origin that is commonly thought to be driven by aberrant angiogenesis. The somatic alterations underpinning angiosarcoma are largely unknown and have not previously been investigated by unbiased next generation sequencing. **Methods:** Thirty nine primary and secondary angiosarcomas were screened by whole genome (n=3), exome (n=8), or targeted re-sequencing of 33 angiogenesis genes (n=28). Somatic alterations were identified using the analysis pipeline of the *Cancer Genome Project*. **Results:** We identified novel driver mutations in two genes, *PTPRB* and *PLCG1*, both of which function to regulate angiogenesis signalling. *PTPRB* mutations were identified in 10/39 (26%) tumours, comprising 11 truncating and 3 missense variants. Four cases harboured 2 different *PTPRB* mutations each. A single recurrent missense variant, R707Q was identified in the *PLCG1* gene in (3/34) 9% of tumours. The enrichment of *PTPRB* and *PLCG1* mutations was highly significant ($q=10^{-9}$; $q=2x10^{-6}$). **Conclusions:** The mutational profile, comprising predominantly truncating mutations, suggests that *PTPRB* operates as a recessive cancer gene in angiosarcoma. This proposition is consistent with the function of PTPRB as a negative regulator of vascular growth factor tyrosine kinase receptors. In contrast, *PLCG1*, which transduces signalling of these receptors, likely operates as a dominant cancer gene with a single recurrent missense mutation found in three cases. Molecular modelling revealed that the R707Q *PLCG1*mutation is predicted to lead to constitutive activation of the PLCG1 enzyme and may therefore represent an attractive therapeutic target. Combining the *PTPRB* and *PLCG1* mutations with other driver mutations we found, shows that 15/39 (40%) tumours harbour at least 1 canonical driver mutation in angiogenesis genes, including in *H/N/K-RAS* (13%), *PIK3CA* (3%), and *FLT4* (3%). Driver mutations in angiogenesis genes were not mutually exclusive and co-occurred in a single dominant tumour clone. A pertinent question that arises from our study is whether the largely disappointing results from clinical trials of anti-angiogenesis drugs in angiosarcoma are confounded by the apparent redundancy of angiogenesis driver mutations.

**10512 Clinical Science Symposium, Mon, 1:15 PM-2:45 PM**

**Whole-exome and targeted sequencing of angiosarcomas: Target identification and treatment implications.** *Presenting Author: Vinod Ravi, Department of Sarcoma Medical Oncology. The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Angiosarcoma (AS) is a rare, aggressive tumor with vascular differentiation. Mutational landscape of AS is largely unknown. Utility of inhibition of targets/pathways identified by sequencing has not been investigated in AS. **Methods:** Study population included 20 patients with AS with tissue available for sequencing. 6 patients with fresh frozen paired normal and tumor samples underwent whole exome sequencing (WES) to identify somatic mutations. 14 patients with formalin fixed paraffin embedded (FFPE) tumor tissue underwent targeted sequencing of select cancer associated genes at high coverage. These data were filtered for germline SNPs utilizing publicly available databases and the remaining variants were classified on the basis of their being previously reported in the COSMIC database. Retrospective chart review was used to determine utilization of targeted therapies and clinical outcomes. **Results:** Study population (N=20) was predominantly Caucasian (80%), median age 64 years, with localized AS in 15%, nodal involvement in 40%, distant metastases in 45%. 60% of patients had cutaneous AS and 65% had previous history of radiation exposure prior to diagnosis. 65% of patients were alive at last follow-up. WES of patients with normal/tumor paired samples (n=6) showed a total of 485 alterations in 371 genes (range: 4-189 alterations/patient). Alterations were observed in the angiogenesis associated genes *PTPRB* (2/6 patients) *PLCG1* (2/6) as well as *TP53 (*1/6) in addition to other alterations. Targeted sequencing of FFPE samples (n=14) showed 27 alterations in 10/14 patients that were either mutations described in COSMIC or structural variants. These included *MYC & KDR* amplifications and mutations in *TP53, MDM2, KDR, FLT4 & PIK3CA*. 9 patients received 1 or more targeted agents creating 18 episodes of treatment. Clinical benefit rate was 45% when target was absent compared to 71% when target was present. **Conclusions:** Identification of genetic alterations specific to AS using WES should be utilized to construct targeted sequencing panels of select genes that help identify actionable targets and potential prognostic and predictive markers in patients with AS.

**10513 Poster Highlights Session (Board #1), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Integrate whole genomic study of KIT/PDGFRA wild-type (WT) GIST.** *Presenting Author: Margherita Nannini, Department of Specialized, Experimental and Diagnostic Medicine, Sant'Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy*

**Background:** KIT/PDGFRA wild-type (WT) GIST comprise different subgroups with distinct molecular hallmarks, including defects in the succinate dehydrogenase (SDH) complex and mutations of neurofibromatosis type 1 (NF1), BRAF, or KRAS genes. We investigate the genomic profile of WT GIST for each of known mutations, referred as *quadruple* WT GIST, by using a massively parallel sequencing and microarray approach, and compare it with the genomic profile of other GIST subtypes. **Methods:** whole-Transcriptome Paired-End RNA Sequencing was performed on 16 GIST, including 2 KIT/PDGFRA WT GIST patients without SDH-inactivating mutations (GIST_133 and GIST_127), 2 KIT/PDGFRA WT GIST patients harbouring SDHA-mutations (GIST_7 and GIST_10), and 12 KIT or PDGFRA mutated GIST patients (7 harboured exon 11 KIT mutations and 5 harboured exon 18 PDGFRA mutations). Whole-genome gene expression analysis was performed on 9 of the above 16 GIST and extended to include an additional 20 GIST: 1 KIT/PDGFRA WT/SDHA-mutated GIST and 19 KIT or PDGFRA mutated GIST, of which 13 harboured KIT mutations (12 in exon 11 and 2 in exon 9), and 5 harboured PDGFRA mutations (2 in exon 12, 1 in exon 14 and 2 in exon 18). **Results:** the principal component analysis showed that both GIST_133 and GIST_127 are characterized by a gene expression profile profoundly different from both GIST_7 and GIST_10. No private or cryptic mutations of KIT and PDGFRA, as well as no NF-1, BRAF, RAS mutations were found. The supervised gene expression analysis revealed that GIST_133 and GIST_127 were characterized by an overexpression of molecular markers (CALCRL and COL22A1) and of specific oncogenes including tyrosine and cyclin-dependent kinases (NTRK2 and CDK6) and ERG. Overexpression of NTRK2 (TrkB) and of ERG was confirmed also by quantitative PCR. No mutations were identified in NTRK2, and there were no ERG fusions. **Conclusions:** The integrated genomic picture of WT GIST, using massively parallel sequencing and gene expression analyses, showed that *quadruple* WT GIST have an expression signature that is distinct from SDH-mutant GIST as well as GIST harbouring mutations in KIT or PDGFRA, suggesting that they represent another unique group within the family of gastrointestinal stromal tumors.

**10514 Poster Highlights Session (Board #2), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Disregulation of *mir-550* and *let-7e* in intestinal high-risk localized GIST: A GEIS study.** *Presenting Author: Jose Antonio Lopez-Guerrero, Laboratory of Molecular Biology, Instituto Valenciano de Oncologia, Valencia, Spain*

**Background:** Risk classification of gastrointestinal stromal tumors (GISTs) is critical owing to adjuvant systemic treatments with tyrosine kinase inhibitors (TKI). Tumor size, mitotic count, location or tumor rupture are used to assess patient prognosis after surgical resection and have been validated for GIST risk stratification. miRNAs have been involved in the pathogenesis and progression of most tumors. The purpose of this study is to characterize and to validate differentially expressed miRNAs from a series of recurrent and non-recurrent intestinal hig-risk GIST patients. **Methods:** RNA from 14 formalin-fixed and paraffin-embedded (FFPE) intestinal high-risk GIST was extracted and analyzed using the GeneChip miRNA 3.0 Array (Affymetrix). The median of tumor size and mitotic count was 11cm (range: 5-25) and 12.5 (range: 0-113 x50 HPF) respectively. Recurrence [median follow-up: 84 months (1-180)] was reported in 8 patients. Normalization and statistical analysis were performed with Partek Genomic Suite 6.6 software and technical validation was conducted using qRT-PCR. **Results:** A set of 33 miRNAs was significantly deregulated ($p=0.05$; FC=2) comparing relapsed and non-relapsed patients. Principal Components Analysis divided the patients into two groups: one that comprised the three largest GIST from relapsed patients, and another group with the other cases. We identified 134 miRNAs as differentially expressed between these two groups ($p<0.0001$; FC=20). The most significantly downregulated miRNAs were let-7e (FC=-1163,99, $p<0.0001$), miR-17 (FC= -861,879, $p<0.0001$), miR-195 (FC= -785,334, $p<0.0001$), miR-143 (FC= -627,526, $p<0.0001$) and up regulated miR-550 (FC= 204.173, $p<0.0001$) and miR-1184 (FC= 184.493, $p<0.0001$). miR-550 and let-7e were selected for technical validation by qRT-PCR confirming the up- (FC=18.0421) and down-regulation respectively (FC=0.6294). **Conclusions:** Most of the identified miRNAs are involved in cell cycle control and proliferation. We validated the deregulation of *miR-550* and *let-7e* in large intestinal high-risk GISTs. Further studies in independent series of localized GIST with long follow-up are needed in order to demonstrate the prognostic potential of these miRNAs.

**10515 Poster Highlights Session (Board #3), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Second-line treatment in exon 11-mutated GIST patients: Imatinib dose escalation or sunitinib? Retrospective analysis of a multi-institutional experience.** *Presenting Author: Bruno Vincenzi, Department of Medical Oncology, Campus Bio-Medico University of Rome, Rome, Italy*

**Background:** Data from metastatic GIST patients harbouring exon 11 mutation who received a second line treatment with sunitinib or imatinib dose escalation were retrospectively analysed to compare survival. **Methods:** 123 exon 11 mutated advanced GIST patients were included. All patients progressed on imatinib 400 mg/die and received, on discretion of physician, a second line treatment with either imatinib (800 mg/die) or sunitinib (50 mg/die 4 weeks on/2 weeks of or 37.5 mg/day continuous daily dose). The type of exon 11 mutation was recorded (deletion versus others) and correlated with survival and response according to RECIST or CHOI criteria **Results:** 79 patients (64%) received a second line treatment with imatinib, 44 (36%) sunitinib. For 94 patients the exact mutation was available: exon 11 mutation was represented by a deletion in 42 cases (45%), by other gene aberrations in 52 (55%). Median follow-up was 61 months. The median time to progression (TTP) in patients receiving sunitinib and imatinib was 10 (95% CI 9.7-10.9) and 5 months (95% CI 3.6-6.7) respectively (P=0.012). No significant difference was found in overall survival (OS) (58 versus 62 respectively, P=0.883). Interestingly, the impact of deletion in exon 11 was statistically significant longer in patients treated with imatinib (TTP 24 versus 6 months, P=0.02), while it was irrelevant in patients treated with sunitinb (P=0.683). A border line statistically significant difference was identified also in terms of OS in the group of patients treated with imatinib as second line (71 months in not deletes exon 11 patients vs 54 months in deleted ones, P=0.063). No difference was detected in the group of patients treated with sunitinb according to the mutation status in the exon 11 (P=0.370). **Conclusions:** In exon 11 mutated GIST patients progressing on a first line treatment with imatinib 400 mg/die, a second line treatment with sunitinib is associated with an improvement in TTP without any impact on survival. Deletion in exon 11 seems to be relevant for sensitivity to imatinib-based therapy as second line in terms of TTP, while the impact of mutation was not identified in patients treated with sunitinib.

**10516 Poster Highlights Session (Board #4), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Metabolomic profiling of gastrointestinal stromal tumor (GIST) in human tissue samples and xenografts.** *Presenting Author: Danny Yakoub, Sylvester Comprehensive Cancer Center, University of Miami, Miller School of Medicine and Jackson Memorial Hospital, Miami, FL*

**Background:** There is a growing need for novel agents to treat resistant GIST. The goal of this study was to characterize and identify potential therapeutic targets in the metabolic profile of GIST. **Methods:** Tumor, adjacent control tissue samples from 7 patients (five exposed to imatinib) and two tumor samples from xenografts in nude mice models (non-exposed) were extracted for analysis. $^{1}$H-NMR spectra, using a 500MHz spectrometer equipped with a cryoprobe head, were acquired and processed. Energy state, glucose (cytosolic glycolysis versus mitochondrial Krebs cycle), protein and lipid metabolism (indicators of proliferation and invasiveness) metabolomic profiles were assessed globally in correlation with clinical and histopathologic findings. **Results:** Findings suggest shift from cytosolic glycolysis (glucose decrease and increased lactate with minimal changes in pyruvate) towards the mitochondrial Krebs cycle (elevated glutamine and glutamate synthesis) in all tumor samples. Aspartate, myoinositol, and cell membrane phospholipids such as phosphocholine/glycerophosphocholine were greater in untreated GIST xenografts compared to treated tumors. Alanine, taurine, proline, ADP and phosphocholine were significantly higher in tumor tissue extracts compared to control (imatinib treated) ($p<0.05$). Tumor stage, mitotic index or mutation type did not correlate with metabolomic profile. Differences were accentuated among untreated patients. Partial Least Squares-Discriminant Analysis (PLS-DA) model successfully separated tumor tissues from controls (R2Y=0.56, Q2Y=0.22). **Conclusions:** Metabolomic profiling of patient and xenograft GIST samples exposed to KIT inhibitors suggest that cytosolic glycolysis and phospholipid biology may be important not only in the GIST phenotype but may be ameliorated with KIT inhibition by imatinib. Further understanding of GIST metabolomics may lead to the identification of new therapeutic targets.

**10517 Poster Highlights Session (Board #5), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Improvement of existing risk classifications in primary gastrointestinal stromal tumors (GIST).** *Presenting Author: Piotr Rutkowski, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland*

**Background:** The reliable risk assessment of relapse and survival after initial resection are needed for a proper selection of GIST patients for adjuvant therapy. **Methods:** We analyzed group of registered prospectively 692 primary GISTs CD117(+) treated surgically with curative intention between 1999-2009, with no adjuvant imatinib. Median follow-up time was 34 months. We analyzed the factors influencing on 1-year and 5-year disease-free survival time (DFS; calculated from the date radical operation) and 5-year overall survival (OS). We also compared the reliability of existing risk classification (NIH, NCCN-AFIP according to Miettinen-Lasota, TNM-AJCC, revised NIH according to Joensuu, nomograms according to Gold et al and according to Rossi et al) using Receiver Operating Characteristic (ROC) curves tests. **Results:** With univariate analysis the following negative prognostic factors for DFS have been identified: male sex, mitotic index 5-10/50 and >10/50 HPF ($p<0.001$), primary tumor size 5-10 cm and >10 cm ($p<0.001$), non-gastric location ($p<0.001$), R1 surgery or tumor rupture ($p<0.001$), presence of exon 11 *KIT* 557_558 del or exon 9 KIT mutations ($p=0.009$). The negative prognostic factors for OS were: age <40 ($p=0.045$), mitotic index 5-10/50 and >10/50 HPF ($p<0.001$), primary tumor size 5-10 cm and >10 cm($p<0.001$), R1 surgery or tumor rupture ($p<0.001$). These factors were found also statistically significant in multivariate analyses. All existing risk classification demonstrated prognostic value for assessment of differences in DFS and OS, and we have not found significant differences between them when compared with ROC tests. In addition, the reliability of all these classifications was improved when gender/age and mutational status were added. The additive value of mutational status for better risk assessment was the most significant when used in intermediate risk groups according to different classifications ($p<0.01$). **Conclusions:** The reliability of existing classifications for the risk assessment of disease recurrence and death after resection of primary GIST can be improved by adding mutational status, with the mostly significant refinement of better stratifications in intermediate risk groups.

**10518 Poster Highlights Session (Board #6), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Interrelationship of primary and secondary mutations in gastrointestinal stromal tumors during TKI therapy.** *Presenting Author: Peter Hohenberger, University Medical Center Mannheim, Department of Surgery, Mannheim, Germany*

**Background:** Gastrointestinal stromal tumors (GISTs) show *KIT* or *PDGFR*$\alpha$ gain-of-function mutations in 85% as the primary oncogenic drivers. Although the use of tyrosine kinase inhibitors (TKI) like imatinib has greatly improved therapy, the occurrence of secondary resistance to TKIs is a challenging problem. Secondary mutations in *KIT/PDGFR*$\alpha$ are believed to be the most important mechanism of drug resistance. We analyzed whether this might be a random process or whether these effects could be correlated to primary tumor characteristics and primary drug therapy. **Methods:** 58 patients undergoing surgery or CT-guided biopsy of progressive GIST lesions while being on TKI therapy and with known mutations from their primary tumor formed the basis of our study. Paraffin-embedded specimens were used to examine the primary and secondary mutations in exons 8, 9, 11, 13, 14, 17 of *KIT* and exons 12, 14 18 of the *PDGFR*$\alpha$by macrodissection, genomic DNA extraction, PCR amplification, designed primers for exons, Sanger-sequenced twice. **Results:** Point mutation was the most common type of 2ndary mutation (52/58, 89.7%). Codon 654 of *KIT* exon 13 (n=20) and codons 820 to 822 of *KIT* exon 17 (n=28) were the predominant regions of 2ndary mutations. Secondary mutations in KIT exon13 were exclusively found in tumors with primary mutations in *KIT* exon11. GISTs of non-gastric origin had a higher frequency to develop secondary mutation in activation-loop (AL, exon 17) of *KIT* than those with gastric origin (67.7% vs. 35.7%, $P=0.047$). Mean duration of TKI treatment did not influence significantly AL vs non-AL mutations. With respect to the TKIs used, secondary mutations in the activation-loop were more often found after multiple TKIs (imatinib, sunitinib, nilotinib, sorafenib) than after just imatinib, but the difference was not quite statistically significant (85.7% vs. 50.0%, $P=0.066$). **Conclusions:** The development of secondary tyrosine kinase mutations in advanced GISTs during treatment with TKIs is not a random effect. Correlations between primary vs. secondary mutations and initial tumor site can be demonstarted. Besides, it seems possible that the use of different TKIs itself may impact on the development as well as type of secondary mutations.

**10519 Poster Highlights Session (Board #7), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Neoadjuvant administration of radiation therapy and intratumoral autologous dendritic cells in patients with localized high-risk soft tissue sarcomas.** *Presenting Author: Shailaja KS Raj, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

**Background**: Patients with high grade, large (<5 cm) soft tissue sarcomas (STS) can develop metastases after surgical therapy with no proven benefit to adjuvant chemotherapy. Our in vivo murine model demonstrated that standard external bean radiation therapy with experimental intratumoral injection of dendritic cells (DC) produces tumor-directed immunity. Our protocol, established that preoperative RT +DC regimens safe in patients with large high grade STS with a significant anti autologous tumor cell immune response. We hypothesize that release of tumor antigens to the intratumoral dendritic cells results in the cross priming of an effector anti tumor cell response. **Methods:** 32 patients were enrolled in two (phase I & II) trials given radiation neoadjuvantly, up to 50Gy,5days a week, combined with intratumoral injection of dendritic cells, followed by surgery and compared to 54 historic controls treated at Moffitt Cancer Center during the same period with radiation. Dendritic cells were prepared using culture of mononuclear cells with granulocyte-macrophage colony stimulating factor GM-CSF and interleukin-4. **Results:** 9/17 patients on the phase I developed tumor-specific immune responses, which lasted from 11 to 42 weeks. The remaining immunological results will be presented at the meeting. In multivariate analysis using Cox-proportional hazards model, tumor size (>=10cm) was associated with poorer OS ($p=0.028$; HR=3.6 with 95%CI=1.1-11.4) and with DFS ($p=0.021$; HR=2.8 with 95%CI=1.2-6.9). A trend to better overall survival (OS) and progression free survival (DFS) of the patients, in the dendritic cell vaccine arm was seen, when compared to the historic controls but this was not statistically significant by univariate analysis (OS: $p=0.29$; DFS: $p=0.24$). **Conclusions**: Neoadjuvant therapy with radiation and intratumoral autologous dendritic cells in high risk soft tissue sarcoma patients is safe. Tumor specific immune responses were seen with CD4 positive T cells in the earlier group of patients. Clinical trial information: 16441.

**10520 Poster Highlights Session (Board #8), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Trivalent ganglioside vaccine and immunologic adjuvant versus adjuvant alone in metastatic sarcoma patients rendered disease-free by surgery: A randomized phase 2 trial.** *Presenting Author: Richard D. Carvajal, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Recurrence after resection of metastatic sarcoma is common. The gangliosides GM2, GD2 and GD3 are strongly expressed on many sarcomas. The generation of anti-ganglioside antibodies might control micrometastases and improve outcomes. **Methods:** We conducted a randomized phase 2 study of the immunological adjuvant OPT821 with a KLH conjugated ganglioside vaccine targeting GM2, GD2 and GD3 (vaccine) or placebo (control) in patients (pts) with metastatic sarcoma following complete metastastectomy. Randomization was stratified by disease state (relapsed disease vs metastasis at diagnosis) and for those with relapse by disease-free interval ($<12$ vs $\geq 12$ months) and number of relapses (1 vs $>1$). Pts received 10 injections at weeks (wks) 1, 2, 3, 8, 16, 28, 40, 52, 68 and 84. Imaging was performed at wk 16 and every 12 wks subsequently. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS) and serologic response. **Results:** We randomized 136 pts: median age 51 (range 17-84); 52% male; 77% ECOG PS 0 (range 0-1); 90% with relapsed disease; 14% had $\geq 4$ metastases resected. Histology included leiomyosarcoma (n=48), spindle cell (n=19), undifferentiated/pleomorphic (n=18), osteosarcoma (n=14), synovial (n=12), liposarcoma (n=12) and others (n=13). Toxicities included grade 1/2 injection site reactions (79%), fatigue (32%), fever (15%) and flu-like symptoms (10%) and were more frequent with complete vaccine. With 89 PFS events observed, median PFS and 1-year PFS rate were 6.4 months (mos) and 35%, respectively, with no difference between arms. With a median follow-up of 18 mos and 22 pts deceased, the 1-year OS rate was >90%. Serologic responses (IgM and/or IgG) to GM2 and GD2 were observed in 98% and 21% of pts treated with complete vaccine and control, respectively. At wks 40-68, induction of high (>160) IgM and IgG titers was observed in 52% and 24% of pts receiving vaccine and 0% and 2% of pts receiving control. **Conclusions:** A sustained serologic response to vaccination was induced with the complete vaccine. No difference in PFS was observed between arms. Follow-up for OS is ongoing. Clinical trial information: NCT01141491.

**10521 Poster Highlights Session (Board #9), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Combined KIT and CTLA-4 blockade in patients with refractory GIST and other advanced sarcomas.** *Presenting Author: Alexander Noor Shoushtari, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Few effective treatments (tx) exist for patients (pts) with tyrosine kinase inhibitor (TKI)-resistant gastrointestinal stromal tumors (GIST) and other advanced soft tissue sarcomas (STS). In a murine GIST model, we showed that the efficacy of KIT inhibition is immune-mediated via decreases in indoleamine 2,3-dioxygenase (IDO), with improved antitumor effects using combined KIT and CTLA-4 blockade (Balachandran, Nat Med 2011). **Methods:** This Phase Ib trial used a standard 3+3 design of ipi 10 mg/kg (q3 week [wk] x4 induction + q12 wk maintenance) plus escalating doses of dasatinib (das; 70 mg QD, 100 mg QD, 70 mg BID). Pts with refractory GIST or advanced STS and $\geq 1$ prior tx were eligible. Primary objective was to estimate the maximum tolerated dose (MTD). Secondary objectives included response assessed by RECIST1.1, Choi, and immune-related response criteria (irRC) at week 12 and q6 wks afterward. **Results:** 13 pts were treated: median (range) age 56 (40-72), 7 male, prior tx = 4 (1-8). Histologies: 8 GIST, 2 leiomyosarcomas, 3 other. All GIST pts progressed on imatinib and sunitinib; 7 had prior sorafenib. Potential immune-mediated toxicities included grade (G) 1/2 rash (n=6), diarrhea (n=4), pruritus (n=2). Other common G1/2 toxicities included fatigue (n=8), anemia (n=6), edema (n=5), nausea (n=5) and pleural effusion (n=3). At das 70 mg QD, one dose-limiting toxicity (DLT) was seen: G3 upper GI hemorrhage. Two DLTs were observed at das 100 mg QD: G3 ALT elevation and G3 upper GI hemorrhage. 3/8 GIST pts achieved a durable Choi response (24, 25, 59+ wk). No irRC or RECIST responses were observed. Durable irRC SD was achieved in 1 pt with GIST (59+ wk) after 4 prior TKIs and 1 pt with high-grade sarcoma (34+ wk) after 5 prior tx. 4/5 pts completing ipi induction had radiologic SD vs wk 12 scans (24, 24, 33+, 59+ wk). Median ALC increased from b/l to wk 7 (1100 to 1550, p=0.04) with no association with clinical benefit. **Conclusions:** In this completed Phase Ib trial, the recommended phase 2 dose is das 70 mg QD + ipi 10 mg/kg. Disease stability was seen post-ipi induction, suggesting an immune-mediated effect. Analysis of tumor IDO expression and other immune correlates from serial biopsies obtained from a follow-up GIST cohort is ongoing. Clinical trial information: NCT01643278.

**10522 Poster Highlights Session (Board #10), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**PD-L1 expression and immune infiltrates in sarcoma.** *Presenting Author: Sandra P. D'Angelo, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background**: Programmed death-1 (PD-1) is a member of the CD28 family of T-cell costimulatory receptors that attenuates immune responses by negatively regulating T-cell proliferation and function. The prognostic and predictive implications of programmed death-ligand 1 (PD-L1) has been described in multiple malignancies but are unknown in sarcoma. We previously demonstrated PD-L1 expression by western blot and flow cytometry in 65% of sarcoma cell lines. We now examined PD-L1 expression by IHC in sarcoma specimens and tumor-associated immune cells and correlated expression with clinical parameters and outcomes. **Methods**: 50 sarcoma patients treated at Memorial Sloan Kettering Cancer Center who were consented to our IRB approved tissue procurement protocol were selected. Correlative clinical information was collected.Using the DAKO PD-L1 IHC assay and archival formalin-fixed paraffin embedded tissue specimens; PD-L1 expression was examined. Positive was defined as >1% of tumor cells (minimum of 100 evaluable cells) with plasma membrane staining. Staining intensity was not used to define positivity. Macrophage (M) and lymphocyte (L) PD-L1 status was determined qualitatively. Associations between PD-L1 expression in tumor, M and L and clinical-pathological characteristics were performed. **Results**: Median age 46 years (range, 22 - 76), 66% male. Disease status: 70% primary disease/locally recurrent, 26% metastatic and 4% unknown. Tumor, L and M PD-L1 expression was noted in 12%, 30% and 58%, respectively. L and M infiltration was present in 98% and 90%, respectively. There was no association between clinical features, overall survival and PD-L1 expression in tumor or immune infiltrates. **Conclusions**: L/M infiltration is common in sarcoma. PD-L1 tumor expression is uncommon with the highest frequency observed in GIST. There was no association between PD-L1 expression and OS. Forthcoming studies include a characterization of the immune infiltrates and expansion to additional tumor specimens.

| Histology | n | % Tumor PD-L1 + | % L PD-L1 + | % M PD- L1 + |
|---|---|---|---|---|
| Angiosarcoma | 3 | 0 | 100 | 100 |
| GIST | 14 | 27 | 100 | 100 |
| Leiomyosarcoma | 4 | 0 | 0 | 25 |
| Liposarcoma | 5 | 0 | 20 | 60 |
| Synovial Sarcoma | 3 | 0 | 33 | 0 |
| Radiation associated pleomorphic sarcoma | 1 | 100 | 100 | 100 |
| Other | 20 | 5 | 10 | 70 |
| Overall | 50 | 12 | 30 | 58 |

**10523 Poster Highlights Session (Board #11), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Results of the prospective T-DIS randomized phase II trial comparing interruption versus continuation of trabectedin after six cycles of treatment in patients (pts) with advanced soft tissue sarcoma (ASTS).** *Presenting Author: Axel Le Cesne, Institut Gustave Roussy, Villejuif, France*

**Background:** Trabectedin (T) maintenance beyond 6 cycles (cy) of treatment in responding pts with ASTS is associated with improved outcomes (Retrospective on database analysis; ASCO 2013). Herein, the impact of T discontinuation on progression-free survival (PFS) and overall survival (OS) was prospectively analyzed by the French Sarcoma Group in a national non-comparative randomized phase II trial. **Methods:** After the initial 6 cy of T (1.5 mg/m$^2$ as 24-h infusion every 3 weeks), pts free from progressive disease (PD) were randomly assigned either to continuous treatment (C arm) or therapy interruption (I arm) with T. Pts who declined randomization could continue with T. Pts allocated to the I arm could restart T in case of PD. Primary endpoint was PFS rate at 6 months (m) weeks after randomization. **Results:** FromFebruary 2011 to March 2013, 178 pretreated pts have been enrolled. At inclusion, the pts had a median age of 57.5 years (range19-82) and a median performance status of 1 (range 0-3) and most had leiomyosarcoma (30%), liposarcoma (18%) or synovial sarcoma (12%). Among evaluable pts (n=178), the rate of non-progression after the initial 6 cycles of T was higher than expected (29.7%). After 6 cy of T, 27 and 26 non progressive pts were randomized to C and I arm, respectively (30% of included pts). After randomization, a median number of T cy were similar in both arms: 5 (range 2-17) for C arm and 5 (range 1-12) for I arm. In December 2013, the median PFS after randomization was 7.2 m in C and 3.7 m in I arm ($p$=0.05), respectively, with the 6-m PFS of 50% and 16% for C and I arm. The 12-m OS rate after randomization was 86% (62.4-95.3) and 74% (44.1-89.2) for C and I arm, respectively. T has been reintroduced in 19/21 pts who progressed in I arm. **Conclusions:** The rate of non-progression after 6 cycles of T was higher than previously reported, probably due to a better selection of ASTS pts in referral centers and a better management of T. Interruption of T resulted in a rapid PD in the vast majority of pts, independently of the response achieved after initial 6 cy of T. Therefore, T treatment has to be given until PD, intolerance or patient refusal. Clinical trial information: 2010-022613-26.

**10524 Poster Highlights Session (Board #12), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**A randomized phase II study comparing trabectedin (T) and best supportive care (BSC) in patients (pts) with translocation-related sarcomas (TRS).** *Presenting Author: Shunji Takahashi, Department of Medical Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan*

**Background:** T binds to the minor groove of DNA and blocks DNA repair machinery following the inhibition of cell cycle and proliferation. In addition, T inhibits interactions of transcription factors including TRS-related transcription factors with the DNA in a competitive manner. This is the first time that the progression-free survival (PFS) of T is compared with BSC as a second or later line treatment in pts with TRS in a multi-center, open, phase II trial. **Methods:** Main inclusion criteria were the following: histologically proven TRS; unresponsiveness or intolerability to standard chemotherapy regimens (pts with extraskeletal Ewing sarcoma (EES), myxoid liposarcoma (ML), or synovial sarcoma (SS) should have received anthracyclines); at least 1 measurable baseline lesion (RECIST v1.1); confirmed disease progression (per RECIST) compared with the image assessment performed during the previous 6 months(m). Pts stratified by subtype (alveolar rhabdomyosarcoma, ESS, ML, SS vs other TRS) were randomly assigned 1:1 to T (1.2 mg/m$^2$ in 24h continuous infusion every 21 days) or BSC. The primary endpoint was PFS by independent review assessment (IR). This study had 80% power for a one-sided 5% significance level test given a hazard ratio (HR) (T relative to BSC) of 0.50. Sample size goal was 74 pts with an event goal of 52 events by IR requiring a total of 60 events by investigator's assessment (IA). PFS and overall survival (OS) were analyzed using a stratified log-rank test. **Results:** Data cut-off date was 8$^{th}$ February 2014. Total of 76 pts were enrolled. Number of pts for efficacy analysis was 73 (T: 37 pts and BSC: 36 pts). Median PFS (90% confidence interval(CI))for T and BSC were 5.6 m (4.2-7.5) and 0.9 m (0.9-1.0), respectively ($p<0.0001$; HR=0.07, 90% CI: 0.03-0.14). Median OS (95% CI) for T and BSC were not reached (NR) (12.8-NR) and 8.0 m (7.0-NR), respectively ($p=0.025$; HR=0.38, 95% CI: 0.16-0.91) under permission of crossover. **Conclusions:** T is an active drug in TRS pts pretreated by available chemotherapies with a significant increase in PFS and OS. Clinical trial information: JapicCTI-121850.

**10525 Poster Highlights Session (Board #13), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**A four-arm randomized phase II trial with NGR-hTNF given at low or high dose with or without doxorubicin in soft tissue sarcomas (STS).** *Presenting Author: Stefano Ferrari, Istituto Ortopedico Rizzoli, Bologna, Italy*

**Background:** NGR-hTNF, a tumor targeted antivascular agent, exhibits a biphasic dose-response curve with activity shown at low dose (LD) or high dose (HD). Vascular effects at LD are driven by early vessel normalization that enhances intratumoral doxorubicin (D) uptake and late vessel damage, while at HD by rapid vessel disruption. **Methods:** Advanced STS patients (pts), stratified by prior D dose ($>$ or $\leq$ 300 mg/m$^2$), were randomly assigned to receive NGR-hTNF alone at LD (0.8 $\mu$g/m$^2$/d1/q1w) in arm A or at HD (45 $\mu$g/m$^2$/d1/q1w) in arm B, or with D (60 mg/m$^2$/d1/q3w) at LD in arm C and at HD in arm D. Progression free survival (PFS) was primary endpoint with tumor assessment done q6w until progressive disease (PD). Using a 2-stage design, each regimen was rejected if $\leq$2/14 and $\leq$7/24 pts were PD free at 3 months after 1st and 2nd stage, respectively ($\beta$=20%; $\alpha$=10%; n=96). Secondary aims: adverse events (AEs), tumor response by RECIST criteria and early metabolic response (MR), quantified by fractional changes in SUV using FDG-PET according to EORTC criteria **Results:** In all, 69 pts (median age 55 years; men 38; PS $\geq$ 1 31; median prior lines 2, range 0-7) received 767 weekly cycles (mean 11; range 1-51). Main grade 3/4 AEs were neutropenia (23%) and chills (7%). Primary endpoint was met only for arm C (LD NGR-hTNF plus D), with 7/14 and 15/28 pts PD free at 3 months after 1st and 2nd stage, respectively. Median PFS was 1.3 months (95% CI, 1.1-1.5) for arm A, 1.5 (1.1-1.9) for B, 3.6 (2.3-4.9) for C and 1.4 (0.9-1.9) for D ($p=0.005$ for trend). As best response per RECIST, 28 (45%) of 62 evaluable pts had stable disease (SD): 1/12 in arm A, 6/12 in B, 17/26 in C (median length 4.3 months; range 2.9-23.2) and 4/12 in D. In arm C, median PFS was 2.9 and 4.3 months for naive and pretreated pts, respectively, while median OS was 9.8 months (HR=0.46 vs other pooled arms; $p=0.01$). By PET imaging done at 3 weeks, 10 (23%) of 43 assessable pts had partial MR (5 SD/5 PD per RECIST), with mean change in SUV of -37% ($\pm$12), 25 pts stable MD (8 SD/17 PD) and 8 progressive MD (5 SD/3 PD). PET sensitivity in predicting PD or non-PD per RECIST was 12% and 72%, respectively. **Conclusions:** LD NGR-hTNF plus D shows safe and favourable clinical activity particularly in pretreated STS. Clinical trial information: NCT00484341.

**10526 Poster Highlights Session (Board #14), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**NCI #8412: A randomized phase II trial of AZD6244 alone and AZD6244 plus temsirolimus for soft-tissue sarcomas.** *Presenting Author: Zeynep Eroglu, City of Hope, Duarte, CA*

**Background**: Outcomes for advanced soft-tissue sarcomas (STS) are poor given their relative insensitivity to chemotherapy. AZD6244 (AZD) is a MEK1/2 inhibitor that suppresses STS proliferation in vitro. mTOR inhibitors (mTORi) possess modest activity against STS, and resistance rapidly develops via MAPK pathway feedback activation. The combination of AZD and the mTOR inhibitor temsirolimus (Tem) synergistically inhibits STS cell line growth. Therefore, a randomized, phase II trial of AZD vs. AZD plus Tem in advanced STS was conducted. **Methods**: Adults with advanced STS who received $\leq$2 prior chemotherapeutics were eligible; pediatric-type sarcomas and brain metastases were excluded. 69 subjects were randomized to AZD 75 mg PO bid (n=34) and allowed to crossover upon progression, or to AZD 50 mg PO bid plus Tem 20 mg IV weekly (n=35), with 28 day cycles. Primary endpoint was progression-free survival (PFS). Secondary objectives were to compare: response rate, 4-month PFS rates, and toxicities; and changes in ERK-phosphorylation in stimulated PBMCs pre- and post-treatment. **Results**: While there was no difference in PFS between the single agent vs. combination arm for the overall cohort (median 1.9 vs. 2.1 months), an improved median PFS was observed in the combination arm (N=11) over single agent (N=10) in the pre-specified leiomyosarcoma stratum (median 3.7 vs. 1.8 months; $p=0.01$). 4-month PFS rate was 24% for both arms in the overall cohort, but 50% (95% CI 0.19-0.81) with the combination vs. 0% with AZD alone in the leiomyosarcoma cohort. One PR and 4 SD were seen with the combination arm in leiomyosarcoma patients, and 2 SD in AZD alone. 18 of 34 AZD6244 patients crossed over, with 5 patients receiving $\geq$ 6 cycles after crossover. Most common grade 3/4 adverse events in the combination arm were mucositis (29%), lymphopenia (26%), neutropenia and anemia (20% each); hypertension (12%) was observed with AZD alone. Correlative studies showed that AZD significantly inhibited ERK phosphorylation. **Conclusions**: The combination of AZD and Tem appears to be an active regimen in the leiomyosarcoma subset. Emerging preclinical data revealing activation of the mTOR pathway in leiomyosarcoma development may explain this result. Clinical trial information: NCT01206140.

**10527 Poster Highlights Session (Board #15), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Alliance A091102: Phase II study of MLN8237 (Alisertib) in advanced/metastatic sarcoma.** *Presenting Author: Mark Andrew Dickson, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** About 13,000 cases of soft tissue and bone sarcoma are diagnosed annually in the US. Despite surgery many patients (pts) develop recurrent disease. Response rates (RR) to chemotherapy are low; new agents are needed. In gene array studies Aurora Kinase A (AURKA) is commonly overexpressed. Inhibition of AURKA by shRNA or by a specific AURKA inhibitor blocks in vitro proliferation of multiple sarcoma subtypes. MLN8237 (alisertib) is a novel, oral, ATP-competitive, selective small-molecule inhibitor of AURKA. **Methods:** This multi-center phase II study of alisertib in pts with advanced/metastatic sarcoma was conducted through the Alliance for Clinical Trials in Oncology (A091102). Adequate performance status, organ function, and measurable disease (RECIST v1.1) were required. Pts enrolled into histology-defined cohorts: 1) liposarcoma (LPS), 2) leiomyosarcoma (LMS), 3) undifferentiated sarcoma (US), 4) malignant peripheral nerve sheath tumor (MPNST), or 5) other. Alisertib 50mg PO BID d1-d7 was given every 21 days until progressive disease (PD) or unacceptable toxicity. The primary endpoint was confirmed RR in each of 5 cohorts. Progression-free survival (PFS) was a secondary endpoint. 1 confirmed response in the first 9 pts expanded enrollment in a cohort to 24 using a Simon 2-stage design. **Results:** 72 pts were enrolled at 24 sites (12 LPS, 10 LMS, 13 US, 10 MPNST, and 27 Other). Median age was 55 (range 20-84); 54% were male; 58/38/4% were ECOG PS 0/1/2. 1 confirmed PR in the Other cohort (angiosarcoma) expanded to 2nd stage accrual. The histology-specific cohorts ceased at the 1st stage. Overall, 76% have PD; 25% have died, with median follow-up of 4.4 months (0.4-11.9). 12-week PFS was 73% (LPS), 44% (LMS), 23% (US), 57% (MPNST), and 39% (Other). Common grade 3-4 adverse events included (%): mucositis (13), anemia (14), leukopenia (22), and neutropenia (40). **Conclusions:** Alisertib was well-tolerated in this study of multiple sarcoma histologic subtypes. Rare responses, yet prolonged stable disease, were observed. Although failing to meet the primary RR endpoint, PFS was promising. Alisertib warrants further study in sarcoma. Clinicaltrials.gov: NCT01653028. Funded by the Alliance for Clinical Trials in Oncology Clinical trial information: NCT01653028.

**10528 Poster Highlights Session (Board #16), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Phase II study of oral ENMD-2076 administered to patients (pts) with advanced soft tissue sarcoma (STS).** *Presenting Author: Herbert H. F. Loong, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

**Background:** The use of angiogenic and Aurora kinase inhibitors has been shown to abrogate tumor growth in STS. ENMD-2076 is an oral Aurora A and angiogenic kinase inhibitor that has demonstrated single-agent activity in STS cell lines and inhibition of sarcoma growth for a patient in a phase 1 clinical trial setting. **Methods:** This is a single-center, open-labeled phase II study of ENMD-2076 in advanced STS pts treated with ≤1 line of prior therapy in the advanced/metastatic setting. Pts were commenced on 275mg daily dose (on a 28-day cycle. Treatment-emergent adverse events were assessed by CTCAE (4.0). Radiographic or clinical tumor measurements occurred every 2 cycles (RECIST 1.1). **Results:** 10 pts were enrolled from 2/2013 – 11/2013 and evaluable for efficacy. Median age is 58 yrs (41 – 72). Male: Female 1:9. Histology: Leiomyosarcoma / pleomorphic sarcoma / angiosarcoma: 7/2/1. Pts received the following prior systemic therapies: doxorubicin/gemcitabine/others: 2/3/5. At time of abstract submission, median follow-up is at 7 months (2-12). 3 pts continue on study. Median number of cycles administered per pt = 2 (1-8). 2 pts had confirmed partial response (PR) and 1 pt with confirmed stable disease (SD) of > 6 months. Clinical benefit rate (PR+SD >6 months) was 30%. Median OS has not been reached. Median PFS at 1.8 months (95% CI: 1.2 – not reached). ENMD-2076 has generally been well tolerated with primarily grade 1 and 2 adverse events (AEs). Specifically, drug-induced hypertension occurred in 6 pts (grade 1-2: 4 pts, grade 3: 2 pts). Proteinuria, all grade 1-2, occurred in 6 pts. Other drug related grade 3 or 4 AEs include (pts): elevated transaminases (1), leukopenia (1), and diarrhea (1). 1 pt developed Posterior Reversible Encephalopathy Syndrome (PRES) presenting as grade 4 loss of consciousness at Cycle 1 Day 15 required ICU admission. Full neurological recovery was attained after cessation of treatment. **Conclusions:** ENMD-2076 has shown activity in patients with advanced STS, with meaningful clinical benefits and a side effects profile typical of this class of agent. PRES is a rare but fully reversible side effect of ENMD-2076. Clinical trial information: NCT01719744.

**10529 Poster Highlights Session (Board #17), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Long-term follow-up of the CESS 81 and CESS 86 Ewing sarcoma trials.** *Presenting Author: Herbert Juergens, University Hospital of Muenster, Muenster, Germany*

**Background:** Since 1980 patients with Ewing sarcoma have been treated according to consecutive protocols (CESS) of the German Society of Pediatric Oncology and Hematology (GPOH)(supported by Deutsche Krebshilfe). Post treatment surveillance also includes long term follow-up (supported by BMBF/DLR 01ER0807). The observation time now covers a period of more than 30 years. **Methods:** 673 patients (pts) entered into the CESS 81 (n=183) (1980-1985) and CESS 86 (n=490) (1985-1992) Ewing sarcoma trials were analyzed. 375 pts (59%) were male, 278 (41%) female. 549 pts (82 %) had localized, 124 (18%) metastatic disease. Primary tumor location was lower extremity in 37%, pelvis in 26%, other axial sites in 29%, and upper extremity in 8%. The median age at diagnosis was 14.8 years (range 0.7 - 41.4). The median age of survivors at last time of observation was 28.9 years (range 8.8 - 63.3). Median follow-up time of survivors was 15.5 years (range 0.3 - 30.6). Data were retrospectively analyzed with descriptive statistics and survival analyses, and complemented by questionnaire information. **Results:** 315 pts (47%) were alive at last follow-up, 358 pts (53%) have died. The cause of death was DOD in 318 pts (89%), DOC in 31 pts (9%), and death of other cause in 9 pts (2%). Events were observed in 361 pts: local relapse in 19%, distant relapse in 64%, combined relapse in 13%, and secondary malignancies in 4%. Self-reported late morbidity was available from 128 of 315 survivors: 19.5% cardiac and 6.2% renal abnormalities. In 5 pts (3.9%) secondary amputation was reported. The analysis of late functional outcome is ongoing. 10-year event-free survival (EFS) was 0.49 (SE=0.02) in localized, and 0.21 (SE=0.04) in metastatic disease. 10-year overall survival (OS) was 0.54 (SE=0.02) in localized, and 0.23 (SE=0.04) in metastatic disease. **Conclusions:** Long-term observation is crucial in pediatric cancer survivors. Nearly half of patients of the earliest phase III Ewing sarcoma trials are long-term survivors. Approx. 90% of patients with recurrence died from disease. Patient-related outcome scores are currently investigated in a long-term observation study for inclusion into long-term follow-up guidelines and to better predict the long-term quality of survivorness.

**10530 Poster Highlights Session (Board #18), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Survival of adolescents and young adults (AYAs) with skeletal Ewing sarcoma: A Dutch population-based study.** *Presenting Author: S.E.J. Kaal, Department of Medical Oncology, Radboud University Medical Center, Nijmegen, Netherlands*

**Background:** Ewing sarcoma is most prevalent among children and adolescents. Although increasing age in general is associated with poorer survival, little is known about survival in adolescents and young adults (AYA: 15-39 years) compared to children (0-14 yrs). **Methods:** In this cohort study data from all patients diagnosed with skeletal Ewing sarcoma between 1989 and 2011 were obtained from the Netherlands Cancer Registry. Patients were divided in three age groups: children (age 0-14), AYAs (age 15-39) and older adults (age 40+). One, 3 and 5 year overall survival (OS) estimates by age group were determined and sex, period (1989-1994 vs 1995-2000, 2001-2006, 2007-2011), site (axial vs extremity) and stage (with or without metastases) adjusted Hazard Ratios (HR) and 95% Confidence Intervals (95%CI) were calculated using a Cox Proportional Hazard Regression model. **Results:** In total 180 children, 247 AYAs, and 29 older adults with skeletal Ewing sarcoma were identified. AYAs appear to be more often male compared to children (64% and 53% respectively, $Chi^2$ p-value=0.02) and were more often diagnosed with metastatic disease (31% and 22% respectively, $Chi^2$p-value=0.05). Five-year OS for AYAs was 46% (95%CI: 39-52%) compared to 68% (95%CI: 60-74%) in children and 33% in older adults (95%CI: 16-50%). Table shows 1, 3 and 5 year OS survival data. AYAs have an almost twofold increased risk of death compared to children; the gender, site, stage, and period adjusted HR was 1.9 (95%CI 1.4-2.6) for AYAs compared to children. **Conclusions:** As compared to children AYAs with skeletal Ewing sarcoma more often are male, present with metastatic disease at diagnosis and have a worse survival even after adjustment for tumor stage, site, gender and treatment period. Since detailed data about treatment were not available, no conclusion can be drawn about the effect of treatment on survival. Furthermore, differences in tumor biology should be considered.

**1, 3, and 5 years OS percentages (with 95% confidence intervals) in patients with skeletal Ewing sarcoma.**

| Age group | 1 yr OS | 3 yr OS | 5 yr OS |
|---|---|---|---|
| Children | 94 % (90-97) | 73% (66-79) | 68% (60-74) |
| AYAs | 87% (82-91) | 50% (44-57) | 46% (39-52) |
| 40 + | 66% (45-80) | 38% (20-55) | 33% (16-50) |

**10531 Poster Highlights Session (Board #19), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Eliciting early-response signals from first-in-human clinical trials and validation of prognostic scores in aggressive biology bone cancers: The MD Anderson experience.** *Presenting Author: John Andrew Livingston, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** There have been no new US FDA approved therapies for bone sarcomas (osteosarcoma, Ewing's sarcoma, and chondrosarcoma) in the last three decades. Current treatment options are limited and the prognosis of aggressive bone cancers remains extremely poor. Rarity poses an additional challenge in developmental therapeutics for bone sarcoma. Advanced relapsed/ refractory bone cancer patients may be enrolled in targeted therapy phase 1 trials which may provide unique insight and an opportunity to elicit early response signals. **Methods:** We systematically analyzed the characteristics and outcomes for advanced bone sarcoma patients referred for treatment on phase I trials at MD Anderson Cancer Center (MDACC) from 7/2005 to 11/2013 with an emphasis on targeted agents. In addition we sought to validate the Royal Marsden Hospital (RMH) score and the MDACC score as survival stratification tools within this population. **Results:** Among the 92 patients analyzed [Ewing's sarcoma N=47, osteosarcoma N=22, chondrosarcoma N=16, chordoma N=5, Other N= 2] median age at phase I trial referral was 24 (range 11 to 79), 58 (63%) were males; ECOG PS was zero in 25 pts (27 %), the number of metastatic sites were > 2 in 26 pts (28 %). The median number of prior chemotherapy regimens was 3 (range 0 to 11) and 57 pts (62 %) had prior radiation. Both RMH score (HR = 5.8 (2.9, 11), $p < 0.0001$) and MDACC score (HR = 3.2 (1.9, 5.6), $p < 0.0001$) were successfully validated. Responses were seen in IGF1R +/-mTOR therapy in Ewing's sarcoma and Apo2L/TRAIL in chondrosarcoma. No responses were seen in osteosarcoma. Ten pts (11%) had stable disease. Clinical benefit rate (CR+ PR+SD > 6 mo) was 18% (17 pts). **Conclusions:** Both the RMH and MDACC prognostic scores were validated for predicting overall survival in patients with bone cancers who were referred for phase 1 trials. Responses were seen with targeted therapies in Ewing's sarcoma and chondrosarcoma, however prognosis remains poor. Novel approaches are urgently needed for bone sarcomas.

**10532 Poster Highlights Session (Board #20), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Results of a randomized prospective clinical trial evaluating maintenance chemotherapy in patients with high-grade, operable osteosarcoma: A report from the Latin American Group of Osteosarcoma Treatment.** *Presenting Author: Antonio Sergio Petrilli, Instituto de Oncologia Pediatrica IOP/ GRAACC - UNIFESP, Sao Paulo, Brazil*

**Background:** Preclinical models show that a daily antiangiogenic regimen at low-dose may be effective against chemotherapy-resistant tumors. In patients (pts) with high grade, operable osteosarcoma (OST) of the extremities, efficacy of maintenance therapy with continuous oral cyclophosphamide and methotrexate was investigated. **Methods:** Pts ≤30yrs with high-grade OST were eligible for registration at diagnosis. Eligibility for randomization included: 1. Non-metastatic pts 2. high-grade extremity OST 3. receipt of two cycles pre-operative methotrexate, doxorubicin, cisplatin (MAP); 4. complete macroscopic resection of primary tumor. The study design includes a backbone of 10 weeks of preoperative therapy using MAP. Following surgery, non-metastatic pts were randomized by blocks to complete 31 weeks of MAP or to receive 73 weeks of maintenance therapy following MAP; while metastatic pts received maintenance therapy in combination with MAP since the beginning of treatment. The primary end point was event-free survival (EFS) from randomization. **Results:** Of the 682 pts registered (April, 06 to July, 13) from 3 countries (27 sites), 535 were evaluable, mean age at enrollment of 13.5 years, mean time to diagnosis of 3.8 months and metastatic disease in 38% of the pts. The multivariate analysis showed that metastases at diagnosis ($p<0.001$), necrosis grades 1 and 2 ($p=0.001$) and amputation ($p=0.02$) were associated with a shorter EFS. In the whole cohort of pts, overall survival (OS) was 62% at 5 years and event free survival (EFS) was 50%. For non-metastatic pts, OS was 72% and EFS was 60%. There was *no significant* difference in *EFS*between pts who received MAP+maintenance chemotherapy *compared*with *MAP alone* (61% vs 64%, log-rank test $p=0.3$). **Conclusions:** OST survival rates were improved by the use of this regimen compared with previously reported results by the group. However, with current follow-up, EFS for MAP+maintenance chemotherapy is not statistically superior to MAP alone in pts with high-grade resectable OST of the extremities. Further follow-up for events and survival continues.

**10533^ Poster Highlights Session (Board #21), Tue, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**A nonrandomized phase II trial of sorafenib (S) and everolimus (E) in unresectable metastatic osteosarcoma (OST) patients (pts) relapsed after standard chemotherapy.** *Presenting Author: Giovanni Grignani, Sarcoma Unit, Division of Medical Oncology, IRCCS Istituto di Candiolo, Candiolo, Italy*

**Background:** After standard therapy OST relapse is an ominous event almost uniformly fatal in non resectable cases. Our group explored the activity of the multikinase inhibitor S demonstrating a short-lasting tumor growth arrest and 8% objective responses (OR). We hypothesized that other pathways might be responsible for S failure and we showed mTOR as a reasonable co-target to hit by means of E. **Methods:** Pts>17 years with relapsed unresectable OST, progressing after standard treatment, were eligible to receive S 400 mg b.i.d + E 5 mg once daily until progression (PD) or unacceptable toxicity. We designed a Simon two-stage study with progression-free survival rate at 6 months (PFS@6m) as the primary endpoint. With $\alpha=5\%$, $\beta=10\%$, 37 pts were needed to test if PFS@6m was ≤25%=P0 (9 pts) or ≥50%=P1 (19 pts). Secondary endpoints were PFS, overall survival (OS), RECIST 1.1 OR, safety and their correlations with molecular markers of targeted pathways. We estimated PFS and OS by Kaplan-Meier method with their 95% confidence intervals (95% CI). All tests were two sided. **Results:** We enrolled 38 pts (15 females) from June 2011 to June 2013. PFS@6m was 45% (95%CI 28-61%, 17 pts). Median PFS and OS were 5 (95%CI 2-7) and 11 (95%CI 9-14) months, respectively. We observed 2 (5%) partial responses (PR), 2 minor responses (5%), 20 (53%) stable diseases (SD) for an OR of 10%. PR/SD lasted ≥ 6 months in 8 (21%) pts (6, 6, 7, 8, 8, 8, 10, 11). 1 pt interrupted the study because of lung metastasectomy after 10 months of disease control. Treatment was feasible but demanded both dose reductions and short interruptions for both drugs in 25 (66%) pts due to toxicity Treatment was permanently discontinued in 2 (5%) pts due to toxicity. Results of the correlation of ERK1 and pS6 expression with primary and secondary endpoints will be presented at the meeting. **Conclusions:** S + E showed activity in terms of PFS@6m as second- or further-line treatment in advanced unresectable OST with some long-lasting responses. Toxicity was manageable but required short interruptions, dose reductions and few permanent discontinuations. Despite some hints of activity, S + E failed to reach the prespecified target of PFS@6m. Clinical trial information: NCT01804374.

**10534 General Poster Session (Board #241), Mon, 8:00 AM-11:45 AM**

**Efficacy of novel proteasome inhibitory platinum complex against osteosarcoma.** *Presenting Author: Kentaro Igarashi, Department of Orthopaedic Surgery, Kanazawa University, Kanazawa, Japan*

**Background:** We have developed novel proteasome inhibitory mononuclear platinum compound; 1Pt. We have already reported in vivo study of this compound against osteosarcoma cell lines. Now, we performed comparative studies of our novel proteasome inhibitory platinum compounds against cisplatin resistant osteosarcoma cell lines. And we performed in vitro study using orthotopic mouse model. Then, we also accessed expression of apoptosis related protein after drug exposure. **Methods:** The novel proteasome inhibitory platinum complex was synthesized by Prof. Odani. Cisplatin and proteasome inhibitory platinum were used in this study. Three cell lines (MG63, 143B, and LM8) and three cisplatin resistant cell lines (MG63cis-R, 143BcisR, LM8-cisR) were used. Cell survival after a 72 hrs exposure to these compounds was assessed by WST-8 assay, and IC50 value was calculated for each compound. Apoptosis was assessed by DNA fragmentation and Annexin V / PI assay. DNA double-strand breaks were assessed by acetylation of histon H2AX. Proteasome inhibitory activity was assessed by 20S proteasome assay kit. Expression of apoptotic related protein was accessed by western blotting. In vivo, 143B was transplanted to the tibia of nude mice, and treated with each drugs. **Results:** Both compound strongly caused concentration-dependent cytocidal effect. IC50 value of 1Pt was relatively high. 1Pt does not show cross resistance to cisplatin. Apoptosis induction and acetylation of histon H2AX were observed. Proteasome activity was surpressed after 1Pt administration. Expression of apoptotic related protein was up-regulated after 1Pt exposure. In orthotopic mouse model, 1Pt showed stronger anti-tumor effect, in dose escalation model, compared to cisplatin. **Conclusions:** 1Pt showed moderate anti-tumor activity against osteosarcoma cell line in vitro and showed suppression of proteasome activity. 1Pt had no cross resistance to cisplatin. In ortotopic mouse model, 1Pt showed stronger anti-tumor activity compared to cisplatin.

**10535 General Poster Session (Board #242), Mon, 8:00 AM-11:45 AM**

**Impact of excision repair cross-complementation group 1 (ERCC1) protein on survival of patients with osteosarcoma treated with cisplatin-based chemotherapy.** *Presenting Author: Kentaro Igarashi, Department of Orthopaedic Surgery, Kanazawa University, Kanazawa, Japan*

**Background:** Excision repair cross-complementation (ERCC) genes encode proteins that participate in nucleotide excision repair, and these proteins are crucial for preventing DNA damage caused by cisplatin and its low expression correlates with better survival after cisplatin-based chemotherapy in several cancers. We retrospectively evaluated the relationship between expression of the excision repair cross-complementation 1 (ERCC1) protein and outcome in patients with osteosarcoma treated with cisplatin-based chemotherapy. **Methods:** Medical records and tissue samples from 105 patients with a histologically confirmed diagnosis of high-grade osteosarcoma previously treated with cisplatin-based chemotherapy (K2 protocol) were retrospectively analyzed. They were 61 males and 44 females with the mean age of 23.3 years (range 5–76). A Immunohistochemical staining of biopsy specimen was used to assess the expression of ERCC1. **Results:** Thirty-two (30%) samples were ERCC1-positive. Metastasis at diagnosis, chondroblastic subtype, poor response to chemotherapy, and positive ERCC1 expression were associated with poor event free survival ($P = 0.044$, $P = 0.039$, $P = 0.003$, and $P = 0.001$ respectively). Trunk location, metastasis at diagnosis, chondroblastic subtype, poor response to chemotherapy, and positive ERCC1 expression were associated with poor overall survival ($P = 0.006$, $P < 0.001$, $P = 0.012$, $P = 0.018$ and $P < 0.001$ respectively). Patients with an ERCC1-negative tumor had a significantly longer event-free survival (113.7 versus 55.5 months; $P = 0.001$) and overall survival (198.9 versus 99.6 months; $P < 0.001$) compared with the group positive for ERCC1. Multivariate analysis for event-free survival and overall survival confirmed that the absence of ERCC1 expression correlated with longer event-free survival (HR 2.297, 95% CI 1.284–4.106, $P = 0.005$) and longer overall survival (HR 3.220, 95% CI 1.329–7.800, $P = 0.010$). **Conclusions:** We confirmed that ERCC1 expression is predictive of outcome in osteosarcoma patients treated with cisplatin-based chemotherapy. Patients with ERCC1-negative tumors showed an increased survival rate.

**10536 General Poster Session (Board #243), Mon, 8:00 AM-11:45 AM**

**Molecular targeted therapy for osteosarcoma using glycogen synthase kinase-3 beta (GSK-3$\beta$) inhibitors.** *Presenting Author: Shingo Shimozaki, Department of Orthopedic Surgery, Kanazawa University, Kanazawa, Japan*

**Background:** Chemotherapy for osteosarcoma has improved the 5-year survival rate in osteosarcoma patients to 70%. However, development of new therapies for osteosarcoma is warranted, as chemotherapy is associated with several disadvantages such as toxicity and drug resistance. Although use of molecular targeted therapies has been reported for many types of cancer, their use in osteosarcoma treatment has not been reported yet. Glycogen synthase kinase-3 beta (GSK-3$\beta$) has been reported to sustain tumor cell survival, proliferation, and invasion in some types of cancer. Accordingly, GSK-3$\beta$ has emerged as a potential therapeutic target for the treatment of cancer. **Methods:** Four osteosarcoma cell lines and 1 osteoblast cell line were used for this study. Each cell line was treated with the GSK-3$\beta$ inhibitors, AR-A014418 and SB-216763. GSK-3$\beta$ activity was analyzed for all cell lines using western blotting analysis. Cell viability and proliferation were analyzed using the WST-8 assay kit and the BrdU ELISA kit, respectively. Apoptosis that occurred after treatment with GSK-3$\beta$ inhibitors was analyzed using the TUNEL imaging assay kit. **Results:** The expression of the active form of GSK-3$\beta$ was high in all osteosarcoma cell lines as determined by western blotting analysis. Cell proliferation was suppressed in the 4 osteosarcoma cell lines 48 hours after the administration of GSK-3$\beta$ inhibitors, but not in the osteoblast cell line. The $IC_{50}$ of the GSK-3$\beta$ inhibitors for each osteosarcoma cell line was below 20 $\mu$M. The t-test analysis showed a significant difference in cell proliferation in the osteosarcoma cell lines between the AR-A014418-treated group and the control group. Apoptosis was seen in all osteosarcoma cell lines but not in the osteoblast cell line. **Conclusions:** It was suspected that the activity of GSK-3$\beta$ was strongly associated with cell proliferation in osteosarcoma. Our findings indicate that GSK-3$\beta$ inhibitors could have a therapeutic effect on osteosarcomas in vivo. In the future, we aim to investigate the role of GSK-3$\beta$ in osteosarcoma and to perform in vivo studies in mice transplanted with osteosarcoma cells to understand the mechanism underlying the therapeutic effect of GSK-3$\beta$ inhibitors in this tumor.

**10537 General Poster Session (Board #244), Mon, 8:00 AM-11:45 AM**

**Is non-HD–MTX based, dose-dense, combination chemotherapy a valid choice in osteosarcoma in developing world?** *Presenting Author: Jyoti Bajpai, Tata Memorial Hospital, Mumbai, India*

**Background:** Recent meta-analysis in osteosarcoma (OGS) revealed superiority of high-dose-methotrexate (HD-MTX) containing 3-drug combination chemotherapy (CTh) compared to 2-drug regimens with 5y-EFS of 54% and 46%, respectively ($p = 0.03$). The use of HD-MTX requires in-patient treatment with stringent monitoring. Non HD-MTX based CTh regimens merit evaluation especially in resource constrained scenarios. **Methods:** This prospective study evaluated the efficacy & toxicity of dose-dense CTh regimen comprising doxorubicin, ifosfamide, and cisplatin. Response to CTh was graded based on histological necrosis (HN). Good responders (GR) were defined as those with $\geq$ 90% HN. Survival analysis was performed using the Kaplan-Meier method and compared the log-rank test. Baseline disease status and nutritional parameters were correlated with outcomes. **Results:** Majority were males (61%) with a median age of 18 yrs. Thirteen (36 %) had metastatic disease. The mean lesion size was 11.5cm. Seventeen (47%) were malnourished, 9 (25%) anemic, 12 (33%) iron deficient and 15 (41%) were B12 deficient at presentation. Post CTh 21(91%) with non-metastatic and 6 (46%) with metastatic disease underwent surgery. For either group GR was 67%. At the median follow-up of 2.2yrs, 30 (84%) were surviving and 21 (59%) remained progression free. Patients with non-metastatic disease had an OS and PFS of 95% and 70% while patients with metastatic disease have an OS & PFS of 61% and 40% respectively. Survival difference between the two groups was statistically significant. Other prognostic factors like ECOG score of $\geq$ 2 & Hb levels $\leq$ 10.6 gm% had a significant impact on PFS (p=0.01 & 0.03) and OS (p =0.01& 0.05). On multivariate analysis presence of metastasis was an independent prognostic factor. During CTh 41% patients had febrile neutropenia after the first cycle and were managed successfully. **Conclusions:** Non-HD-MTX based dose-dense CTh results in acceptable disease control and toxicity in patients with non-metastatic OGS. Patients with metastatic disease probably warrant more aggressive regimens.

**10538 General Poster Session (Board #245), Mon, 8:00 AM-11:45 AM**

**A controlled, nonrandomized clinical research on chemotherapy combined with re-endostatin for stage IIB ostosarcoma.** *Presenting Author: Hairong Xu, Department of Orthopedic Oncology Surgery, Beijing Ji Shui Tan Hospital, Peking University, Beijing, China*

**Background:** The aim of this study was to investigate the efficacy and safety of chemotherapy combined with re-endostatin (endostar) against stage IIB ostosarcoma. **Methods:** Patient of stage IIB ostosarcoma enrolled in Beijing Jishuitan Hospital from January 2008 to April 2012 were divided into combined group and control group. The chemotherapy regimen was as follows: methotrexate 10 g/m$^2$ iv $d_1$, ifosfamide 3 g/m$^2$ iv $d_1$-$d_5$, cisplatin 120 mg/m$^2$ iv $d_1$, doxorubicin 30 mg/m$^2$ iv $d_1$-$d_3$. Based on the same chemotherapy, endostar was added in combined group (15 mg/m$^2$ iv $d_1$-$d_{14}$, 21 days was a cycle, for 4 cycles). **Results:** A total of 388 patients were enrolled in this study, and 58 cases were excluded in the final analysis. A total of 330 patients could be evaluated, in which 272 cases were in control group and 58 in combined group. Patients were followed up 6-59 months with a median period of 20.2 months. In the control group, 1-, 2- and 3-year distant metastasis-free survival rates were 79%, 70% and 65%, respectively, while those of combined group were 93%, 86% and 77% ($p = 0.045$). In the control group, 1-, 2- and 3-years of progression-free survival rates were 76%, 66% and 60%, respectively, while those of combined group were 90%, 83% and 74% ($p = 0.025$). In the control group, 1-, 2- and 3-year overall survival rates were 94%, 84% and 79%, while those of combined group were 98%, 94% and 85% ($p = 0.220$). The side effects in two groups were mainly in grade 1-2, and the common grade 3-4 side effects were leucopenia, anemia, hepatic dysfunction, nausea and vomiting. There was no difference in side effects of the two groups. **Conclusions:** The combination of chemotherapy and endostar can significantly improve the distant metastasis-free survival and progression-free survival in osteosarcoma patients, with tolerable side effects, worthy of further study.

**10539 General Poster Session (Board #246), Mon, 8:00 AM-11:45 AM**

**Dendritic cells immunotherapy for patients with malignant bone and soft tissue tumors.** *Presenting Author: Hideji Nishida, Department of Orthopedic Surgery, Kanazawa University, Kanazawa, Japan*

**Background:** We evaluated the safety and feasibility of autologous dendritic cell (DC) immunotherapy for patients with malignant bone and soft tissue tumors. **Methods:** Forty one patients were enrolled and immunized with DCs. Patient tumors comprised twenty one malignant bone tumors, seventeen malignant soft tissue tumors, and three metastases. 1st generation of DC immunotherapy was started in 2008. Autologous DCs were generated ex vivo and pulsed with original tumor lysate and OK-432. For the 2nd generation, we added TNF-$\alpha$- pulsed with tumor lysate. 3rd generation was DC immunotherapy incorporated low dose cyclophosphamide. Each patient received 2-5 x $10^6$cells one time a week for 6 weeks. **Results:** Immunizations were well tolerated by patients with only local redness at the injection site in 9 cases. Levels of interferon-gamma and interleukin-12 cytokines were increased after DC immunotherapy in twenty six patients (65%), eighteen of whom (44%) subsequently developed delayed-type hypersensitivity. At the final follow-up, one patient had partial response, eight patients had stable disease and thirty two patients had progressive disease. **Conclusions:** Although improvement of clinical efficacy requires further research, toxicity-free immunization by tumor lysate- and OK-432-pulsed DCs is safe and feasible in patients with malignant bone and soft tissue tumors.

**10540 General Poster Session (Board #247), Mon, 8:00 AM-11:45 AM**

**Outcome and prognostic factors in localized osteosarcoma with uniform chemotherapy protocol: A single-center experience of 234 cases.** *Presenting Author: Vijaya Murugan, DR BRA IRCH, All India Institute of Medical Sciences, New Delhi, India*

**Background:** Data on outcome of localized Osteosarcoma (OS) treated with uniform protocol is limited from Asia. **Methods:** This is a single institutional review of patients treated between Jan 2004-Dec 2012, and evaluated on per protocol analysis. All patients received uniform chemotherapy protocol with cisplatin, doxorubicin as neo-adjuvant chemotherapy (NACT), followed by surgery and adjuvant chemotherapy (ACT) based on risk stratification. **Results:** 234 OS patients were treated with median age 17 years (range: 2–66), Male: Female: 2:1, tumor diameter 9 cm (range: 1-25) and symptom duration 4 months (range: 1-36). Sites of disease were extremities 93%, pelvis 2 % and head & neck 5%. Of them 218 (93.2%) received NACT and 16 (6.8%) underwent upfront surgery. Post-NACT, 4(1.7%) were in CR; 152(66%) in PR with ORR 67.7%. Of the 218 patients who received NACT, 198 (90.8%) underwent surgery (70.2%- Limb salvage, 29.8%-Amputation). On histological examination, 47(28.4%) achieved >90% tumor necrosis while 118(71.6%) achieved <90% tumor necrosis. Adjuvant chemotherapy was given to 198 (84.6%) patients with median of 5 cycles. At median follow-up of 68 months (range: 2–119), 5-year EFS, overall survival were 39.5%, 51.5% respectively. Multivariate analysis showed tumor site and tumor necrosis as significant risk factors for EFS and OS respectively. **Conclusions:** This is largest single institutional study of localized osteosarcoma from Asia which constituted 70% of entire cohort with delayed presentation. More than 2/3$^{rd}$of patients had successful limb salvage chemotherapy after NACT. Extremities OS with post NACT tumor necrosis >90% had best outcome.

**Multivariate analysis.**

| | EFS | | | OS | | |
|---|---|---|---|---|---|---|
| **Variable** | **HR** | **95% CI** | **P Value** | **HR** | **95% CI** | **P value** |
| **Tumor site** | 2.45 | 1.30-4.50 | 0.01 | ----- | ------ | ------ |
| **Extremities** | | | | | | |
| **Head and neck, pelvis** | | | | | | |
| **Necrosis** | | | | 2.54 | 1.01-6.33 | 0.05 |
| **>90%** | | | | | | |
| **<90%** | | | | | | |

**10541 General Poster Session (Board #248), Mon, 8:00 AM-11:45 AM**

**Gemcitibine (G) and docetaxel (D) in relapsed and unresectable high-grade osteosarcoma after failure of standard multimodal therapy.** *Presenting Author: Emanuela Palmerini, Istituto Ortopedico Rizzoli, Bologna, Italy*

**Background:** The prognosis of relapsed and unresectable high-grade osteosarcoma is poor and has remained unchanged for decades. Increased survival for metastatic soft tissue sarcomas was previously shown with the combination G+D compared to G alone (Maki R, JCO 2007). Thus, we explored G+D activity in patients (pts) with relapsed and unresectable osteosarcoma / spindle cell pleomorphic sarcoma. **Methods:** Pts progressing after standard treatment were eligible to receive G 900 mg/m$^2$day 1, 8 + D 75 mg/m2 day 8, every 21 days, until progression or unacceptable toxicity. The primary end point was progression-free survival (PFS) at 4 months (mo). Secondary objectives were overall survival (OS) and disease control rate (DC), defined as complete response (CR), partial response (PR) or stable disease (SD) lasting at least 6 months. **Results:** We enrolled 46 pts. Median age was 18 (8-71): 26 pts pediatric pts, 20 adult. Line of treatment: 14 pts in 1$^{st}$line; 32 pts were in ≥ 2nd line (up to 5). Pattern of metastases: 26 pts lung only, 20 multiple sites. Histology: 35 pts classic osteosarcoma, 11 high grade spindle cell sarcoma (HGS). ECOG: 31 pts 0, 11 pts 1, 4 pts 2. 41 pts were evaluable for RECIST response (2 pts off study for D allergic reaction, 1 pt for G4 skin toxicity, 2 pts with no measurable lesions). 4-mo PFS rate was 47%. 4-mo PFS was significantly better for ECOG 0 pts (ECOG0: 57% vs ECOG 1: 37% vs ECOG 2: 0%; p= 0.01), with a trend to superiority in pts with lung only metastases (lung only: 58%; multiple sites: 35%; p=0.09), and classic osteosarcoma (classic osteosarcoma 50% vs. HGS 22%; p=0.2), while there was no difference according to age or line of treatment. PFS and OS at 6 mo were 23% and 71%, respectively. Tumor responses: CR: 0/41, PR: 5/41 (12%), SD 18/41 (44%), progressive disease (PD) 18/41 (44%); DC: 8/41 (20%). **Conclusions:** G+D demonstrated activity in pre-treated relapsed high grade classic osteosarcoma pts, especially in pts with ECOG 0 and lung only disease. This combination should be included in the therapeutic armamentarium of metastatic osteosarcoma as an active line of therapy.

**10542 General Poster Session (Board #249), Mon, 8:00 AM-11:45 AM**

**Osteosarcoma of the head and neck (OHN): A multicenter case series of 79 adult patients in the Netherlands.** *Presenting Author: Eline Boon, Department of Medical Oncology, Radboud University Medical Center, Nijmegen, Netherlands*

**Background:** OHN is rare and behaves differently from osteosarcoma in the extremities. There is an ongoing debate about the value of (neo-) adjuvant chemotherapy in OHN. In this study we describe the general practice and outcome of patients (pts) treated for OHN in the Netherlands, with special attention to the efficacy of chemotherapy on overall survival (OS). **Methods:** A retrospective cohort study was conducted within the Dutch Head and Neck Society. All pts >16 years of age treated for OHN between 1993-2013 were included in this analysis. Review of pathology for tumors with uncertain grading was performed. Kaplan-Meier survival analysis and log rank testing were performed. **Results:** Seventy-nine pts with OHN were included, 42 (53%) female, median age 46 years (range 16-95). Twenty-five (32%) pts had a prior malignancy, 19 (24%) pts received previous radiotherapy to the head and neck region. Most common tumor location was the jaw, with 32 (40%) mandibular and 26 (33%) maxillary tumors. A total of 17 (22%) pts received (postoperative) radiotherapy. All 12 (15%) low grade OHN pts underwent a resection, without chemotherapy and had a 5 year OS of 90%. Fifty-six (71%) pts had a high grade OHN; 50/56 (89%) were operated and 25/50 (50%) received (neo-) adjuvant chemotherapy. In the 50 resected high grade OHN pts, 5 year OS was 73% versus 36% for pts treated with or without (neo-) adjuvant chemotherapy, respectively (p = 0.004). The 5 years local recurrence rate in high grade resected OHN pts was 15% versus 63% in pts treated with and without (neo-) adjuvant chemotherapy, respectively (p = 0.006), whereas the risk of distant metastases was not significantly different (13% versus 39%, respectively p = 0.08). The 5 year OS of the 56 high grade OHN was 30% versus 56% in pts with or without a prior malignancy, respectively (p = 0.08). **Conclusions:** Pts with high grade resected OHN have a better OS when treated with (neo-) adjuvant chemotherapy. Remarkably, local recurrence rate is significantly lower in resected OHN pts treated with (neo-) adjuvant chemotherapy, whereas no significant difference in distant metastases rate was shown.

**10543 General Poster Session (Board #250), Mon, 8:00 AM-11:45 AM**

**Mouse models to study cancer stem cells in osteosarcoma.** *Presenting Author: Nino Carlo Rainusso, Texas Children's Hospital, Baylor College of Medicine, Houston, TX*

**Background:** Osteosarcoma (OS) is the most common malignant bone tumor in children and young adults. Many patients suffer disease recurrence and eventually die from metastatic disease that has spread to the lungs. Clearly, more research is needed to understand the biology and molecular mechanisms driving OS metastasis and chemoresistance. The identification of cancer stem cells (CSCs) in solid tumor malignancies, mainly carcinomas and brain tumors, has expanded our knowledge about tumor heterogeneity and its role in tumorigenesis, metastasis and therapy resistance. However, similar research accomplishments have not been established in sarcomas. **Methods:** We performed our experiments aimed to identify OS stem cells using two distinct mouse models: a genetically engineered mouse model that carries an osteoblast-specific p53 mutation and a syngenic (DLM8 tumor cells orthotopically injected in C3H mice) mouse model. **Results:** We observed that murine tumor cells obtained from freshly isolated tumors developed sphere-like structures (sarcospheres). Sarcophere forming capacity was significantly increased in tumor cells obtained from metastatic lesions. We found that both OS models contain ALDH Hi (stem-like) cells. The high expression of ALDH ranged from 0.7 to 17%. Further analysis showed that distal metastases contained up to 10 times more ALDH Hi cells than the primary bone tumors. Moreover, we performed microarray analysis of primary bone tumors, pulmonary nodules and CSCs in both primary and metastatic sites, and found that 159 genes were differently expressed between bone and metastatic lung OS tumors. Our preliminary data showed that genes involved in the biologic processes of bone development, mesenchymal differentiation and skeletal morphogenesis were enriched in ALDH Hi cells in primary bone tumors, and genes involved in immune response, inflammatory response and cytokines/chemotaxis were up-regulated in ALDH Hi cells in metastatic tumors. **Conclusions:** We have identified putative OS stem cells in two immunocompetent mouse models of metastatic OS. Our preliminary data have shown that CSC content seems to be increased in metastases.

**10544 General Poster Session (Board #251), Mon, 8:00 AM-11:45 AM**

**Association of ABCG2 polymorphism with clinical efficacy of imatinib in patients with gastrointestinal stromal tumor.** *Presenting Author: Dong Hoe Koo, Division of Hematology/Oncology, Department of Internal Medicine, Kangbuk Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

**Background:** Imatinib is a substrate of drug metabolizing enzymes, including those of the cytochrome P450 (CYP) system, and of several drug transporters. Differences in imatinib pharmacokinetics among individual patients may be influenced by genetic polymorphisms and be associated with clinical imatinib efficacy. This study evaluated the correlation of genetic polymorphisms with trough imatinib levels and clinical efficacy in GIST patients. **Methods:** A total of 209 patients with GIST who had received imatinib (400 mg daily) were genotyped for 6 single-nucleotide polymorphisms in 3 genes (CYP3A5 6986A>G; ABCB1 1236C>T, 2677G>A/T, and 3435C>T; and ABCG2 34G>A and 421C>A) via blood samples. Imatinib plasma trough levels and progression-free survival (PFS) were analyzed for association with each genotype. **Results:** With a median follow-up of 39.6 months (range, 16.7-97.5 months), the estimated 5-year PFS rate was 67.5% (95% CI, 59.9-75.1). Among the CYP3A5, ABCB1, and ABCG2 genotypes, there were no significant differences in imatinib plasma trough levels or PFS, while ABCG2 421C>A was associated with PFS. The 5-year PFS rate in patients with the AA variant of ABCG2 421C>A (92.3%; 95% CI, 77.8-100.0) was significantly superior to that of patients with CC/CA genotypes (65.0%; 95% CI, 56.9-73.1) (P = 0.047). **Conclusions:** The ABCG2 421C>A genetic variation could influence clinical efficacy in terms of PFS in patients with advanced GIST undergoing imatinib treatment.

**10545 General Poster Session (Board #252), Mon, 8:00 AM-11:45 AM**

**Impact of underestimation of risk on treatment duration and recurrence in GIST patients.** *Presenting Author: Annie Guérin, Analysis Group, Inc., Montréal, QC, Canada*

**Background:** Adjuvant imatinib therapy has been shown to reduce risk of recurrence and improve survival in gastrointestinal stromal tumor (GIST) patients (pts) who had complete tumor resection. Though different tools are available, the revised NIH criteria are most widely used to assess recurrence risk and help determine treatment duration. This study analyzed the impact of risk under-estimation on under-treatment and recurrence in GIST pts. **Methods:** An online questionnaire was used to collect chart data on 506 pts with primary resectable KIT+ GIST from 109 US oncologists. By comparing the risk of recurrence evaluated by NIH criteria based on primary tumor characteristics vs. physicians' assessment noted in pts' charts, pts' recurrence risks were categorized as underestimated, consistent, or overestimated. Under-treatment was defined for high risk pts as <36 months of planned adjuvant imatinib therapy (NCCN Guidelines). The impact of underestimated risk on under-treatment and recurrence were analyzed using GEE logistic and Cox proportional hazard regression models, adjusting for potential confounding factors. **Results:** Risk of recurrence was underestimated in 37.5% of pts (53.4% consistent; 9.1% over-estimated). Among the 65.8% of pts who were at high risk (NIH criteria), 50.8% had their risk underestimated. Pts with intermediate tumor size, intermediate mitotic count, and non-gastric primary tumor were the most likely to have their risk underestimated; 46.8% of underestimated pts had a tumor >5-10cm, 64.7% had a mitotic count 6-10/50 HPF, and 70.0% had non-gastric tumor. High risk pts who had their risk underestimated (vs. not underestimated) were more likely to be under-treated (OR=2.26, $p$=.001). Among all GIST pts, those with underestimated risk (vs. not underestimated) had a significantly higher hazard of recurrence (hazard ratio=1.81, $p$=.028). **Conclusions:** Underestimation was found to lead to under-treatment in high risk pts and an overall higher risk of recurrence. Given the high proportion of pts with underestimated risk, these findings suggest that with more consistent and systematic approaches to assess risk, overall recurrence-free survival could be improved in GIST patients.

**10546 General Poster Session (Board #253), Mon, 8:00 AM-11:45 AM**

**Correlation of PET/CT and CT RECIST response in GIST patients with PDGFRA D842V gene mutations treated with crenolanib.** *Presenting Author: Jennifer Madeline Matro, Fox Chase Cancer Center, Philadelphia, PA*

**Background:** Crenolanib (CP-868,596) is an orally bioavailable, selective inhibitor of platelet derived growth factor receptor (PDGFR) tyrosine kinase, with in vitro studies demonstrating activity against PDGFRA D842V mutant cell lines. A phase II study evaluated antitumor efficacy of crenolanib in patients (pts) with advanced gastrointestinal stromal tumor (GIST) with PDGFRA D842 related mutations and deletions. An exploratory objective evaluated metabolic response after 1 cycle of therapy as a predictor of RECIST response, so positron emission tomography/computerized tomography (PET/CT) data was available for a majority of pts. We present the results of this exploratory objective. **Methods:** Pts with advanced GIST with PDGFRA D842 related mutations and deletions, including D842V, with residual measurable disease were eligible for enrollment at 1 of 2 study sites. Pts with a baseline PET/CT and a follow-up PET/CT after 1 cycle were included in this analysis. One nuclear medicine specialist interpreted the scans and provided SUV estimates for index lesions at baseline and after 1 treatment cycle. RECIST measurements were provided by the local interpreting radiologist. **Results:** 12 pts treated with crenolanib had both a baseline and follow-up PET/CT after 1 cycle. Baseline FDG avidity was lower than expected for GIST based on published reports, with the exception of 1 pt who had average initial standardized uptake value (SUV) of 33. Average SUV excluding this pt was 4.6. The table shows PET metabolic response after 1 cycle and CT RECIST best response. 7 of 12 (58%) pts had non-concordant PET and CT responses, including one with partial response (PR) on PET but progressive disease (PD) on CT. **Conclusions:** In this small exploratory analysis, pts with PDGFRA D842 related mutations had lower than expected SUV activity on PET, and metabolic response did not predict response by RECIST. These results suggest that PET/CT may not be an optimal method for predicting, evaluating and following response among GIST pts with PDGFRA D842 related mutations. Clinical trial information: NCT01243346.

**Radiographic response.**

| # of patients | PET Metabolic Response | CT RECIST |
|---|---|---|
| **3** | SD | SD |
| **2** | PD | PD |
| **2*** | PD | SD |
| **2*** | SD | PD |
| **1*** | PR | SD |
| **1*** | PR | PD |
| **1*** | SD | PR |

Abbreivation: SD, stable disease. *Indicates noncorrelation.

**10547 General Poster Session (Board #254), Mon, 8:00 AM-11:45 AM**

**MDCT and clinicopathologic characteristics of small bowel gastrointestinal stromal tumors (GISTs) in 102 patients: A single-institute experience.** *Presenting Author: Akshay D Baheti, Department of Imaging, Dana-Farber Cancer Institute, Boston, MA*

**Background:** SB is the 2nd most common site of GISTs and has worse prognosis than gastric GIST. We evaluated clinical presentation, pathology and imaging features of SB GIST. **Methods:** Imaging and clinicopathologic data of 102 pts (53M, 49F; mean age: 55 yrs; range: 19-83 yrs) with jejunal/ ileal GIST treated at our institute between 2002 and 2013 was reviewed. 2 radiologists in consensus reviewed imaging of treatment-naive primary in 41 pts and follow-up imaging in all pts. **Results:** 90/102 pts weresymptomatic at presentation (abdominal pain= 50, GI bleed= 40). Site of origin: jejunum= 64, ileum= 38. Risk stratification: low= 21; intermediate= 17; high= 64. Mean tumor size= 8.5 cm (range: 1-28 cm). On baseline CT (n= 41), tumors were predominantly well circumscribed and smooth/ mildly lobulated in contour. 22/41 tumors were exophytic, 16 had both exophytic and intraluminal components and 3 were intraluminal. 16/41 tumors were homogenous; 25 were heterogenous. Cystic/ necrotic areas (HU<20) were seen in 16/41 and calcification in 9. 14 homogenous (87%) and 16 heterogenous (64%) tumors had mitotic index $^{2}$5. CT demonstrated tumor-bowel fistula in 7/41, intraperitoneal rupture in 2 and bowel obstruction in 4. Amongst 102 total pts, metastases developed in 51 (27 at presentation), predominantly involving peritoneum and liver (refer table). 7/8 (87%) pts presenting with intraperitoneal rupture developed metastases. Metastases elsewhere were always associated with hepatic/ peritoneal metastases. At last follow-up, 28 pts were deceased (median survival 65 months, range: 22-179 months). **Conclusions:** SB GISTs were often symptomatic at presentation, high risk on pathology and had greater propensity for peritoneal metastases. On CT, they were predominantly large, well-circumscribed, exophytic tumors with or without cystic/ necrotic areas. Complications like rupture and bowel obstruction must be looked for.

| Metastases | P without L | L without P | P+L | Total |
|---|---|---|---|---|
| **Jejunum** | 8 | 7 | 16 | 31 |
| **Ileum** | 11 | 4 | 5 | 20 |

Abbreviations: L, liver; P, peritoneum.

**10548 General Poster Session (Board #255), Mon, 8:00 AM-11:45 AM**

**Do CT features predict the behavior of treatment-naive gastric GIST?** *Presenting Author: Ailbhe C O'Neill, Dana-Farber Cancer Center Institute, Boston, MA*

**Background:** Risk stratification of gastric GIST is currently based on size and mitotic count. Patients with large primary tumors often undergo neoadjuvant treatment with imatinib which limits the assessment of mitotic count in the final resection specimen. Since most patients with gastric GIST undergo pretreatment CT, risk-assessment based on the CT features would be helpful. Therefore, we aimed to assess if pre-treatment CT features can predict the metastatic potential and overall survival (OS) of gastric GIST. **Methods:** In this IRB approved retrospective study, CT images of 164 patients with pathologically confirmed treatment-naive gastric GIST (88 men; mean age 60 years, SD 13.8) were reviewed in consensus by two radiologists blinded to clinicopathologic features and outcome. The metastatic spread and OS was then recorded using available imaging studies and electronic medical records (median follow up 33 months, IQR 18-56). Predictors of metastatic disease were analyzed using univariate and multivariate (logistic regression) analysis. Effect of the identified predictors on OS was assessed using Log-Rank test. **Results:** Metastatic disease developed in 51 patients (31%) and 25 (15%) patients died. Tumor size ≥10cm (p=0.02, OR 5.27), irregular/lobulated margin (p=0.009, OR 3.45) and hyperenhancing solid component (p=0.0015, OR 6.68) were independent predictors of metastatic spread. Presence of two or more of these three features predicted a worse OS (p=0.002). **Conclusions:** Irregular/ lobulated margin, presence of hyperenhancing solid component and tumor size ≥10 cm on pretreatment CT predict worse outcome of gastric GIST.

| CT feature | Patients with metastases (%) | Univariate analysis (p value*) | Multivariate analysis (p value) | Odds ratio (95% CI) |
|---|---|---|---|---|
| **Size** | | | | |
| **≥10 cm** | 32/41 (78%) | <0.0001 | 0.008 | 5.27 (1.54-18.05) |
| **<10 cm** | 19/123 (15%) | | | |
| **Margin** | | | | |
| **Irregular/lobulated** | 42/71 (59%) | <0.0001 | 0.02 | 3.45 (1.21-9.85) |
| **Smooth** | 9/93 (10%) | | | |
| **Cystic areas** | | | | |
| **>50%** | 34/49 (69%) | <0.0001 | 0.11 | |
| **<50%** | 17/115 (15%) | | | |
| **Exophytic >50%** | | | | |
| **Present** | 44/102 (43%) | <0.0001 | | |
| **Absent** | 7/62 (11%) | | | |
| **Density** | | | | |
| **Homogenous** | 7/72 (10%) | <0.0001 | | |
| **Heterogenous** | 44/92 (48%) | | | |
| **Hyperenhancing solid component^** | | | | |
| **Present** | 36/80 (45%) | <0.0001 | 0.0015 | 6.68 (2.04-21.86) |
| **Absent** | 5/63 (8%) | | | |

* Fisher's exact test, ^ Unenhanced CT in 21.

**10549 General Poster Session (Board #256), Mon, 8:00 AM-11:45 AM**

**Correlation of *KIT* and *PDGFRA* mutational status with clinical benefit in patients (pts) with gastrointestinal stromal tumor (GIST) treated with sunitinib (SU) in a worldwide treatment-use (TU) trial.** *Presenting Author: Peter Reichardt, HELIOS Klinikum Bad Saarow, Bad Saarow, Germany*

**Background:** This study retrospectively explored the role of *KIT* and *PDGFRA* mutations in response to SU therapy in pts with imatinib (IM)-resistant/intolerant GIST in a worldwide TU trial. **Methods:** SU was administered at a starting dose of 50 mg/day on a 4-week-on, 2-week-off schedule in the TU study. Clinical outcome data (PFS and ORR, both investigator-assessed per RECIST 1.0, and OS) from the TU study were correlated with *KIT/PDGFRA* mutational data obtained with IRB approval in the present correlative study. Tumor tissue utilized for molecular status determination was obtained pre-IM, post-IM−pre-SU, or post-SU treatment. All available data were used in all analyses regardless of time of collection. Mutational status was provided by investigators following local laboratory analyses. The primary analysis compared median PFS in pts with primary *KIT* exon 11 vs. exon 9 mutations using a 2-sided log-rank test. Similar methods were used for OS; ORRs were compared using a 2-sided Pearson $\chi^2$ test. **Results:** Of 1124 pts in the TU study, genotyping data were available or generated for 230 (20%), all of which were included in the present study. Study population and clinical outcomes were representative of the full TU study population. Prior IM therapy was discontinued due to resistance in 92% of pts and intolerance in 8%. 197 pts (86%) had primary *KIT* mutations, mainly in exon 11 (62%) or exon 9 (18%). Of 101 pts with additional *KIT* mutation data (44%), 26 (26%) had another *KIT* mutation (12% in exon 13, 12% in exon 17, 1% in exon 11, and 1% classified as "other"). 12 pts (5%) had a primary *PDGFRA* mutation, including 5 (2%) in exon 18. Pts with primary *KIT* exon 9 mutations had better outcomes vs. those with exon 11 mutations: median PFS, 12.3 vs. 7.0 months (HR, 0.59; P=0.011); median OS, 26.3 vs. 16.3 months (HR, 0.55; P=0.002); ORR, 19.0% vs. 6.3% (P=0.012). There were insufficient data to analyze the effects of *PDGFRA* or additional *KIT*mutations. **Conclusions:** The distribution of *KIT*/*PDGFRA* mutations in IM-resistant/intolerant pts with GIST and clinical outcomes observed with SU treatment were consistent with previous reports. Clinical trial information: NCT01459757.

**10550 General Poster Session (Board #257), Mon, 8:00 AM-11:45 AM**

**Analysis of serum protein biomarkers and circulating tumor (ct) DNA for activity of dovitinib in patients (pts) with tyrosine kinase inhibitor (TKI)-refractory gastrointestinal stromal tumors (GIST).** *Presenting Author: Changhoon Yoo, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

**Background:** Dovitinib is a multikinase inhibitor targeting VEGFR, FGFR, PDGFR beta, and KIT. Serum protein biomarkers and ctDNA were analyzed for the correlation with the outcomes of dovitinib in a phase II study for TKI-refractory GIST (Br J Cancer 2013;109:2309). **Methods:** In total of 30 pts, predose serum samples were collected at day 1 of cycle 1 (n=30) and cycle 2 (28). Eight serum proteins were assessed by ELISA (Table 1). Mutation analysis was performed via BEAMing from ctDNA, isolated from baseline samples. Pts were classified by quartiles (Q) of biomarker levels and grouped as appropriate for the analyses. **Results:** With dovitinib treatment, FGF23, VEGF, VEGF-A, PIGF, and IL-8 increased by 1.5 fold (p=0.02), 1.3 (p=0.006), 1.3 (p=0.004), 6.0 (p=0.002), and 1.8 (p=0.04), respectively, and sVEGFR2 decreased by 0.8 fold (p=0.001) from baseline. Although baseline serum proteins were not associated with efficacy outcomes, pts whose sVEGFR2 decreased more (Q1-Q3) with dovitinib treatment showed better progression-free survival (PFS) than those with a smaller decrease (Q4; median 4.2 months [mo] vs 2.7 mo; p=0.02). Primary KIT mutations were identified via serum in 5 pts (2 for exon 11, and 3 for exon 9), and 100% concordant with results via tissue. Secondary KIT mutations were detected in 11 pts (37%) via serum: 10 had mutations on exon 17/18 and one on both exon 13 and 17. The presence of secondary mutations showed a tendency for shorter PFS (median 3.4 mo vs 4.2 mo; p=0.11) and significantly associated with shorter overall survival (median 5.5 mo vs 9.8 mo; p=0.02). **Conclusions:** Dovitinib modulates serum levels of circulating proteins involved in VEGF and FGF signaling. The change of sVEGFR2 might predict the outcomes of dovitinib. Secondary KIT mutations could be successfully detected from ctDNA and was associated with poor prognosis.

| Protein name | Abbreviation |
|---|---|
| **Soluble vascular endothelial growth factor receptor 1-2** | sVEGFR 1-2 |
| **Vascular endothelial growth factor and type A** | VEGF, VEGF-A |
| **Placental growth factor** | PIGF |
| **Basic fibroblast growth factor** | bFGF |
| **Fibroblast growth factor 23** | FGF 23 |
| **Interleukin 8** | IL-8 |

**10551 General Poster Session (Board #258), Mon, 8:00 AM-11:45 AM**

**Regorafenib treatment for advanced, refractory gastrointestinal stromal tumor: A report of the U.K. Managed Access Program.** *Presenting Author: Marco Maruzzo, Sarcoma Unit, Royal Marsden Hospital, London, United Kingdom*

**Background:** Tyrosine kinase inhibitors (TKI) have revolutionized the treatment of gastrointestinal stromal tumours (GIST) although most patients develop resistance to first and second-line therapies. Regorafenib, an oral multi-targeted TKI, has demonstrated benefit in previously treated GIST patients. **Methods:** We assessed safety and preliminary activity of regorafenib in patients treated within the Managed Access Programme (MAP). All consecutive patients with advanced GIST who had progressed on or were intolerant of imatinib and sunitinib were recruited from the Royal Marsden Hospital and University College Hospital. We retrospectively reviewed the data for response, toxicity and treatment duration. Response was assessed by RECIST and Choi criteria. Toxicity was graded according to CTCAE v4.0 criteria. **Results:** 20 patients were included in the MAP in the UK between 3/2013 and 9/2013. Median age was 68 (range 45-87), 65% of patients were male. Performance Status was 0-1 for 18 patients (90%), 2 for 2 patients (10%). The median treatment duration was 29 weeks (range 1-50). 18 patients were assessable for response and all patients attained a best response of at least stable disease. At a median follow-up of 6.7 months, there were 2 partial responses (11%) by RECIST and 7 partial responses (39%) according to Choi's criteria. One patient who had a PR on regorafenib had not benefited from previous sunitinib. 3 patients had disease progression and 3 patients discontinued treatment due to unacceptable toxicities; fistulation, myalgia and fatigue. 10 (50%) patients had grade 3 toxicities and 11 (55%) patients required a dose reduction. 5 patients started at reduced dose due to previous significant TKI toxicity, however 2 patients were able to be dose escalated. Median PFS and OS have not yet been reached but notably, prolonged stable disease was seen in 1 patient with exon 9 mutation and 1 patient with PDGFR D842V mutation. **Conclusions:** These data demonstrate encouraging activity of regorafenib in routine clinical practice. The documented adverse events are in line with previous trial data. Updated survival data and the role of RECIST/Choi response criteria in predicting survival will be presented.

**10552 General Poster Session (Board #259), Mon, 8:00 AM-11:45 AM**

**Second primary malignances (SPMs) in patients with gastrointestinal stromal tumors (GIST): The potential influence of imatinib treatment.** *Presenting Author: Anna Estival, Institut Català d'Oncologia Badalona- HU Germans Trias i Pujol, Barcelona, Spain*

**Background:** GISTs are relatively uncommon and predominantly sporadic tumors of the gastrointestinal tract. The high incidence of SPMs observed in patients (p) with GIST (13-20 %), has suggested a possible cause-and-effect relationship between treatment with imatinib and SPMs. Whether this concomitant occurrence is a causal association or a coincidence is not yet resolved. **Methods:** We have retrospectively analyzed the incidence of synchronous and metachronous SPMs, in all p diagnosed with GIST and treated at a single institution between 1997 and 2012. **Results:** A total of 95p were diagnosed with GIST, 18 (19%) of whom developed SPMs. For these 18p, the median age at GIST diagnosis was 61.7 years (range, 27-75). The GIST was located in the stomach in 10p (52.6%) and in the small bowel in 8 (47.4%). The SPMs were more frequent in the colon (4p), breast (4), kidney (3), esophagus (2), lymphoproliferative disease (2), bladder (2), adrenal gland (1), prostate (1), pancreas (1), vocal cord (1) and oligodendroglioma (1). 3p had more than one SPM and only one p had the diagnosis of Neurofibromatosis as a genetic sydrome. Of 14p with metachronous SPMs, GIST was the first tumor in 8p, with a median time of 53.9m (range, 4-169) between tumors. GIST was the second tumor in the remaining 6p, with a median time to diagnosis of 34.3m (range, 5-98). Only 4 of our 18p (22.2 %) received imatinib, two of whom were diagnosed with SPMs after having been treated with Imatinib. **Conclusions:** We have observed SPMs in 19% of p with GIST. The cause of this association is difficult to determine but it seems unrelated to imatinib treatment. The potential non-random association between GIST and other malignances merits further investigation.

**10553 General Poster Session (Board #260), Mon, 8:00 AM-11:45 AM**

**Prognostic value of miR-196, IDO, and AXL in patients (p) with localized gastrointestinal stromal tumors (GIST).** *Presenting Author: Jose Luis Cuadra-Urteaga, Institut Català d'Oncologia Badalona- HU Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, Spain*

**Background:** GIST is the most common gastrointestinal sarcoma. Miettinen criteria (Mc) define the risk of recurrence. Overexpression of miR-196 has been associated with high risk of relapse, metastasis and poor survival. Overexpression of AXL and IDO have been related to resistance to imatinib mesilate (IM). To date, the prognostic value of these molecular markers has not been examined. **Methods:** We retrospectively reviewed 40 p with localized GIST diagnosed between 2003 and 2012 in a single institution. Clinical and pathological variables and the expression levels of miR-196, AXL and IDO were correlated with outcome. **Results:** 52.5% of p were female; mean age was 59.3 years. GISTs were located mainly in the stomach (50%) and small intestine (42.5%). 67.5% were spindle cell tumors; 70% had $<5$ mitoses per 50 high-power fields. Risk of relapse was high for 45% of p. The capsule was broken in 5 p, and resection was incomplete in 2. cKIT mutations were present in exon 9 in 17.5% of p and in exon 11 in 62.5%. Adjuvant IM was administered in 5 p. 22.5% of p relapsed. Median progression-free survival (PFS) was 39.5 months (m) (95% CI, 7-201 m). A negative effect on PFS was observed for Mc high risk ($P=0.001$), cKIT mutation at exon 9 ($P=0.013$), and a broken capsule ($P=0.034$). Overexpression of miR-196 was associated with shorter PFS in all patients ($P=0.001$) and in the subgroups of p with Mc high risk ($P=0.023$) or with cKIT exon 9 mutations ($P=0.012$). No correlation was observed between expression of AXL or IDO and PFS. Median overall survival was not reached. **Conclusions:** Among p with localized GIST, those with Mc high risk, a broken capsule, or cKIT mutations in exon 9 had shorter PFS. Overexpression of miR-196 has emerged as a potential molecular marker of high risk of recurrence in GiST p which merits further investigation.

**10554 General Poster Session (Board #261), Mon, 8:00 AM-11:45 AM**

**Metastatic pattern of late metastases of gastrointestinal stromal tumors and the contribution radiation therapy for disease control.** *Presenting Author: Peter Hohenberger, University Medical Center Mannheim, Department of Surgery, Mannheim, Germany*

**Background:** Metastases to the liver and the peritoneum are the typical locations of tumor spread in GIST. Effective 2nd and 3rd line therapies beyond imatinib lead to advanced GIST as a chronic disease. Newly arising metastases after 4 years of being stable on TKIs is a rare event. We were interested to analyze the pattern of late metastases and evaluated the effects of radiation therapy to control bone and soft tissue lesions. **Methods:** 731 pts with biopsy proven GIST were treated and followed-up since 2004 with a median follow-up 43.6 months (range, 1-274 mos); data were prospectively documented. There were 394 females (53.9%). 101 (13.8%) pts. presented with M1 disease initially. Of the remaining 630 pts, 358 pts (56.8%) developed tumor recurrence. **Results:** Median time to disease recurrence was 22 months, (range, 2-144) and 312/358 pts (87%) developed metastases within the abdomen: liver n=96, peritoneal n=97, liver+peritoneal n=78, locoregional n=10, locoreg.+hep/per n=21. In 35 pts, extraabdominal sites were found (biopsy 29 pts): bone n=19, multiple sites n=12; soft tissue (STS) n=9, lung/pleura n=7, spleen n=1, brain n=1. All of these locations occurred after at least liver or peritoneal metastases with a median RFS of 58 months (range, 27-105 months). 26 pts had at least two lines of therapy prior to 'atypical' metastases. The median OS of this cohort is 118 months (range, 40-264 months) and 11 pts are still alive. 4/9 pts with STS and 21 sites of pts with bone metastases underwent radiation therapy of 45- 56 Gy, all in parallel to continued TKI therapy. Only one patient showed PD after RT at 6 months. The average duration of local control is 22 months. No unusual mutational pattern was detected in the primary tumors. Interestingly, in 7 pts a 2ndary exon 13 V654A mutation could be found. **Conclusions:** Extraabdominal metasteses of GIST are a rare and late event in the course of disease and occurs only after long-lasting therapy with TKIs. These 'atypical' metastases do not indicate rapid disease progression and may be controlled by radiation therapy if located in the bones or soft tissues. Whether continued TKI therapy contributes to the effective use of RT warrants further exploration.

**10555 General Poster Session (Board #262), Mon, 8:00 AM-11:45 AM**

**Effect of secondary KIT mutations on growth of GIST cells in the absence of selective pressure by imatinib in isogenic models of imatinib resistance.** *Presenting Author: Susanne Grunewald, Department of Medical Oncology, West German Cancer Center, University Hospital Essen, University Duisburg-Essen, Essen, Germany*

**Background:** Secondary mutations of KIT are commonly found in progressing lesions of imatinib (IM)-resistant GIST and represent a major factor of drug resistance. Development of salvage treatments is complicated by the genomic heterogeneity of secondary mutations. We hypothesize that resistant clones require selective pressure to overgrow sensitive GIST and that mixed sensitive/resistant populations may still display drug sensitivity. **Methods:** Based on parental IM-sensitive GIST-T1 (KIT Ex11 57bp del) we have developed IM-resistant isogenic sublines harbouring critical secondary mutations (T670I, D816E, D820A, A829P). Each subline was transduced with specific marker proteins allowing detection of resistant subclones by FACS or IHC. Proliferation and cell viability for individual cell lines and mixed cell populations (+/- IM) were evaluated in vitro and in vivo. **Results:** IM-resistant cell-lines grew faster in the presence of IM compared to no treatment. Resistant sublines were xenogenic in nude mice but were overgrown by parental GIST-T1 in mixed populations in the absence of IM. Tumors derived from mixed GIST populations contained high levels of resistant clones in IM-treated mice. To estimate the proportion of resistant cells within a population necessary to display resistance, we mixed resistant sublines with sensitive cells at known percentages. Sensitivity to IM was lost when the fraction of resistant cells was $>50\%$ compared to parental cells (3- and 6 day time point). **Conclusions:** GIST with acquired resistance likely harbor mixed populations of drug-sensitive and resistant cells which exhibit differential growth rates. Our studies show that tumor populations with low levels of resistant clones may still respond to treatment. Secondary KIT mutations confer a growth disadvantage in the absence of IM. Selective pressure by IM results in partial KIT inhibition which may reduce the oncogenic stress of kinase hyperactivation in GIST harbouring secondary mutations. Altering the selective pressure could therefore delay the emergence of resistant clones and our models could be applied toward optimization of drug selection and dosing strategies.

**10556 General Poster Session (Board #263), Mon, 8:00 AM-11:45 AM**

**Predictive ability of blood neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio in gastrointestinal stromal tumors (GIST).** *Presenting Author: Jennifer M. Racz, Department of Surgical Oncology, University of Toronto, Toronto, ON, Canada*

**Background:** The immune response, specifically the neutrophil-to-lymphocyte ratio (NLR), has recently been shown to be prognostic in untreated, primary GIST. Moreover, the platelet-to-lymphocyte ratio (PLR) has been shown to predict outcome in several gastrointestinal tumors; however, no studies have examined its predictive ability in GIST. This study serves to evaluate the prognostic utility of NLR and PLR in patients undergoing surgical resection for GIST. **Methods:** All patients who underwent surgical resection for primary, localized GIST from 2001 to 2011 were identified from a prospectively maintained database. Demographic profile, clinicopathologic variables, laboratory values and recurrence rates were analyzed. NLR and PLR were both assessed pre-operatively. Survival curves were calculated by the Kaplan-Meier product limit method and compared by the log-rank test. Univariate and multivariate Cox proportional hazard regression models were used to identify associations with outcome variables. High/low NLR and PLR were determined using optimization techniques, and defined as $\geq$2.04/$<$2.04 and $\geq$245/$<$245, respectively. **Results:** 93 patients were included. On univariate analysis, PLR was associated with recurrence-free survival (RFS) (HR .271, 95% CI .078 – .938, p = .039). PLR was also associated with RFS on multivariate analysis (HR .048, 95% CI .003 – .884, p = .041). Patients with low PLR had 2- and 5-year RFS of 94 and 84%, compared with 57 and 57% in those with high PLR. RFS in patients with mitotic rate $\leq$5/50 HPF with low PLR was significantly longer than in those with high PLR (p = .007). Similarly, RFS in patients with tumor size $<$5 cm with low PLR was significantly longer than in those with high PLR (p = .004). NLR was not associated with either RFS (p = .226) or overall survival (p = .994). **Conclusions:** Although there was no association between NLR and survival, a low PLR was associated with improved RFS, especially in tumors with mitotic rate $\leq$5/50 HPF or $<$5 cm. The independent prognostic ability of PLR to predict disease recurrence in these patients suggests that it may play a role in risk stratification schemes when deciding which patents will benefit from adjuvant therapy.

**10557 General Poster Session (Board #264), Mon, 8:00 AM-11:45 AM**

**The relationship between overall survival (OS) and progression-free survival (PFS) in gastrointestinal stromal tumor (GIST).** *Presenting Author: Ipek Özer Stillman, Evidera, Lexington, MA*

**Background:** OS is the gold-standard measure of treatment efficacy in cancer. However, PFS is often used as primary endpoint when OS follow-up is long and/or post-progression therapy is common. In unresectable and/ or metastatic GIST, a previous study showed a moderately strong linear relationship between median PFS (mPFS) and median OS (mOS). This study presents an updated analysis. **Methods:** A systematic literature review identified fourteen clinical trials and five observational studies of sufficient quality from Jan 1995 to Dec 2013 (29 total treatment arms; 2,189 patients). These studies encompassed first and later lines of treatment with targeted therapies. Scatter plots and linear regressions (weighted by the number of patients) were used to evaluate the relation between mOS and mPFS for all arms combined. Sensitivity analyses investigated the impact of treatment line, treatments, and study quality score. **Results:** mOS and mPFS (in months) were positively related with an overall correlation of 0.912 in linear regression (slope = 2.083, standard error [SE] = 0.178; intercept = 5.618, SE = 2.436; adjusted $R^2$= 0.830). Eliminating four influential datapoints using the Difference in Beta Scaled, reduced the estimates for association, though the association was still strong (overall correlation = 0.724). The correlation was greater in later lines of therapy (first line = 0.518; second line = 0.797; third- and later-line = 0.702). **Conclusions:** This study showed a strong relationship between mPFS and mOS in GIST, especially in later lines of therapy. The number of studies included is relatively small and some treatment arms have $<$50 patients, which is not unexpected in a rare disease like GIST. While these findings provide some insight into PFS as a surrogate marker for OS, analyses of patient level data are needed to fully establish its validity in GIST.

**10558 General Poster Session (Board #265), Mon, 8:00 AM-11:45 AM**

**Extra-gastrointestinal stromal tumors (eGISTs): Experience of a cooperative group.** *Presenting Author: Matias Chacon, GATE-D, Buenos Aires, Argentina*

**Background:** eGIST occurs in regions such as omentum, mesentery, retroperitoneum and undefined abdominal and pelvis locations. Some authors hypothesized that the origin are Cajal interstitial cells from the abdominal cavity or the tumors are mural GISTs with extramural growth. Clinical, pathology and molecular profile of eGIST is similar to GISTs. Some publications show higher size and mitotic index than GIST. eGISTs are not consider in risk stratification consensus. Differential diagnosis of abdominal or pelvis mass with other tumors requires expert pathologist. The aim of the study is to evaluate clinical characteristics and mutation profile of consecutive eGISTs from a prospective database. **Methods:** Data from patients (pts) with histologic diagnosis of GIST with no evidence of gastric or intestinal involvement was analyzed. Demographics and medical information was obtained from an Argentinean GIST prospective database. Mutation analysis was performed with HPLCA. Descriptive statistical analysis was used. **Results:** Between 2004 and December 2013, 63 pts with eGISTs were included. Median age was 56 years old (16-87). Thirty three (52%) pts were female. Primary sites were: retroperitoneum 13 pts (21%), mesentery and omentum, 22 pts (35%), pelvis 17 (27%), peritoneum 9 pts, thoracic wall and pleura in two pts. Complete surgical resection was performed in 14 pts (35%). Initial pathology report was other than eGIST in 19 pts (30%). Median size tumor was 8 cm (1-39) and 47% had $>$10 mitoses/50 HPF. Positive C-KIT was in all pts. Median time to recurrence in pts was 11 months (1-12). Liver was the most frequent site of relapsed (9 pts). Exon 9,11,13, 17 KIT and 12, 14, 18 PDGFR mutations were evaluated in 24 pts. Exon 11 KIT deletion was the most frequent mutation (5 pts) and 12 (50%) were Wild type KIT and PDGFR. Imatinib was the systemic in 42 pts. Objective clinical benefit was 60%. **Conclusions:** eGISTs is a rare entity. In our series there was a female predominance located mostly in mesentery and omentum. Higher size and mitotic index was observed. One third of pts were complete resected and pathologic misdiagnosis. Better pre-operative approach should be required in this group of pts and more knowledge is necessary to improve outcome.

**10559 General Poster Session (Board #266), Mon, 8:00 AM-11:45 AM**

**Relationship of grade to prognosis in localized primary angiosarcoma of the breast (PAOB).** *Presenting Author: Manjari Pandey, The University of Tennessee Health Science Center/The West Clinic, Memphis, TN*

**Background:** PAOB is rare and institutional series have provided conflicting data on the impact of grade on prognosis. **Methods:** Using case listing session of SEER 18 (1973-2010) we examined outcomes for patients with PAOB. Analyses were conducted with SEER*Stat 8.1.2, Microsoft Excel 2007 and GraphPad Prism 6. Comparisons were made using the chi-squared test and log-rank test (Mantel-Cox); all p values were 2-sided. **Results:** 226 women with PAOB were identified; median age 49 (range 15-107); 82% white. 72% had localized disease, 15% regional disease, 7% distant disease; 14% had grade 1, 24% had grade 2 and 30% grade 3 disease. Median OS for patients (pts) with localized, regional, and distant disease was 172, 24 and 16 months, respectively ($p<0.001$). Median OS for pts with localized grade 1 and 2 disease was not reached versus 36 months for grade 3 disease ($p<0.0001$); 3-yr OS was 89% v 47%. There was a strong trend for pts with grade 3 disease to undergo mastectomy (44% v 23%) ($p=0.0695$) and 24% of all pts received radiation. Radiation did not improve survival for localized grade 1 and 2 disease ($p=0.6759$) or grade 3 disease ($p=0.5888$); surgery and grade subgroups were too small for meaningful comparisons regarding radiation. **Conclusions:** Histologic grade is a significant predictor of survival for patients with localized PAOB. Regardless of grade, adjuvant radiation did not confer a survival benefit for pts with localized disease.

**10560 General Poster Session (Board #267), Mon, 8:00 AM-11:45 AM**

**A phase I/II study of azacitidine in combination with temozolomide in patients with unresectable or metastatic soft tissue sarcoma or malignant mesothelioma.** *Presenting Author: Gleneara Elizabeth Bates, Columbia University Medical Center, New York, NY*

**Background:** Soft tissue sarcomas are rare tumors, for which complete surgical resection offers the best chance of survival. However, two thirds of diagnosed tumors are unresectable and/or metastatic, with a median survival of 12 months, and chemotherapy is the only treatment option. Temozolomide has been used in soft tissue sarcomas and has shown the most activity in leiomyosarcomas; response rates ranged from 5-15%. Azacitidine has not previously been used in the treatment of soft tissue sarcomas. Because of known effects of hypomethylating agents on caspase-8 genes, and the DNA repair gene MGMT involved in the action of temozolomide, we hypothesized that incorporating azacitidine into the treatment of soft tissue tumors with temozolomide could enhance its efficacy. **Methods:** Between June 2008 and July 2012, 28 patients with soft tissue sarcomas were enrolled. Among the 25 patients who completed the treatment, median age was 61 (range 41-83), 13 male and 12 female; 4 liposarcoma, 2 myxoid liposarcoma, 1 synovial sarcoma, 1 granular cell sarcoma, 1 epithelioid mesothelioma, 1 Ewing's sarcoma, 1 hemangioepithelioma, 7 leiomyosarcoma, 1 spindle cell sarcoma and 6 unspecified sarcoma. Treatment consisted of 10-11 cycles of azacitidine and temozolomide. Dosing: Azacitidine: dose level 1: 25mg/m$^2$ SQ qd; dose level 2: 50mg/m$^2$ SQ qd; dose level 3: 75 mg/m$^2$ SQ qd; combined with temozolomide: 200 mg/m$^2$PO qd x 5; both on days 1-5 of a 28-day cycle. Toxicity was graded by CTCAE IV. **Results:** Median number of cycles administered: 2 (range 1-6). There were nine drug-related adverse events experienced by 3 or more patients, none of which were dose-limiting. The maximum tolerated dose was 200mg/m$^2$ temozolomide and 75 mg/m$^2$ azacitidine. 15 patients died from their disease 2-59 months after enrollment; 10 patients are alive with stable disease. The median overall survival was 22 (95% CI:9-59) months, with a 1-year survival of 64% (95% CI:42-79%). **Conclusions:** We have not yet determined the antitumor effectiveness of this combination. These encouraging data show that temozolomide combined with azacitidine can be administered in their full doses with no dose-limiting toxicities. Clinical trial information: NCT00629343.

**10561 General Poster Session (Board #268), Mon, 8:00 AM-11:45 AM**

**Radiologic signs of adipocytic maturation (AM) in dedifferentiated liposarcoma (ddLPS) patients (pts) treated with trabectedin (T): Correlation with disease control.** *Presenting Author: Sree Harsha Tirumani, Dana-Farber Cancer Center Institute/Brigham and Women's Hospital, Boston, MA*

**Background:** T has been shown to induce histological AM in myxoid liposarcoma (mLPS), but this has not previously been described in ddLPS. In this retrospective analysis, we analyzed the imaging studies in pts with various LPS subtypes (ddLPS, mLPS, pleomorphic LPS (pLPS), unclassified LPS (uLPS)) treated with T to see whether radiologic AM is detectable in clinical assessments. **Methods:** This single institution study, which enrolled 55 pts with LPS, was conducted as part of an expanded access trial of T (NCT00210665). Assessable pre- and post-T imaging studies were available for 48 pts (33M, 15F), including 24 ddLPS, 16 mLPS, 4 pLPS, and 4 uLPS. Mean age at diagnosis was 50 yr (range 24 – 74 yr). T was administered until disease progression, and restaging scans were performed approximately every 6 weeks. Radiologic evidence of AM (change of tumor to fat density), changes in lesion density and size, and best response per RECIST 1.1 were assessed at final T cycle. Clinical benefit and rate (CBR) was based upon CR, PR or prolonged SD ($\geq$ 6 months). **Results:** Median T treatment duration was 11 mos (range, 1-44 mos). T was discontinued in 3 pts (5%) due to adverse events. Best response was PR in 8 (15%; 7 mLPS, 1 ddLPS), SD in 31 (56%; 9 mLPS, 14 ddLPS, 4 uLPS, 2 pLPS) and PD in 11 (20%; 9 ddLPS, 2 pLPS) pts. Radiologic evidence of AM was noted in 8 pts (15%; 6 ddLPS, 2 mLPS), all of whom had SD as best response. Decrease in tumor density was noted in 13 pts (27%; 9 mLPS, 4 ddLPS). Median T treatment duration was 6 months (1-44 mos) in all ddLPS and 13 mos (6-44 mos) in ddLPS with AM. There was a statistically significant correlation between radiologic AM and SD in ddLPS (p=0.0481; Fisher's exact test). Median progression-free survival was 6.5 mos (1 – 44 mos) for all patients and 6 mos for ddLPS. CBR was 60% in all pts and 50% in ddLPS. **Conclusions:** Radiologic AM in ddLPS pts treated with T is seen more often in patients receiving the drug for $\geq$6 mos, and is correlated with objective disease control.

**10562 General Poster Session (Board #269), Mon, 8:00 AM-11:45 AM**

**Detection of *MDM2* gene amplification in soft tissue sarcoma by FISH.** *Presenting Author: Hiroaki Kimura, Department of Orthopedic Surgery, Graduate School of Medical Science, Kanazawa University, Kanazawa, Japan*

**Background:** The *MDM2* (murine double minute-2) gene is an oncogene whose expression plays important roles in controlling the cell cycle and tumorigenesis. The *MDM2* is located on chromosome 12, and has been reported to be amplified in a subset of malignant tumors. In this study, we examined soft tissue sarcomas (STS) specimens for *MDM2* gene amplification by fluorescent in situ hybridization (FISH). **Methods:** 137 cases of formalin-fixed and paraffin-embedded specimens were used for this study. Surgical pathology reports, HE sections, and previous immunohistochemical slides were carefully reviewed. The pathological diagnoses were shown in the Table. The FISH probe for *MDM2* was co-hybridized with CEP12 probe that is specific for chromosome 12. The average number of *MDM2* and CEP12 ratio was calculated and a ratio>2.0 was considered amplified. **Results:** Of 137 STS, *MDM2* amplification was detected in 33 cases (24%). Of the WDLS/ALT, 93% (26/28) showed amplification of *MDM2*. A total of 4 of 4 (100%) DDLS showed amplification of *MDM2*. Two of 10 MPNST and 1 of 7 myxofibrosarcoma also showed amplification of *MDM2*. **Conclusions:** WDLS/ATL are often difficult to distinguish morphologically from benign lipomatous tumors, while DDLS may be challenging to distinguish from other high-grade sarcomas, especially on needle biopsy specimens that lack areas of WDLS. With the increased use of small needle core biopsy in which only limited tissue is available for histologic evaluation, increased utilization of molecular studies to identify the characteristic molecular aberrations of WDLS and DDLS may prove useful in clinical practice. *MDM2* amplification by FISH was a useful adjunct in the diagnostic approach for WDLS vs benignlipomatous tumors and DDLS vs pleomorphic or spindle cell sarcomas.

| Diagnosis | | FISH-positive |
|---|---|---|
| Liposarcomas | | |
| ALT/WDLS | 28 | 26 |
| MXLS | 28 | 0 |
| DDLS | 4 | 4 |
| MFH | 19 | 0 |
| Leiomyosarcoma | 18 | 0 |
| Synovial sarcoma | 12 | 0 |
| MPNST | 10 | 2 |
| Myxofibrosarcoma | 7 | 1 |
| Rhabdomyosarcoma | 7 | 0 |
| Low-grade fibromyxoid sarcoma | 4 | 0 |
| | 137 | 33 |

Abbreviations: ATL, atypical lipomatous tumor; WDLS, well-differentiated liposarcoma; DDLS, dedifferentiated liposarcomas; MFH, malignant fibrous histiocytoma; MPNST, malignant peripheral nerve sheath tumor.

**10563 General Poster Session (Board #270), Mon, 8:00 AM-11:45 AM**

**Phase I study of NBTXR3 nanoparticles, in patients with advanced soft tissue sarcoma (STS).** *Presenting Author: Sylvie Bonvalot, Institut Gustave Roussy (IGR), Villejuif, France*

**Background**: Functionalized hafnium oxide nanoparticles (NBTXR3) have been developed as selective radioenhancers, which may represent a breakthrough approach for the local treatment of solid tumors. This is a unique approach where crystalline nanomaterials with high electron density when exposed to radiotherapy, can allow penetrate into the cell and make feasible the absorption/deposition of a high energy dose within the tumor cell. A phase I/II trial was implemented in patients with locally advanced STS. **Methods**: Patients (pts)received a single intratumor (IT) injection of NBTXR3, volume escalated, followed by 50Gy RTx (see Table). Primary endpoints include feasibility of the IT implantation and safety. Secondary endpoints focus on efficacy such as pathological and RECIST response, IT residency of NBTXR3 over all the RTx period and operability. **Results**: Enrollment was completed for volume 1, 2, and 3 (15 pts). Feasibility of the IT injection was confirmed. The treatment was safe with no SAE, no early DLT and allowed the pts for completion of the planned RTx schedule. No grade 3-4 toxicity occurred, main grade 1-2 toxicities related to NBTXR3 were injection pain/reaction (4 pts), pyrexia (2 pts), abdominal pain (1 pt), pruritus (1 pt) and paresthesia (1 pt). Results demonstrated that a single injection of NBTXR3 provides adequate bioavailability of NBTXR3 IT over five weeks of radiotherapy. No leakage of NBTXR3 to the adjoining healthy tissues was observed. Further, NBTXR3 persistence was established by CT scan before surgery. **Conclusions**: Injection of NBTXR3 was well tolerated. All pts received the planned radiotherapy (50 Gy/25 fractions/ 5 weeks) followed by wide surgical resection of the sarcoma. NBTXR3 with RTx showed a very good safety profile. Encouraging signs of antitumor activity were observed in different sarcoma subtypes, such as undifferentiated sarcoma, rhabdomyosarcoma, and synovial sarcoma, which constitutes a promising feature for this subset of pts whose primary tumor is locally advanced and has an important risk of relapse. Clinical trial information: NCT01433068.

| Volume level | Pts | Tumor volume cc | Injected volume mL |
|---|---|---|---|
| **1** | 6 | 55-1,814 (503) | 1.4-45 (12) |
| **2** | 6 | 85-3,682 (1127) | 4.2-184 (56) |
| **3** | 3 | 360-885 (590) | 36-100.5 (60) |
| **4** | Screening | | |

**10564 General Poster Session (Board #271), Mon, 8:00 AM-11:45 AM**

**Synovial sarcoma: Evaluation of response to treatment with gemcitabin and docetaxel.** *Presenting Author: Sausan Abouharb, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Synovial Sarcoma (SS) is one of the more common subtypes of soft tissue sarcomas, comprising 8-10% of this entity. It is well known that SS responds well to adriamycin/ifosfamide (AI) therapies, however responses to gemcitabine/docetaxel (GT) combination have not been well documented, although commonly used in practice. This study aimed to evaluate response to GT in patients with SS. **Methods:** We retrospectively reviewed medical records of patients diagnosed with SS from 2000 to 2012. All patients had confirmed SS by pathology review. Only patients who were metastatic and treated with GT concurrently were included. **Results:** The study included 51 patients with metastatic disease who received GT concurrently. Majority of patients were white (69%), with a mean age of 42 years (SD 15) when receiving GT. Median time from initial diagnosis to first metastasis was 15 months. Median overall survival from first metastasis was 2.3 years (95% CI 1.8-3.0 years). The majority of patients (96%) had received A and/or I prior to GT therapy, and 86% had documented disease progression prior to start of GT. 21% of patients were taken off GT due to side effects or other reasons. 79% were taken off due to progressive disease. As best response, 10% of patients (n=4) had: complete response (CR) (n=1), near CR (n=1) or partial response (PR) (n=2). 33% (n=14) had stable disease, and 57% (n=24) had disease progression (DP). 9 patients had missing data. Overall 43% may have derived some clinical benefit, and 57% had DP. Median duration of GT therapy was 2 cycles (range 1-3); median of 1.7 months (range 1.2-3.0) in patients who progressed; 4 cycles (range 2-8), median 3.0 months (range 1.6-10.0) in patients with SD, and 8 cycles (range 6-11); median 6.1 months (range 4.7-10.5) in patients with CR/near CR/PR. **Conclusions:** This data shows some efficacy of GT in metastatic SS. Rare responses were seen, and due to limited availability of other active agents in this disease it may not be unreasonable to consider GT after other lines of therapy, (such as A/I, dacarbazine, pazopanib) have been used.

**10565 General Poster Session (Board #272), Mon, 8:00 AM-11:45 AM**

**Clinical features, outcomes, and prognostic factors in patients with extraskeletal osteosarcoma.** *Presenting Author: Sheila Thampi, University of California, San Francisco, San Francisco, CA*

**Background:** Extraskeletal osteosarcoma (ESOS) is a rare subtype of osteosarcoma. We investigated patient characteristics, overall survival for ESOS as compared to skeletal osteosarcoma, and prognostic factors for ESOS. **Methods:** We identified cases of high-grade osteosarcoma with available data regarding tissue of origin (bone vs. soft tissue) in the Surveillance Epidemiology and End Results database from 1973 to 2009. Demographics were compared using chi-squared tests or t-tests. Overall survival was estimated using Kaplan-Meier methods and modeled using Cox proportional hazards methods. Competing risk analysis was utilized to determine differences in incidence of death from cancer. **Results:** 256 / 4,173 (6.1%) patients with high-grade osteosarcoma had ESOS. Patients with ESOS were more likely to be older, have axial tumors, have regional lymph node involvement ($p<0.0001$ for all comparisons), and be female ($p=0.002$). On univariate analysis, five-year overall survival for those with ESOS was inferior [37% (95% CI 30.6 to 43.3) vs. 50.8% (95%CI 49.1 to 52.50; $p<0.0001$]. However, on competing risk analysis, we found no difference in the cumulative incidence of death due to cancer between extraskeletal or skeletal osteosarcoma. This discrepancy was due to a significant interaction between age and tissue of origin such that older patients with ESOS had superior outcomes compared to older patients with skeletal osteosarcoma. On multivariate analysis of overall survival, ESOS was found to be favorable after controlling for differences in metastatic status, age, tumor site, gender, and year of diagnosis (hazard ratio 0.75; 95% CI 0.62 to 0.90; $p=0.002$). Independent adverse prognostic factors in patients with ESOS include distant metastatic disease, larger tumor size, older age, and axial tumor site. **Conclusions:** This analysis reveals distinct patient characteristics in ESOS but similar prognostic factors between ESOS and skeletal osteosarcoma. Contrary to previous reports, the incidence of death from osteosarcoma is similar between both types of osteosarcoma. While older patients have poor overall survival with high-grade osteosarcoma, extraskeletal origin predicts better outcomes.

**10566 General Poster Session (Board #273), Mon, 8:00 AM-11:45 AM**

**Patterns of chemotherapy administration in soft tissue sarcoma (STS) and impact on overall survival (OS): A National Cancer Database (NCDB) analysis.** *Presenting Author: Sujana Movva, Fox Chase Cancer Center, Philadelphia, PA*

**Background:** Patients with AJCC stage III STS (large, deep, high grade) have an expected OS of approximately 50% at 5 years. A meta-analysis of adjuvant chemotherapy in STS showed an absolute benefit in OS for the chemotherapy group. Despite these results, patterns of care and opinions with regard to adjuvant chemotherapy vary. Our aims were to identify factors associated with receipt/non-receipt of chemotherapy, and their impact on OS in patients with high risk STS. **Methods:** Individuals diagnosed with stage III STS between 1998-2010 were identified from the NCDB. Excluded from the analysis were patients who did not undergo surgery for the primary tumor and histologies considered resistant to chemotherapy. Chi-square tests and multivariate logistic regression were used to compare sociodemographic and tumor factors between the groups receiving and not receiving chemotherapy. All-cause mortality was analyzed using the Kaplan-Meier method and Cox proportional hazards regression. The survival analysis cohort was limited to patients diagnosed between 2003-2005 based on availability of survival and comorbidity data. **Results:** 12,198 individuals with stage III STS were identified. 29% of patients received chemotherapy. Patients who were <40, privately insured, earned a higher income, had no comorbidities, had synovial histology, and whose tumors were > 10 cm were more likely to receive chemotherapy on both univariate and multivariate analysis. Race, education level and type of treating facility were not significantly associated with receipt of chemotherapy. Median unadjusted OS in the chemotherapy and non-chemotherapy groups were 83.9 and 48.5 months respectively ($P<0.0001$). The benefit for chemotherapy was also seen on adjusted analysis, (HR 0.77; $P<0.0001$), when controlling for sociodemographic and tumor factors (15 total factors including age, comorbid conditions, race and insurance status). **Conclusions:** Our analysis demonstrates an OS benefit for chemotherapy in stage III STS after adjusting for comorbidities. To our knowledge this is the first retrospective OS analysis restricted to stage III patients that also adjusts for socioeconomic status.

**10567 General Poster Session (Board #274), Mon, 8:00 AM-11:45 AM**

**Phase II study of eribulin mesylate in patients (pts) with advanced soft tissue sarcoma (STS).** *Presenting Author: Yoichi Naito, National Cancer Center Hospital East, Chiba, Japan*

**Background:** Eribulin mesylate is a non-taxane microtubule dynamics inhibitor that has demonstrated an activity in pts with various types of tumor. The efficacy and safety of eribulin mesylate were evaluated in pretreated pts with advanced STS. **Methods:** This was an open-label, multi-center, single-arm, phase II study in Japanese pts with advanced STS. Pts with high or intermediate grade STS had received at least one standard chemotherapy, and also had ECOG performance status 0-1. Progressive disease had to be documented within the last 6 months. Eribulin mesylate (1.4 mg/m$^2$) was administered as a 2-5 minute intravenous infusion on day 1 and 8 of 21-day cycle. The primary endpoint was the progression-free rate at 12 weeks ($PFR_{12wks}$) in 2 independent strata of pts with STS: adipocytic (ADI) or leiomyosarcoma (LMS), and histological types other than ADI/LMS (OTH). Secondary endpoints included response, survival and safety. $PFR_{12wks}$ and responses were assessed by independent review using RECIST criteria. **Results:** A total of 52 pts were enrolled, and 51 pts received eribulin (ADI:16 pts, LMS: 19 pts and OTH:16 pts). Median age was 52 (range: 28-73) and 13 pts (25.5%) was intermediate grade and 38 pts (74.5%) high grade. Fifty-one pts (100.0%) had received anthracycline and 36 pts (70.6%) ifosfamide as prior therapeutic chemotherapy. The $PFR_{12wks}$ in ADI/LMS was 60.0% (21/35 pts; 95% CI 42.1-76.1%), OTH 31.3% (5/16 ; 11.0-58.7), and all subtypes (ALL) 51.0% (26/51 ; 36.6-65.2). The median progression free survival in ADI/LMS was 5.5 months (mo) (95% CI 2.8-8.2 mo), OTH 2.0 mo (1.2-4.1), and ALL 4.1 mo (2.6-5.6). There was no complete response (CR) or partial response (PR) in this study. Stable disease (SD) in ADI/LMS was 80.0%, OTH 50.0%, and ALL 70.6%. The clinical benefit rate (CR + PR + SD>11 weeks) in ADI/LMS was 74.3%, OTH 50.0%, and ALL 66.7%. 1-year overall survival rate in ADI/LMS was 60.0%, OTH 50.0% and ALL 56.9%. The most frequent treatment-related Grade 3 or above toxicities were neutropenia (86.3%), leukopenia (74.5%), lymphopenia (31.4%), anaemia (11.8%) and febrile neutropenia (7.8%). **Conclusions:** Eribulin has shown clinical activity in advanced pre-treated STS patients and it is well tolerated with no new safety signals. Clinical trial information: NCT01458249.

**10568 General Poster Session (Board #275), Mon, 8:00 AM-11:45 AM**

**Alliance A091103: A multicenter phase II study of the angiopoietin-1 and -2 peptibody trebananib (AMG386) for the treatment of angiosarcoma (AS).** *Presenting Author: Sandra P. D'Angelo, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** AS is a rare, aggressive, malignant endothelial cell tumor constituting 1-2% of all soft tissue sarcomas with 35% 5-yr survival. Cytotoxic agents have demonstrated ~15% response rates (RR). Gene-array data has revealed up-regulation of endothelial associated genes, including active members of the angiopoietin system [eg, Tie2 and Angiopoietin 2 (Ang2)]. Trebananib (AMG386) is a novel agent targeting Ang1 and Ang2. **Methods:** Metastatic/unresectable AS, adequate performance status, organ function, and measurable disease (RECIST v1.1) were required. Trebananib 30mg/kg d1, 8, 15, and 22 was repeated q28 days until progressive disease (PD) or unacceptable toxicity. The primary endpoint is confirmed RR (partial or complete by RECIST v1.1); 1 response in 12 pts expanded enrollment to 25. Secondary endpoints include: toxicity, progression-free survival (PFS), and overall survival (OS). Correlatives include: 1) baseline expression of Ang2/Tie2 by immunohistochemistry (IHC), 2) serum levels of Ang1, 3) pre- and post-treatment phospho-receptor tyrosine kinase and 4) MYC/FLT4 amplification status. **Results:** 16 pts were enrolled from 5 participating sites [median age 68 yrs (24-91), 38% male, median number of prior therapies 2.5 (1-7)]. No confirmed responses were observed in 14 evaluable pts; one pt had an 18% decrease. 4/16 had SD, 12/16 have PD; 8/16 have died with a median follow-up of 2.9 mos (0.9-12.7). Estimated median and 12-week PFS rate are 7 weeks (95% 6-8) and 25% (95% CI 11-58%), respectively. Median OS is 28 weeks (95% CI 17-48). Common grade 3-4 adverse events include (pts): thrombosis (2), syncope (1), anemia (1). Two pts died of reasons unrelated to treatment (cardiac, respiratory failure). **Conclusions:** Trebananib was well-tolerated in this phase II study of AS, with no partial/complete responses. Prolonged PFS was observed in 4 pts, lasting 3.5-5.5 mos. Forthcoming results of the associations of correlatives (eg, Ang/Tie2 IHC expression and serum Ang levels) with outcome may help identify patients most likely to benefit. Clinical trial information: NCT01623869.

**10569 General Poster Session (Board #276), Mon, 8:00 AM-11:45 AM**

**Predictive biomarkers of trabectedin (TR) and olaparib (OL) synergism in preclinical models of bone and soft tissue sarcoma (BSTS).** *Presenting Author: Ymera Pignochino, Sarcoma Unit, Division of Medical Oncology, IRCCS Istituto di Candiolo, Candiolo, Italy*

**Background:** TR is a DNA damaging agent as 2nd line-therapy in STS. We speculated that its antitumor activity could be potentiated by a "synthetic lethality" approach targeting key molecules involved in DNA repair. PARP-1 inhibition impedes DNA repair promoting cell death.We tested the antiproliferative effect of PARP inhibitor OL in combination with TR against 20 BSTS cell lines and explored their mechanism of action. **Methods:** The combination of OL and TR was tested against 20 BSTS cell lines. Drug synergism was evaluated by Calcusyn software. Subcutaneous (s.c) and orthotopic BSTS models were obtained in NOD/SCID mice and tumor growth was monitored by caliper and by *in vivo*imaging, respectively. DNA repair machinery was studied by realtime PCR, western blot and immunocytochemistry. Silencing of PARP-1 was induced with specific siRNA. Cell cycle, apoptosis and P-H2AX were evaluated by flow cytometry. Damaged DNA was studied by comet assay. Pearson's correlation, t distribution and p value were calculated for statistical analysis. **Results:** We observed a strong synergism of TR-OL in 18/20 cell lines reaching significant dose reduction index (5.5-1.001). There is a 15-fold range of sensitivity among BSTS histotypes (Ewing's sarcoma > liposarcoma > leiomiosarcoma> osteosarcoma > UPS > fibrosarcoma). Synergism is related with increased G2/M cell cycle arrest, apoptosis and DNA damage. The antitumor and antimetastatic effects of TR-OL were confirmed in s.c and orthotopic models, respectively. Real time PCR, western blot and immunocytochemistry analysis demonstrated that PARP-1 expression and activation are higher in responsive cell lines vs. less sensitive ones. To confirm these data we down-modulated PARP-1 with silencing experiments showing a reduced TR-OL synergism (25±2%, $p<0.05$). mRNA expression analysis of DNA repair machinery in 20 BSTS cell lines showed that PARP-1, RAD51 and BRCA1 are significantly related to synergism. These data were confirmed at protein level in selected experiments. **Conclusions:** PARP-1, RAD51 and BRCA-1 are predictive of TR and OL synergism in BSTS preclinical models, and could represent good candidate biomarkers to be evaluated in clinical trials.

**10570 General Poster Session (Board #277), Mon, 8:00 AM-11:45 AM**

**Late relapse in soft tissue sarcoma: Prognostic factors for recurrence after 3 years.** *Presenting Author: Karim Boudadi, University of Michigan, Ann Arbor, MI*

**Background:** In patients (pts) with localized soft tissue sarcoma (STS), 80% of relapses occur within the first 2 years (yrs) after definitive resection. However, relapse after 3 yrs is not uncommon, and limited data exists to identify higher risk pts. While the possibility of late relapse suggests prolonged surveillance, we performed a retrospective study to identify prognostic factors for relapse > 3 yrs that may help guide long-term follow-up (f/u). **Methods:** A cancer center-based registry identified adult STS pts seen from 1999-2010 at University of Michigan. Pts with resected localized STS with >3 yrs of f/u and who remained disease free > 3 yrs were eligible. The primary endpoint was time-to-relapse, defined from resection to disease relapse. Pts were censored at last f/u if they remained disease free. The Kaplan-Meier method was used to estimate survival functions, and Cox proportional hazard model identified prognostic factors of relapse. **Results:** Of 750 pts with resected localized STS, 232 remained disease free > 3yrs. 37 pts relapsed, 18 (8%) locally, 15 (6%) distantly, and 4 (2%) with both, with a median f/u of 5.1 yrs (3.0-13.8). The relapse-free survival rates at 4, 5, and 6 yrs were 92%, 88%, and 81%, respectively. On multivariate analysis, thoracic location (HR=109.2, 95% CI 4.3-278.3, p=0.005), head/neck location (HR=109, 95% CI 5.7-209.5, p=0.002), size > 10 cm (HR=10.1, 95% CI 0.9-102.6, p=0.05) and positive margins (HR=28.9, 95% CI 5.8-144.1, $p<0.0001$) were associated with higher risk of relapse > 3 yrs. Grade, histology, or chemotherapy did not correlate with relapse in this selected group. For local relapse only, thoracic location, positive margins, and no radiotherapy were associated with increased risk, while positive margins was the sole factor for distant relapse. **Conclusions:** In our series, disease relapse after 3 yrs occurred in 16% of localized STS pts. Tumor size > 10 cm, thoracic or head/neck location and positive margins conferred an increased risk. For pts with high risk STS, standard practice is decreased intensity of surveillance beyond 2-3 yrs. Given the incidence of late relapse, continued f/u is important; strategies to minimize radiation exposure to pts during surveillance will be critical moving forward.

**10571 General Poster Session (Board #278), Mon, 8:00 AM-11:45 AM**

**Phase I study of neoadjuvant gemcitabine combined with radiation therapy for patients with high-risk extremity and trunk soft tissue sarcomas.** *Presenting Author: William W. Tseng, Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Gemcitabine is used in many solid tumors as a sensitizer for radiation therapy. We sought to determine the maximum tolerated dose (MTD) of gemcitabine when given concurrently with preoperative external beam radiation (EBRT) for patients with high-risk extremity and trunk soft tissue sarcoma (STS). **Methods:** Fifty gray of EBRT was given in 25 daily fractions over 5 weeks. Gemcitabine was administered on days 1, 8, 22, 29, 43, and 50 at a starting dose of 400 mg/m$^2$. Dose escalation between cohorts by increments of 100 mg/m$^2$ was done using a toxicity severity weight method (TSWM), incorporating 6 different toxicities (Table). This method is a Bayesian procedure that repeatedly assesses the data to find the drug dose having a posterior total toxicity burden closest to a predetermined clinician-defined target (Bekele and Thall, 2004). Clinicopathologic and outcome data were also collected. **Results:** Thirty-six patients completed the study. Mean tumor size was 6.3 cm and 67% of patients had high grade tumors. Tumor histology consisted of MFH/UPS (n=20), myxoid liposarcoma (n=7), synovial sarcoma (n=5) and myxofibrosarcoma (n=4). Using a TSWM, the MTD for gemcitabine was 700 mg/m$^2$. All patients had tumor resected to microscopic negative margins. Most patients had no postoperative wound complications. Pathologic response with >90% tumor necrosis was achieved in 47% of patients. With a median follow-up of 6.2 years, 5 year overall survival was 86%, locoregional recurrence-free survival was 85% and distant metastasis-free survival was 80%. **Conclusions:** A toxicity severity weight method can be used to guide MTD determination for drugs given as part of multimodality treatment. Neoadjuvant gemcitabine and radiation therapy is feasible in high risk extremity and trunk STS. Major pathologic response can be achieved and after complete resection, disease control rates are excellent, supporting further evaluation of efficacy in phase II and III trials. Clinical trial information: NCT02046304.

| Toxicity | Grade | Severity weight |
|---|---|---|
| Myelosuppression without fever | 3 | 1.0 |
| | 4 | 1.5 |
| Myelosuppression with fever | 3 | 5.0 |
| | 4 | 6.0 |
| Dermatitis | 3 | 2.5 |
| | 4 | 6.0 |
| Hepatotoxicity | 2 | 2.0 |
| | 3 | 3.0 |
| | 4 | 6.0 |
| Nausea/vomiting | 3 | 1.5 |
| | 4 | 2.0 |
| Fatigue | 3 | 0.5 |
| | 4 | 1.0 |

**10572 General Poster Session (Board #279), Mon, 8:00 AM-11:45 AM**

**Trabectedin-related liver toxicity in soft tissue sarcoma patients: Always a good reason to discontinue the treatment?** *Presenting Author: Bruno Vincenzi, Department of Medical Oncology, Campus Bio-Medico University of Rome, Rome, Italy*

**Background:** A transient increase in liver enzymes is a well described side effect developed by almost 40% of soft tissue sarcoma (STS) patients treated with trabectedin, often leading to treatment delays or discontinuation. We retrospectively analysed the correlation between trabectedin-related liver toxicity and treatment outcome. **Methods:** Data from a total of 113 patients receiving trabectedin administered at the dose of 1.5 mg/m$^2$iv 24 hours in 3 reference centers were evaluated. This exploratory analysis was performed to assess the impact of liver toxicity (grade 3-4 AST and ALT increases) on the trabectedin efficacy and outcome in STS patients. All the patients included had metastatic disease or locally advanced inoperable and received at least one previous line of treatment containing anthracycline. All patients received standard steroids premedication. **Results:** Median age was 57 years (range: 27-79 ys) and male/female ratio was 71/42. STS histologies were: liposarcoma 32 cases, leiomeiosarcoma 27, pleomorphic sarcoma 17, synovial sarcoma 13, 24 other histologies. For 45 patients a G3-4 ALT increase in the first two cycles was reported while for 68 was not. Calculations show that hazard ratios for PFS and OS are not statistically significant (HR=1.124; p=0.734 and HR=0.104; p=0.850, respectively). Furthermore, the analysis was repeated dividing the population between patients with G3-4 ALT elevation during treatment vs. patients without such elevation. Again, hazard ratios for PFS and OS are not statistically significant (HR=0.791; p=0.309 and HR=0.930; p=0.810930, respectively). Finally, the analyses was repeated, splitting the population in patients with peak>15 ULN vs. patients with peak<15 ULN and one again no statistical significant differences were identified neither in terms of PFS (HR=0.821 p=0.227) neither in terms of OS (HR=0.927 p=0.463). **Conclusions:** Liver toxicity is a common event during treatment with trabectedin and does not affect outcome. These results should discourage the premature discontinuation of the drug due to the increase in liver enzymes.

**10573 General Poster Session (Board #280), Mon, 8:00 AM-11:45 AM**

**Nilotinib as co-adjuvant treatment with doxorubicin in sarcomas: Phase I trial results—A Spanish Group for Research on Sarcoma (GEIS) study.** *Presenting Author: Javier Martin Broto, Hospital Universitario Son Espases, Palma de Mallorca, Spain*

**Background:** Our group has recently published several relevant aspects of MDR proteins as potential targets in sarcomas: MRP1 expression was significantly correlated with poor prognosis in sarcoma patients, nilotinib was a strong inhibitor of MRP1/Pgp efflux activities and, finally, nilotinib plus doxorubicin (DX) showed to be synergistic regarding apoptosis in several sarcoma cell lines. Experiments in mice revealed that nilotinib plus DX did not increase either liver or cardiac toxicity. Supported by the previous information, a phase I/II trial was designed in order to explore the feasibility of nilotinib as co-adjuvant of DX by inhibiting MRP1/Pgp efflux activity. **Methods:** Nilotinib 400mg/12h was administered fixed from day 1 to 6 and DX on day 5$^{th}$ of each cycle. Three dose-escalation levels for DX at 60 mg/m$^2$; 65 mg/m$^2$ and 75 mg/m$^2$were planned. Cycles were repeated every 3 weeks for a total of 4 cycles. Eligible subtypes were retroperitoneal liposarcoma (LPS) and leiomyosarcoma (LMS) and metastatic high grade chondrosarcoma (CHO). Pharmacodynamic effects of nilotinib on the expression of MRP1 and Pgp RNA were measured by RT-PCR comparing day 1 and 5. **Results:** In the phase I trial, 13 patients were enrolled:7 CHO, 4 LPS and 2 LMS. In 46 administered cycles the most relevant non-hematological toxicities per patient were: alopecia (100%), asthenia (62%), nausea (54%), increased GGT (46%), increased ALP (38%), constipation (31%) and mucositis (23%). All of these were grade 1-2. Concerning non-hematological toxicity, there was 23% G1-2 neutropenia, 54% G3-4 neutropenia, and 61% G1-2 anemia. GCSF was recommended from day 11-17 after observing delayed neutrophil recovery on day 21. In general toxicity was easily manageable. Considering efficacy there were 2 PR (2 LPS), 8 SD (5 CHO, 2 LPS, 1 LMS), 3 PD (2 CHO and 1 LMS). Pgp and MRP1 RNA expression levels decreased by 58.47-fold and 1.47-fold respectively on day 5 of cycle. **Conclusions:** Combination of MRP1-Pgp inhibitor, nilotinib, as co-adjuvant with DX is feasible and it appears does not add substantial toxicity compared to DX alone. Pharmacodynamic study supports this concept. GEIS Group is currently conducting the phase II trial. Clinical trial information: 2011-002368-26.

**10574 General Poster Session (Board #281), Mon, 8:00 AM-11:45 AM**

**Prognostic value of peroxisome proliferator-activated receptor gamma expression on clinical outcome of myxoid liposarcoma.** *Presenting Author: Akihiko Takeuchi, Department of Orthopedic Surgery, Kanazawa University, Kanazawa, Japan*

**Background:** Myxoid liposarcoma (MLS) is considered as low-to-intermediate grade malignancy. However, it also have been reported that MLS metastases to extrapulmonary sites and the biomarker of prognosis has not fully discussed. Peroxisome proliferator-activated receptor gamma (PPAR$\gamma$) is a ligand-activated transcription factor that belongs to the nuclear hormone receptor superfamily. PPAR$\gamma$ plays a central role in the differentiation of adipocytes from precursor cells and is also reported to exhibit anti-tumorigenic effects on a certain malignancy. It has been reported that PPAR$\gamma$ is expressed in liposarcoma and the activation of PPAR$\gamma$ induced apoptosis and promote the terminal differentiation in liposarcoma cells. The purpose of this study is to evaluate the expression of PPAR$\gamma$ in MLS and correlation between PPAR$\gamma$ expression and clinical outcome. **Methods:** Forty-three patients were enrolled in this study. The median age was 45.5 years (range, 14-90 years) and the mean follow-up period was 91 months (range, 13-344 months). The expression of PPAR$\gamma$ was investigated by immunohisochemistry. **Results:** Ten cases showed the high expression of PPAR$\gamma$ (labeling index: LI $\geq$ 50%) and 33 cases were the low expression (LI $<$ 50%). Local recurrence was detected in 9 of 43 (20.9%) patients. Six of 43 (14.0%) patients developed extrapulmonary metastasis. The sites of metastasis were spine in 2 patients. Another 4 sites were femur, retroperitoneum, axilla, and lung, respectively. The metastasis-free survival was significantly higher in the patients with the low expression of PPAR$\gamma$ than those of the high expression (p=0.011). The overall cumulative 5 and 10-year survival of all patients was 97.4% and 92.3%. **Conclusions:** The low expression of PPAR$\gamma$ was a prognostic factor of the metastasis-free survival. It had been reported that FUS-CHOP, specific fusion protein confirmed in MLS, blocked the PPAR$\gamma$ pathways. So, we speculated the high expression of PPAR$\gamma$ might reflect the inhibition of the PPAR$\gamma$ pathways by FUS-CHOP fusion protein. Although the further analysis is necessary, the expression of PPAR$\gamma$ might be a novel prognostic marker of MLS.

**10575 General Poster Session (Board #282), Mon, 8:00 AM-11:45 AM**

**Locally advanced high-grade extremity soft tissue sarcoma: Response with novel approach to neoadjuvant chemoradiation using induction spatially fractionated GRID radiotherapy (SFGRT).** *Presenting Author: Mohammed Mohiuddin, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia*

**Background:** Improved local control and survival has been observed with increasing rate of tumor necrosis >90% with preoperative chemo-radiation for STS. However the rate of necrosis (90%+) following pre-operative chemo radiation remains low (<50%) and likely even less for locally advanced (>8 cm) tumors. The purpose of this study was to increase the rate of tumor necrosis following preoperative chemo-radiation in the management of soft tissue sarcomas (STS) using induction SFGRT. **Methods:** Fourteen patients with locally advanced extremity STS ranging in size from 8 cm to 26 cm (median 11.5 cm) were treated with high dose megavoltage radiation using an SFGRT technique. Single dose of induction SFGRT 18 Gy was delivered using 6 MV photons followed by external beam radiation 50 Gy combined with iphosfamide 2 gm/m2/day x 3 and mesna 2 gm/day x 3 in divided doses every three weeks followed by surgery 4-6 weeks after completing neoadjuvant therapy. **Results:** 12 patients completed the planned treatment. 1 patient had treatment interrupted due to Grade 3 skin reaction and 1 patient underwent an amputation of the foot mid treatment. Follow up ranges from 3 months to 43 months (median 14 mo). 13/14 patients underwent limb salvage surgery with 12 having negative margins. 2 patients have had delayed wound healing. 9/14 (65%) patients had > 90 % tumor necrosis with 2 patients having a pathological complete response. 2 additional patients have had greater than 80% necrosis. There have been no local recurrences and 12 patients are alive with no evidence of disease. **Conclusions:** The combined use of induction SFGRT and external beam radiation/chemotherapy is an effective way to enhance the necrosis and response to neoadjuvant chemo-radiation and potentially improve local control/ limb salvage and survival in locally advanced extremity STS.

**10576 General Poster Session (Board #283), Mon, 8:00 AM-11:45 AM**

**Survival and outcomes of critically ill sarcoma patients admitted to the intensive care unit.** *Presenting Author: Rohan Gupta, The University of Texas at Houston Internal Medicine Residency Program, Houston, TX*

**Background:** Survival and long-term outcomes of the critically ill patients with sarcoma who are admitted to the intensive care unit (ICU) are unknown. As a result, oncologists are often unsure of the utility of aggressive treatment measures in critically ill patients with these rare tumors. **Methods:** Objective: To determine factors that impact survival. We performed a retrospective chart review of all sarcoma patients admitted to the ICU at MD Anderson. Covariates such as histological diagnosis, site, stage, chemotherapy utilization, Charlson comorbidities index, Sequential organ failure assessment (SOFA) scores and reason for admission were reviewed and analyzed for impact on survival. **Results:** 212 ICU admissions were identified between 2005 and 2012. 23 patients had multiple ICU admissions. Of the remainder 191 patients, 17 surgical ICU patients were excluded, leaving a sample size of 172 patients (45.9% males) with the median age of 52 (17-89). Most common histological diagnoses were high grade unclassified sarcoma (25%), osteosarcoma (11%) and angiosarcoma (7.6%). Advanced metastatic disease was present in 73.3% patients. 25% of the patients were untreated at the time of admission to the ICU. Among patients on treatment, 34.3 % received doxorubicin based therapy and 11.6% received gemcitabine based therapy. 76.7% were alive after their first ICU admission. Post hospital, 30 days and 60 days survival were 70.3%, 60.5% and 55.2% respectively. Non-survivor group had maximum SOFA score of 16 (0-24) compared to survivor group 7 (0-22). 42.5% of the non survivors had $>$ 2 organ dysfunctions compared to 6.82% of survivors. Reasons for admission to ICU that predicted poor outcome were acute kidney injury (70% in non-survivors vs 34.8 % in survivors), acute respiratory failure (90% vs 31.8%), septic shock (40% vs 25%), cardiac arrest (17.5% vs 2.3%) and pneumonia (47.5% vs 23.5%). **Conclusions:** Significant numbers of critically ill sarcoma patients with advanced disease survive the initial ICU stay. Organ dysfunction can be predictive of survival of sarcoma patients being admitted to the ICU. Patients with disseminated disease with predictors of poor survival should be considered for early transition to supportive care or hospice.

**10577 General Poster Session (Board #284), Mon, 8:00 AM-11:45 AM**

**Prognostic factors for high-grade soft tissue sarcomas (STS) in the extremities treated by perioperative chemotherapy with ifosfamide (IFO) and doxorubicin hydrochloride (ADM): Using the data from Japan Clinical Oncology Group trial (JCOG0304).** *Presenting Author: Kazuhiro Tanaka, Oita University, Yufu, Oita, Japan*

**Background:** STS are rare malignant tumors and relatively resistant against chemotherapy. We have previously reported the efficacy of perioperative chemotherapy with ADM and IFO for STS in the extremities (JCOG0304) in ASCO 2011(abstract ID:#10078). In the present study, we carried out analysis of the factors influencing on survival of the patients in JCOG0304. **Methods:** Patients with operable, high-grade non-round cell STS (T2bN0M0) in the extremities were treated with preoperative ADM 60mg/m$^2$ plus IFO 10g/m$^2$ for 3 courses with 3-week interval, followed by operation and postoperative 2 courses of the same regimen. The histological grade of the tumor was assessed using both FNCLCC system (FNCLCC grade) and positivity of Ki67 in the tumor cells (MIB-1 grade). Promising prognostic factors identified by log-rank test were included in multivariate Cox regression model. **Results:** A total of 72 patients were enrolled in JCOG0304 and 70 all eligible patients were analyzed for this study. The clinical factors regarding age, sex, performance status, histologic subtype, tumor differentiation score, mitosis, and necrosis of biopsy specimen did not significantly influence on overall survival (OS). Although FNCLCC grade was also not associated with OS, histologic grade assessed using MIB-1 (grade 2 vs 3) was only the factor significantly associated with OS (HR 4.12 (95%CI:0.89-19.09), p=0.049). MIB-1 was also associated with OS on multivariate analysis (HR:4.05 (95%CI:0.86-19.15), p=0.077). **Conclusions:** Among factors tested in the present study, only MIB-1 grade was associated with survival of the patients treated in JCOG0304. This is the first clinical trial demonstrating that MIB-1 expression is prognostic factor of the patients with operable STS in the extremities. The results indicate that MIB-1 system might be useful for the better evaluation of histological grade of STS. Clinical trial information: C000000096.

**10578 General Poster Session (Board #285), Mon, 8:00 AM-11:45 AM**

**Primary epithelioid angiosarcoma.** *Presenting Author: Silvia Stacchiotti, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

**Background:** Epithelioid angiosarcoma (EAS) is a rare sarcoma. Complete surgical resection, when feasible, is the mainstay of therapy. Relapse rate after complete resection of primary tumor ranges from 45 to 70%, with a median survival (OS) of about 5 years. A multidisciplinary approach combining surgery, radiotherapy (RT) and/or chemotherapy (CT) is advocated by many, but there are no definitive data on the efficacy of (neo)adjuvant CT. **Methods:** We retrospectively reviewed all primary, localized, completely resected EAS observed at our institution (INT) from 1/2005 to 6/2013. We considered patients (pts) in whom at least one phase of treatment (surgery and/or RT and/or CT) was performed at INT. We excluded pts not amenable to complete surgery. Diagnosis was centrally reviewed. **Results:** Fifty-one pts were identified (46 surgically treated at INT). M/F: 16/35. RT-related: 20. Primary tumor site: breast, 29 (skin/gland: 22/7); extremities, 10; other, 12. Single versus multifocal: 39/13. Median tumor size of monofocal lesions: 5 cm (range 1-21). 20/51 (39%) pts received RT; 31/51 (60%) pts were treated with CT, of whom 4 were unresectable at baseline and 11 multifocal. Median number of cycles: 5 (range 3-8). Regimens were: anthracycline + ifosfamide,12 pts; gemcitabine +/- taxanes, 18. Median follow-up (FU) was 34 months (range 5-96; 4 pts lost to FU). 14 pts relapsed (Local-LR/Distant-DR 4/10). All LR were observed in post-RT skin EAS. 3/10 DR occurred in $<$5 cm tumors. RFS and OS were 68/62% and 85/68% at 2/5 yrs. Median time to relapse was 8 months (range 2-35). Following distant relapse, OS from relapse was 22/22% at 2/5 yrs (13-month median OS). Among 31 pts treated with CT, RFS and OS were 62/62% and 88/60% at 2/5 yrs. Ten pts received GEMTAX; their RFS and OS were 75/75% and 100/100% at 2/5 yrs, as compared to the others receiving CT, whose RFS and OS were 69/50 and 83/50 at 2/5 yrs. **Conclusions:** In this series of 51 pts, RFS and OS were apparently better than in published studies. More than half of pts received CT. Those receiving CT had worse prognostic factors, but their outcome was similar to those who did not receive any (neo)adjuvant CT. Amongst CT regimens, GEMTAX was associated with a better outcome. In this rare sarcoma, these data suggest hypotheses to test in prospective studies.

**10579 General Poster Session (Board #286), Mon, 8:00 AM-11:45 AM**

**Pazopanib in uterine sarcoma (UtS): Review of two European Organisation for Research and Treatment of Cancer (EORTC) and GSK clinical trials 62043 and 62072 on pazopanib for soft tissue sarcoma (STS).** *Presenting Author: Isabelle Laure Ray-Coquard, Centre Léon Bérard, Lyon, France*

**Background:** Pazopanib has been introduced recently in the treatment for patients with advanced STS. Multiple chemotherapies have been investigated for the treatment of advanced and recurrent UtS, but most of them result in only moderate response rates (RR) and duration. **Methods:** In this retrospective analysis we investigated the outcome of UtS pts treated with pazopanib in the two EORTC clinical trials, the phase II 62043 (n= 142) and the phase III trial 62072 "Palette study" (n= 246). **Results:** Forty-four pts with a UtS were treated with pazopanib. Histology was leiomyosarcoma (89%) and undifferentiated UtS (3%), 84% had histological grade 3 disease. Median age was 55 years (range 33-79 ; 16% $>$ 70y), 41% had performance status (PS) 0, 59% PS 1. At start of pazopanib 73% had lung metastases, 27% bone metastases, 25% liver metastases, 39% other metastases, and 14% had local recurrence. Most pts (83%) stopped pazopanib due to progressive disease, 14% due to toxicity. 28/44 pts (64%) reported a grade 3-4 adverse event while on treatment similar to the toxicity profile reported in non UtS pts. Five pts achieved a partial response (PR), 25 patients had stable disease. Thus 68% pts achieved clinical benefit, similar to that reported with non UtS. Median PFS was 3.0 months (95% CI 2.5 - 4.7) versus 4.5 (95% CI 3.7 – 5.1) with other STS; median OS was 17.5 months (95% CI 11.1 – 19.6) versus 11.1 (95% CI 10.2 – 12.9). As subsequent treatment, 27 (66%) patients received futher chemotherapy after progression and 9 (22%) underwent surgery. Due to the limited number of pts we could not identify significant predictive factors for the outcome of these patients. But, comparing uterine leiomyosarcomas, RR is 12.8% in these two trials versus 5.3% with leiomyosarcomas of non-uterine origin. **Conclusions:** Pazopanib shows similar efficacy in UtS as in non UtS. Median OS for UtS is longer compared to other subtypes in this small group. As post-study treatments were more often given to UtS pts compared to other STS pts, this might have contributed to the better OS.

**10580 General Poster Session (Board #287), Mon, 8:00 AM-11:45 AM**

**Correlation of different CT densities of untreated dedifferentiated liposarcoma (ddLPS) with rate of growth.** *Presenting Author: Sree Harsha Tirumani, Dana-Farber Cancer Center Institute/Brigham and Women's Hospital, Boston, MA*

**Background:** The biologic behavior of ddLPS is spatially and temporally heterogeneous. On imaging, untreated ddLPS shows widely varied CT densities. In this study, we retrospectively analyzed tumor growth rate as a function of tumor density. **Methods:** We identified 44 patients (pts) with ddPLS (35M, 18F; mean age at diagnosis= 59 years, range, 35 – 82 years) who had one or more resections and no intervening chemo or radiotherapy. Two radiologists reviewed CT imaging immediately obtained before the surgical resection (pre-surgery) and up to a maximum of one year before the surgery (baseline) to note the density of the nonlipomatous elements and the rate of growth during that period. Clinical and histopathological data were extracted from the electronic medical records. **Results:** We observed three distinct densities of the nonlipomatous components in our study: soft tissue density (SD) (>20HU), fluid density (FD) (-10 to +20HU), and mixed density (MD) (combination of soft tissue, fluid or fat). Tumors were of intermediate grade (36 SD, 9 MD, 5 FD) or high grade (18 SD, 2 MD, 1FD). Grade was unavailable for 1 tumor. Pre-surgery scans showed 72 tumors including 55 SD, 11 MD, and 6 FD. Baseline scans were available for 35 of the 72 lesions and included 26 SD, 5 MD, and 4 FD. The respective median growth rates per month were 40% (SD), 28% (MD), and 72% (FD). There was a change in density in 1/ 5 MD lesions (to SD) and 3/4 FD lesions (to SD). **Conclusions:** ddLPS has three distinct densities on imaging. Fluid density lesions have rapid growth rate and often convert to soft tissue density. Whether fluid density lesions need more aggressive management given their rapid growth rate needs further evaluation.

**10581 General Poster Session (Board #288), Mon, 8:00 AM-11:45 AM**

**Improved survival in an exhaustive population based on a cohort of liposarcoma (LPS) patients treated in expert centers according to clinical practice guidelines (CPG'S): Experience from Rhone Alpes (RA) region.** *Presenting Author: Olfa Derbel, Centre Léon Bérard, Lyon, France*

**Background:** Liposarcoma (LPS) represents the most common soft-tissue sarcoma.The aim of this prospective and exhaustive population-based study is to explore the impact of medical practices conformed to CPG's on survival of patients with localized LPS in a region of 6 million inhabitants. **Methods:** Between 2005 and 2007, 133 patients out of 141 with an initial diagnosis of localized LPS and residing in the RA region (France), were enrolled. The prognostic impact of adherence to CPGs on progression-free survival (PFS) and overall survival (OS) was assessed with a multivariate Cox model analysis including all potential prognostic factors (PF). **Results:** The median age was 61 years (range 26-89). Sex ratio: M/F was 1.5; the histological subtypes were: well differentiated LPS (n=86, 64.5%), dedifferenciated LPS (n=29, 22%), myxoid (n=12, 9%) and pleiomorphic (n= 6, 4.5 %). Histological grade was low in 96 patients (73%), intermediate in 16 (17%) high in 12 (9%) and unknown in 2 (1%), 48.8% of tumors were localized in limbs (n=65), 44.3% in retroperitoneum (n=59) and 6.8% in other sites (n=9). The adherence to CPGs for patients with localized LPS was 53%, for initial surgery. In multivariate analysis, adherence of surgery to CPGs was the strongest independent prognostic factor (PF) of PFS (HR: 0·32; 95% CI [0·16-0·61]), along with age at diagnosis ≤60 years (HR: 0·42; 95% CI [0·21-0·83]), grade (low vs. high, HR: 0.16, 95% CI [0.07-0.37]; intermediate vs. high, HR: 0.8, 95% CI [0.34-1.85]) and tumor site (limbs vs. retroperitoneal tumors HR: 0·49, 95% CI [0·24-1·01]; head, neck and thoracic vs. retroperitoneal tumors HR: 0·12, 95% CI [0·02-0·93]). For OS, independent PF were adherence to CPGs for surgery (HR: 0.36 95% CI [0.15, 0.84]), age at diagnosis ≤60 years (HR: 0·34; 95% CI [0·14-0·85]) and grade (low vs. high, HR: 0.05, 95% CI [0.02-0.15]; intermediate vs. high, HR: 0.53, 95% CI [0.22-1.29]). **Conclusions:** In this exhaustive population-based study, adherence to CPGs is one of the major significant PF of survival for localized LPS patients. Organization of rare cancer care and physician's education are urgently needed.

**10582 General Poster Session (Board #289), Mon, 8:00 AM-11:45 AM**

**Predictors of overall survival in patients diagnosed with desmoplastic small round cell tumor (DSRCT).** *Presenting Author: Alexander Noor Shoushtari, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** DSRCT is a rare, aggressive, and poorly understood neoplasm characterized by the EWS-WT1 translocation. Prognosis is poor despite upfront multimodality therapy with surgery, radiation (RT), and high-dose chemotherapy. We performed a retrospective review of patients (pts) with DSRCT at Memorial Sloan Kettering Cancer Center (MSKCC) to assess the association between overall survival (OS) and various clinical and therapeutic variables. **Methods:** We collected demographic/clinical data on pts diagnosed with DSRCT from 1995-2011 who had pathologic review and ≥1 oncologic consultation at MSKCC. Living pts were censored at time of last contact. First-line therapies were classified as follows: optimal (R0/R1) vs suboptimal (R2) surgery; consolidative RT; auto transplant; and chemotherapy: high-dose cyclophosphamide (HDCy) vs. standard Ewing's regimen [sER] vs other. Univariate (UVA) and multivariate (MVA) analyses were performed. **Results:** 191 patients were identified; 152 (80%) male, median age 22.6 years (yr) (range 4-62), 67% Caucasian. Most common primary site was abdomen and pelvis (A/P, 94%). Pts had disease (dz) present in A/P only (40%) or A/P plus: liver/spleen (21%), extra-abdominal (17%), or multiple distant sites (21%). Median OS (mOS) was 2.4 yr (range 0.04-12) with a median f/u 6.5 yr. UVA revealed mOS varied by site of dz, with A/P alone superior to A/P plus liver/spleen or multiple distant sites (2.8 vs 2.5 vs 2.3 yr, p=0.001). Age was not associated with mOS (p=0.90). MVA for mOS in 148 pts with complete covariates identified: optimal surgery vs suboptimal (3.2 vs 2.4 yr; HR 0.48, CI 0.29-0.78, p=0.003); consolidative RT vs no RT (3.2 vs 2.4 yr; HR 0.53, CI 0.31-0.91, p=0.021); and sER chemotherapy vs HDCy (2.7 vs 2.4 yr; HR 0.59, 0.38 – 0.93, p=0.024) as associated with improved OS. **Conclusions:** This is the largest DSRCT case series reported to date and represents the first MVA of the impact of multimodality therapy. Although overall prognosis remains dismal, R0/1 surgery and consolidative RT were associated with improved OS. sER was associated with improved OS over HDCy, but the magnitude of benefit was small. Further research and collaborations are needed to improve outcomes in these patients.

**10583 General Poster Session (Board #290), Mon, 8:00 AM-11:45 AM**

**Defining the chemotherapy (CT) response in well-differentiated (WD) and dedifferentiated (DD) liposarcomas (LPS) of the retroperitoneum (RP): A tertiary referral cancer center experience.** *Presenting Author: Neeta Somaiah, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** WD/ DD LPS is the most common LPS subtype, predominantly arising in the RP. Surgery is the primary treatment, but recurrences are frequent. CT is usually reserved for unresectable cases and the reported RECIST response rate (RR) is 12% (Italiano et al. 2012). However, in our experience, RECIST does not capture morphological changes consistent with response on imaging. Our objective was to review RR to CT and describe radiologic patterns of response. **Methods:** Search of the tumor registry for patients (pts) with RP WD/DD LPS who received CT at MD Anderson Cancer Center from 2003-2013 yielded 48 pts. The pathology database registered 316 new pts with RP WD/DD LPS in the same time frame. Data was collected from the electronic charts and the Social Security Death Index. Here we report the results for the first 48 pts; updated analysis with RECIST and imaging characteristics by an independent radiologist will be presented at the meeting. **Results:** Of 48 pts, 40 had WD/DD confirmed on pathology and were included; 2 had only WD LPS. Median age was 58 (48-65). Male/female ratio was 22/18. Nineteen pts received neoadjuvant CT (Group 1); 15 received CT for recurrent disease after upfront surgery (Group 2) and 6 received CT only (group 3). Based on the radiology report, response to first-line CT was: partial response (PR) 15/40, stable disease (SD) 19/40 and progression (PD) 6/40. Majority (36) received combination CT, mostly doxorubicin (A)-ifosfamide (I) (RR by CT regimen summarized in Table 1). In Group 1, 15/19 recurred after a follow-up of 30.4 months (m) (15.6-42). In groups 2 and 3, progression-free survival after starting CT was 5.4 m (2.1-9.0). One/two-year survival was: Group 1 100%/79%; Group 2 100%/93%; Group 3 77%/39%. Median survival was 50.5 m (29-194) for all patients. **Conclusions:** Combination CT yields a RR of 37% in WD/DD LPS. Analysis of the imaging characteristics will help us better understand response patterns in relation to RECIST.

**Response to CT in WD/DD LPS.**

| | First line | | | Second line | | |
|---|---|---|---|---|---|---|
| | PR | SD | PD | PR | SD | PD |
| A | 0 | 3 | 0 | 0 | 0 | 0 |
| A+I | 15 | 13 | 3 | 0 | 1 | 0 |
| A+DTIC | 0 | 2 | 2 | 0 | 0 | 1 |
| Gemcitabine | 0 | 0 | 1 | 1 | 0 | 0 |
| Gemcitabine+Docetaxel | 0 | 1 | 0 | 3 | 0 | 7 |
| DTIC | 0 | 0 | 0 | 0 | 0 | 1 |
| I | 0 | 0 | 0 | 1 | 0 | 0 |
| Trabectedin | 0 | 0 | 0 | 0 | 1 | 0 |

**10584 General Poster Session (Board #291), Mon, 8:00 AM-11:45 AM**

**Prognostic factors in hemangioendotheliomas (HE): Analysis based on the Surveillance, Epidemiology, and End Results (SEER) program.** *Presenting Author: Monica Reddy Muppidi, Roswell Park Cancer Institute, Buffalo, NY*

**Background:** HE are rare vascular soft tissue (ST) tumors with variable clinical biology. Prognostic factors and treatment (rx) options are poorly defined. This study aimed to describe patient (pt) and tumor features of HE and identify predictors of survival using the SEER database (1973-2010). **Methods:** HE and epithelioid HE (EHE) pts were identified using codes 9130/3, 9133/3. Demographics, tumor features and rx were retrieved. We sorted age cohorts based on Adolescent and Young Adult Oncology Progress Review Groups into children (0-15 yrs), young adults (16-39), adults (40-64), elderly (>65). Overall survival (OS) and disease specific survival (DSS) were compared using multivariate (MVA) proportional hazards methods controlling for age, gender, race, grade, stage, radiation (RT), surgery (S), size, year and histology. Analyses were done using SAS version 9.4. **Results:** 606 pts (296 EHE) were identified; median age 52 yrs (0-97), 52% female. 72% pts were > 40 yrs and most were white (85%). 443 pts had grade (G) 3 tumors. 36% cases were diagnosed from 2001-10, compared to 20% from 1973-1980. 52% had locoregional disease and 29% were metastatic. ST (38%), liver (18%) and bone (14%) were most common sites affected. 65% underwent S and 24% received RT. Tumor size data available on 406 pts revealed 27% tumors < 5cm. At a median follow-up of 70 months (m), the median OS was 35m (95% CI 27, 46); 5-yr OS was 43%. 5-yr DSS was 58%. In a univariate model on 401 pts (excluding 205 pts with missing data), age > 40, tumor grade 2/3, size > 5cm, distant disease and absence of S predicted for poorer OS. MVA for OS confirmed worse prognosis for adults (HR 3.6; 95% CI 1.3, 9.97), elderly (HR 12.85; 4.57, 36.14), G2 tumors (HR 1.74; 1.01, 3), size 5-10cm (HR 2.92; 1.69, 5.06), size > 10cm (HR 2.45; 1.29, 4.63), distant disease (HR 3.04; 1.97, 4.7) and no S (HR 1.71; 1.22, 2.42); all p-values < 0.05. Females had improved DSS (HR 0.69; 0.48, 0.98; p=0.04) but similar OS. Race, EHE histology and RT did not affect DSS or OS. **Conclusions:** Recognizing inherent bias using SEER data, age, tumor size and grade were predictive factors for survival in this study, the largest of its kind in HE. Surgical resection is important for improving outcome in HE.

**10585 General Poster Session (Board #292), Mon, 8:00 AM-11:45 AM**

**Multicenter retrospective analysis of 31 patients with aggressive angiomyxoma.** *Presenting Author: Roberta Sanfilippo, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy*

**Background:** Aggressive angiomyxoma is a rare mesenchymal neoplasm of perineum and pelvic region. Surgery is the main treatment, but local recurrences are frequent. Responses to hormonal therapy have been anecdotally reported. **Methods:** Aggressive angiomyxoma patients (pts) treated since August 1999 at two institutions (Istituto Nazionale Tumori, Milan, Italy, and Centre Léon Bérard, Lyon, France), and within the Italian Rare Cancer Network (RTR) were reviewed. Data regarding surgical and systemic therapy and survival were collected. **Results:** We identified31 patients (mean age: 43 years; F/M= 25/6). Anatomic site of occurrence was the perineum in 11/31 pts (35%) and the pelvis in 20/31 (65%) pts. Twenty-nine pts (93%) underwent at least one surgical procedure (R0/R1= 19; R2=9). Following complete surgery (R0 and R1), the local relapse rate at 2 yrs was = 21% (4/19 pts), with a median relapse-free survival (RFS) of 39 mos, Eleven patients (35%) received hormonal therapy for locally advanced disease. Eight patients received GnRH agonist as first-line therapy (6 pts as a single therapy and 2 patients in combination with tamoxifen). Seven were evaluable for response, with 2 CR, 3 PR and 2 SD, and a median PFS of 22 mos. One of these 8 pts, stopped her treatment while in CR and restarted treatment at the time of progression, obtaining a new CR. Two pts treated with GnRH agonist as first-line therapy were added an aromatase inhibitor after progression and reached a CR and a PR, respectively. Two patients received aromatase inhibitors as first-line therapy and reached a SD as their best response. One pt received tamoxifen as first-line therapy, with a PR as her best response. Median overall survival has not been reached, since all patients were alive at the time of this analysis. **Conclusions:** This is a large series of pts with aggressive angiomyxoma. Our results confirm the high rate of local recurrences after surgery. Hormonal therapy is an effective therapeutic option, which is able to result in sustained CRs in a fraction of pts. Treatment strategy of this disease needs to be defined.

**10586 General Poster Session (Board #293), Mon, 8:00 AM-11:45 AM**

**The role of pazopanib in various histologic subtypes of metastatic soft tissue sarcomas.** *Presenting Author: Kwai Han Yoo, Department of Medicine, Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

**Background:** Soft tissue sarcomas (STS) are a rare and heterogeneous group of tumors, and known to have limited treatment options.We investigated the treatment outcome of pazopanib, an oral multi-tyrosine kinase angiogenesis inhibitor, in patients with advanced STS. **Methods:** A total of forty-four patients with relapsed or refractory STS with metastatic disease received pazopanib for salvage chemotherapy after one or more cytotoxic regimens. All patients were analyzed by histologic subtype, FNCLCC grade and existence of liver involvement and locoregional disease. **Results:** The majority of patients were male (n=26, 59%) and one (n=9, 20.5%) or two (n=15, 34.1%) previous chemotherapy was introduced. Common histologic subtypes were as follows; leiomyosarcoma (n=9), angiosarcoma (n=6), malignant perpheral nerve sheath tumor (n=5) and liposarcoma (n=2). 9 patients (20.5%) achieved confirmed partial response and 16 patients (.36.5%) revealed stable disease, resulting in disease control rate (DCR) of 56.8% (95% CI, 41.8-71.8). The median progression free survival (PFS) and overall survival (OS) were 100 and 199 days, respectively. The non-liposarcoma group (such as leiomyosarcomas, angiosarcomas and osteosarcomas, n=38) demonstrated significantly prolonged PFS than pediatric type and liposarcoma group (including rhabdomyosarcomas and small round cell sarcomas, n=6) (P<0.001). The median PFS were 132 and 115 days for angiosarcomas (n=6) and leiomyosarcomas (n=9), while rhabdomyosarcomas (n=3) and liposarcomas (n=2) patients demonstrated 27 and 39 days, respectively. **Conclusions:** Pazopanib demonstrated better antitumor activity for the patients with angiosarcoma and leiomyosarcoma compare to liposarcoma and pediatric type sarcoma.

**10587 General Poster Session (Board #294), Mon, 8:00 AM-11:45 AM**

**A phase 1b food effect study of the first-in-class, oral, selective inhibitor of nuclear export (SINE) selinexor (KPT-330) in patients (pts) with advanced sarcomas.** *Presenting Author: Mrinal M. Gounder, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Sarcomas are heterogeneous diseases with multiple genetic abnormalities. XPO1 inhibition can restore the activity of multiple tumor suppressor proteins (TSP) including p53, Rb, and p27; and reduce cyclins and Akt. Selinexor is an oral XPO1 inhibitor that showed potent anti-sarcoma activity in preclinical ASPS, lipo- and bone sarcomas, and preliminary clinical activity in a phase 1 study. **Methods:** Oral selinexor was given at 30 mg/m$^2$ twice weekly in capsule or tablet form based on an ongoing Phase 1. Appetite stimulants and anti-nausea agents were given. Pharmacokinetic (PK) analyses were performed under fasting and fed states (low vs high fat content). Paired tumor biopsies were obtained. Response evaluation was every 8 weeks (RECIST 1.1). All pts had documented progressive disease (PD) on study entry. **Results:** 16 evaluable pts (7 M/9 F; median age 55 yrs; median prior regimens: 3; ECOG PS 0/1: 11/6) including 5 leiomyo- (LMS), 4 lipo- (LPS), 3 synovial (SS), and 4 other sarcomas. Grade 3-4 toxicities in cycle 1 included thrombocytopenia without bleeding (12%) and hyponatremia (6%). The most common grade 1/2 AEs in cycle 1 were: nausea (59% G1/6% G2), fatigue (29%/29%), diarrhea (41%/6%), anorexia (18%/6%). PK in 11 patients showed similar exposures ($AUC_{0\text{-}inf}$ 3675 vs 3574 ng·hr/mL) of the drug in capsules or tablets; however, food (regardless of fat content) was associated with ~15% increased exposure versus fasted state. Analyses of tumor biopsies during treatment showed that selinexor resulted in nuclear localization of p53 and FOXO1, reduction in XPO1, reduced Ki67 index, increased apoptosis. Response was evaluable in 16 pts: (a) LMS: 3 stable disease (SD, 1 pt with 12% shrinkage), 2 PD; (b) LPS: 4 SD (1 pt with 10% shrinkage); (c) SS 3 PD; (d) chondrosarcoma: 1 SD, 1 PD; (e) chordoma: 1 SD; (f) spindle cell: 1 PD. 9 of the 16 pts remain on study (75-121 days). **Conclusions:** Selinexor should be taken with food and is generally well tolerated in pts with supportive care. Tumor shrinkage and disease stabilization was observed in a variety of soft tissue sarcomas leading to expansion of the study. Additional studies of selinexor in soft tissue sarcomas are planned. Clinical trial information: NCT01896505.

**10588 General Poster Session (Board #295), Mon, 8:00 AM-11:45 AM**

**Malignancy grade and immunohistochemical myogenic/rhabdomyoblastic differentiation as an outcome determinant in retroperitoneal liposarcoma.** *Presenting Author: Alessandro Gronchi, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy*

**Background:** To explore the impact of malignancy grade and myogenic/rhabdomyoblastic differentiation on the natural course of retroperitoneal liposarcoma, uniformly treated at a single institution. **Methods:** All consecutive patients affected by primary WD/DD retroperitoneal liposarcoma surgically treated at our institution between January 2002 and December 2011 were retrospectively evaluated. Tumors were stained for mdm2 and 5 myogenic markers (smooth muscle alpha-actin [1A4], h-caldesmon, calponin, desmin, myogenin). French National Federation of the Centers for the Fight Against Cancer criteria (FNCLCC grade: 1,2,3) were applied. A diagnosis of myogenic differentiation was rendered when at least one myogenic marker was expressed. A diagnosis of rhabdomyoblastic component was rendered only if myogenin was positive. Overall survival (OS), local recurrence free survival (LRFS) and distant metastases free survival (DMFS) were calculated according to grading and absence/presence/type of myogenic differentiation. **Results:** 146 patients were identified. Median follow-up was 35 months (IQ, 22-66). 54 patients were affected by WD and 92 by DD liposarcoma. Among the latter, 60 were G2 and 32 G3. Myogenic differentiation was present in 52 cases (29/59 G2, 23/32 G3). 8 cases had a rhabdomyoblastic component (3/59 G2 and 5/32 G3). 5-yr OS were 92%, 51%, 24%; LRFS were 77%, 43%, 45% and DMFS were 100%, 82%, 32% for WD liposarcoma, G2 and G3 DD liposarcoma, respectively ($p < 0.001$). The outcome on the short run was strongly associated to the absence/presence of myogenic differentiation or rhabdomyoblastic component (3-yr OS 70%, 56% and 38%, respectively $< 0.001$). In particular all patients affected by G3 DD liposarcoma with a rhabdomyoblastic component died within 1 yr, recurring shortly after surgery with widespread disease. **Conclusions:** Beside FNLCC grade, absence / presence of myogenic differentiation with or without rhabdomyoblastic component significantly predicted the outcome of retroperitoneal liposarcoma. They should be factored in the treatment decision making and possibly used to stratify patients in clinical trials.

**10589 General Poster Session (Board #296), Mon, 8:00 AM-11:45 AM**

**Extraskeletal myxoid chondrosarcoma: A retrospective analysis of 69 patients with localized disease and molecularly confirmed diagnosis.** *Presenting Author: Anna Paioli, Istituto Ortopedico Rizzoli, Bologna, Italy*

**Background:** Extraskeletal myxoid chondrosarcoma (EMC) is a rare sarcoma of uncertain origin, marked by specific chromosomal translocations: t(9;22)(q22.3;q12.2), t(9;17)(q22.3;q12) and t(9;15)(q22.3;q21.3), and usually characterized by indolent course. Surgery +/- radiotherapy is the mainstay of treatment. In order to better evaluate prognostic factors and outcome, a retrospective pooled analysis of all patients surgically treated for localized EMC in two referral institutions for treatment of sarcoma (Istituto Ortopedico Rizzoli, Bologna, Italy; Istituto Nazionale Tumori, Milano, Italy) was carried out. Diagnosis was centrally reviewed in all cases. **Methods:** All patients (pts) with molecularly confirmed diagnosis of localized EMC, surgically treated between period 1994-2012 at either institution, were included. **Results:** 69 pts were identified (22 female; 47 male); median age: 55 years (range: 15-81). Tumor location was: extremities 49 (71%), limb girdles or trunk 20 (29%), with a median size of 8 cm (range: 2-38). 56 (81%) pts had primary disease and 13 (19%) recurrent. Median overall survival (OS) was 47 months (range 1-284).OS at 5- and 10-year was 88% and 82% respectively. 35 (51%) pts relapsed [12 local recurrence (3 with lung metastasis) and 26 distant recurrence (20 lung and 6 locoregional lymphnodes)], with a 5-year post-relapse survival of 76%. Event free survival (EFS) at 5- and 10- year was 51% and 26%. Size influenced EFS (5 year EFS was 75%, 47% and 39% for size $<5$ cm, 5-9 cm and $>9$ cm, respectively; p 0.001), while sex, tumor location and radiotherapy did not. EFS did not significantly differ by type of translocation but the median time to recurrence was 60 months in pts with t(9:22) and 25 months with t(9:17). 13 pts received systemic treatment for metastatic disease with 3 PR. **Conclusions:** A prolonged survival can be expected in patients with EMC, despite a high rate of local and distance recurrence. Size is significantly associated with outcome. The use of radiotherapy does not increase the EFS. Patients bearing t(9:22) recur later than those with t(9:17). Some PR were reported after chemotherapy treatment.

**10590 General Poster Session (Board #297), Mon, 8:00 AM-11:45 AM**

**Aplidine in patients with dedifferentiated liposarcomas: A French Sarcoma Group (FSG) study.** *Presenting Author: Antoine Italiano, Institut Bergonié, Bordeaux, France*

**Background**: Dedifferentiated liposarcomas (DDLPS) exhibit a strong activation of the JUN/JNK pathway which plays a crucial role in the dedifferentiation process. Aplidine is a novel anticancer drug requiring an activation of the JNK pathway to induce apoptosis in several tumors models. **Method**s: This was a multicentric single-arm phase 2 clinical trial based on two-stage Simon's design which assessed safety and efficacy of aplidine in patients (pts) with advanced DDLPS. All pts had to have documented progressive disease (PD) as per RECIST 1.1 based on two imaging of less 3-months interval. Pts received aplidine 5 mg/m$^2$ every two weeks until PD or unacceptable toxicity. The primary endpoint was the 3-month non-PD rate according to RECIST. Based on the following hypotheses: 20% 3-month non-PD rate (H0), 40% acceptable 3-month non-PD rate (H1), 10% type I error rate, 90% power, a total of 37 assessable pts were necessary (17 for the first stage + 20 for the second stage). Following the inclusion of the first 17 pts, if $\geq$ four pts were progression-free at 3 months, the accrual was planned to continue. Accrual started in August 2012 and finished in May 2013 in six centers of the French Sarcoma Group. **Results**: As of May 27 2013, 24 pts (12 males, 12 females) were included in the study. Median age was 63 years (48-83). All the patients had at least one grade 1 or 2 adverse events (AE) possibly related to the drug whereas 11 pts (7.5%) had grade 3 or 4 AE. The most frequent adverse events were nausea, fatigue, anorexia and myalgia. The planned interim statistical analysis performed after central histological and radiological review showed that only one patient out of the first 17 evaluable patients had stable disease. Aplidine did not reach the primary endpoint to justify continuing accrual after the 1$^{st}$step of the study. Molecular analyses showed that JUN expression and amplification status were not correlated with outcome. **Conclusions**: The rapid accrual of this study demonstrates the feasibility of histology-specific research in sarcomas. Aplidine is not worth for further investigations in DDLPS. Clinical trial information: NCT01876043.

**10591 General Poster Session (Board #298), Mon, 8:00 AM-11:45 AM**

**Brain metastases in sarcoma patients: Incidence and outcome.** *Presenting Author: Mathias Hoiczyk, Department of Medicine (Cancer Research), West German Cancer Center, University Hospital Essen, University Duisburg-Essen, Essen, Germany*

**Background:** Soft tissue sarcomas (STS) are biologically heterogeneous tumors that share a similar clinical behavior. Metastases most often occur in the lung, bones and the liver. Little data is available on incidence, prognosis, treatment and outcome of patients with cerebral metastases. **Methods:** The institutional sarcoma patient database (n=1912) and the PACS system were queried for patients with sarcomas and cerebral metastases in the years of 2003-2013. Patient characteristics and outcomes were retrospectively analyzed and overall-survival was calculated from the time of diagnosis of cerebral metastases. **Results:** 17 male and 14 female patients were identified with a median age of 38 years (range 20-73). Synchronous metastases were found in 10 (< 6 months) and metachronous metastases in 21 patients. Most frequent histologies were leiomyosarcoma (n=5), undifferentiated pleomorphic/spindle cell sarcoma (n=5), alveolar soft part sarcoma (ASPS) (n=5 from a group of 14 patients), Ewing sarcoma (n=3) and liposarcoma (n=3). Median time from diagnosis of sarcoma to diagnosis of metastases was 12 months (range: 0–155 months). Imaging was performed following work-up of CNS symptoms. 10 out of 28 patients received metastasectomy which was associated with a trend towards an improved post-metastases survival (14 vs. 4 months; p=0.3). Median time from diagnosis of cerebral metastases until disease specific death or last follow-up was 8 months (range: 0–130 mo). 6 patients had isolated cerebral metastases among which 3 long-term survivors were observed (59, 75 and 130 months at last FU). Long-term survival was not seen in patients with additional metastatic sites (median OS of 6 months). **Conclusions:** Cerebral metastases from STS are exceedingly rare (<3%) especially at the time of diagnosis for localized tumors. Restriction of CNS imaging to patients with symptomatic disease is reasonable for the majority of STS. In contrast, the risk of CNS metastases is high in ASPS (36%) and imaging studies should be included in routine diagnostic work-up. Long-term survival can be observed in STS patients with isolated brain metastases who undergo local treatment.

**10592 General Poster Session (Board #299), Mon, 8:00 AM-11:45 AM**

**Activity of chemotherapy in a series of patients with locally advanced or metastatic pleomorphic rhabdomyosarcoma: A retrospective analysis.** *Presenting Author: Michela Libertini, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

**Background:** Pleomorphicrhabdomyosarcoma (pRMS) of the adult is a rare and controversial sarcoma marked by skeletal muscle differentiation. Few data are available on the efficacy of chemotherapy in pRMS, and no definitive data support the efficacy of treatment strategies usually applied for other rhabdomyosarcoma subtypes. We reviewed response to chemotherapy in patients with pRMS treated within the Italian Rare Cancer Network (RTR). **Methods:** We retrospectively reviewed adult patients with pRMS treated at our institution or within RTR since 2001, focusing on patients treated with chemotherapy. Response was evaluated by RECIST. **Results:** Fifty-seven patients with pRMS were selected. Thirty-six of 57 patients received chemotherapy. Among them, 26 patients (M/F: 21/5–mean age: 55; range 21-80 years; locally advanced/metastatic at the onset 18/8) were evaluable for response. Twelve of 18 patients progressed to metastatic disease after local treatment. 12/20 patients in the advanced phase were evaluable having received at least one chemotherapeutic regimen. **Conclusions:** Our data suggesta moderate activity of chemotherapy in pRMS. Interestingly, 3/3 pre-treated patients who received gemcitabine in the advanced setting had a PR.

| | Patients with locally advanced disease | | | | |
|---|---|---|---|---|---|
| **Treatment** | **CR** | **PR** | **SD** | **PD** | **Subtotal** |
| **Anthracycline-based** | 2 | 1 | 3 | 3 | 9 |
| **Anthracycline-based + concomitant RT** | 0 | 2 | 7 | 0 | 9 |

| | | Patients with metastatic disease | | | | |
|---|---|---|---|---|---|---|
| **Treatment** | **Prior chemotherapy** | **CR** | **PR** | **SD** | **PD** | **Subtotal** |
| **Anthracycline-based** | 2 | 0 | 1 | 2 | 4 | 7 |
| **Ifosfamide-based** | 5 | 0 | 0 | 0 | 5 | 5 |
| **Gemcitabine** | 3 | 0 | 3 | 0 | 0 | 3 |
| **Trabectedin** | 2 | 1 | 0 | 0 | 1 | 2 |
| **Topotecan** | 1 | 0 | 0 | 1 | 0 | 1 |
| **Metronomic cyclophosphamide** | 1 | 0 | 0 | 0 | 1 | 1 |
| **Metronomic etoposide** | 1 | 0 | 0 | 0 | 1 | 1 |

**10593 General Poster Session (Board #300), Mon, 8:00 AM-11:45 AM**

**Mitomycin C, doxorubicin, and cisplatin: as a safe and effective preoperative chemoradiation cocktail for soft tissue sarcomas.** *Presenting Author: Meera Sridharan, Mayo Clinic, Rochester, MN*

**Background:** Soft tissue sarcomas are rare malignancies, often treated with a multidisciplinary approach at high volume centers. This project investigates one such approach employed at the Mayo Clinic, utilizing mitomycin C 6 mg/m2/day, doxorubicin 30 mg/m2/day, cisplatin 45 mg/m2/day for two cycles concomitantly with radiation prior to surgical resection. **Methods:** Following institutional review board approval, the charts of 58 patients (39 male) who received the aforementioned regimen from 2008 through 2012 were retrospectively reviewed. Factors relevant to prognosis and survival were analyzed by Kaplan-Meier methods using JMP statistical software. Survival data was censored at 3 years. Patients with sarcomas greater or equal to 5 cm in dimension were selected for this treatment. **Results:** The histologic subtypes included: undifferentiated sarcoma, liposarcoma, leiomyosarcoma, synovial sarcoma, malignant peripheral nerve sheath tumor, rhabdomyosarcoma, mesenchymal chondrosarcoma and fibrosarcoma. The median age at presentation was 62 years (range 33-78 years) with a median follow up of 37 months (range 6-68 months). Tumors were located primarily in the extremities (44/58; 76%), with a median size of 9.9 cm (range 5 -22 cm). All patients were able to achieve surgical resection. Median tumor necrosis was 72.5% (range 5 -100%) with fibrosarcoma having the poorest response to treatment (median necrosis 20%, n=8). 37 patients (64%) received additional pre- or post-op chemotherapy with doxorubicin and ifosfamide. 23 patients (40%) received intraoperative radiation. The 3-year event free survival (EFS) was 71%. Two of 58 patients (3.4%) suffered a local relapse within 9 (7-11) months. Though not statistically significant, patients who achieved $>$ 90% necrosis or who received pre-or postoperative chemotherapy had superior EFS (84% vs 65% and 78% vs 57% respectively). The postoperative complications included: infection (14), wound dehiscence (1), hematoma (2), and fluid collections (5). **Conclusions:** Preoperative concomitant chemoradiation with mitomycin C, doxorubicin, and cisplatin is a safe and effective regimen for soft tissue sarcomas.

**10594 General Poster Session (Board #301), Mon, 8:00 AM-11:45 AM**

**Phase II study of gemcitabine (GEM) plus sirolimus (SIR) in previously treated patients with advanced soft tissue sarcoma (STS): A Spanish Group for Research on Sarcomas (GEIS) study.** *Presenting Author: Xavier Garcia del Muro, Institut Català d'Oncologia L'Hospitalet, Barcelona, Spain*

**Background:** Combination of chemotherapy and targeted agents could be a strategy to improve efficacy. In preclinical sarcoma models, combination of GEM with SIR enhances apoptosis in vitro and increases anti-tumor efficacy in vivo. A phase I study by our group showed that the combination of both drugs is feasible. **Methods:** Patients (pts) with advanced STS, previously treated with doxorubicin, no prior GEM, ECOG PS 0-2, and adequate hematological, renal and hepatic function, were included in this phase II study, receiving GEM 800mg/m$^2$ iv at 10mg/m$^2$/minute on days 1 and 8 every 3 weeks plus oral SIR at 5mg daily and, after an amendment because of toxicity, SIR was reduced to 3 mg for the remaining patients. Tumor samples from pts were examined for pS6 expression by immunohistochemistry. The primary endpoint was progression-free rate (PFR) at 3 months. A one-sample binomial design was used (PFR P0=20%, P1=40%, $\alpha$=0.15, $\beta$=0.20), requiring at least 9 of 25 pts free of progression at 3 months to be considered positive. **Results:** From May 12 to May 13, 28 pts were enrolled at 8 centers. 1 patient was ineligible because of histology. Median age was 53 (22-71). PS: 0-11, 1-14; 2-2 pts. Histologic types were: LMS 5, UPS 5, Lipo 3, SS 3, MPNST 2, EES 2, other 7 pts. All pts were pretreated with anthracyclines. 12 pts received 5 mg and 15 pts received 3 mg of SIR. The median number of cycles administered was 2 (1-6). PFR at 3 and 6 months was 44% and 20% respectively, with 12 pts being free of progression at 3 months. Median progression-free survival was 1.85 months (95% CI, 0.7-2.9) and median overall survival was 9.1 months (95% CI, 6.1-12.2). No objective responses were observed. Most common grade 3-4 toxicities were neutropenia (44%) with 2 episodes of neutropenic fever, infection (15%), thrombopenia, hepatotoxicity and pneumonitis (11% each). Other toxicities of varying grades included asthenia, emesis, diarrhea and mucositis. No association between pS6 staining and outcome was found. **Conclusions:** The study achieves its primary endpoint. Nevertheless, the combination of GEM and SIR appears to have modest clinical activity and significant toxicity in pts with advanced STS. Clinical trial information: NCT01684449.

**10595 General Poster Session (Board #302), Mon, 8:00 AM-11:45 AM**

**Diversity and heterogeneity in molecular analysis of advanced sarcomas: The clinical, regulatory, and financial challenge for drug development and precision medicine.** *Presenting Author: Vivek Subbiah, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Therapeutic options are limited for advanced sarcomas. Search for molecular alterations could lead to identification of novel therapies for refractory sarcoma patients. Rarity poses an extreme challenge in drug development. **Methods:** We reviewed the charts of patients with advanced sarcoma patients who were referred to the phase 1 clinic at MD Anderson Cancer center and had molecular profiling done by commercially available CLIA certified labs. We analyzed the preliminary responses to matched therapy in these patients. **Results:** Among the 57 pts analyzed, median age =48 years (M: F=25:32), median ECOG PS=1, median no. of prior therapies=3. Most common subtypes were leiomyosarcoma (n=13; 22%), rhabdomyosarcoma (n=8; 14 %), liposarcoma (n=7; 12 %), osteosarcoma (n=7; 12 %), clear cell sarcoma (n=3), and synovial sarcoma (n=3). Forty-five/57 (78%) patients had $>$ 1 genomic aberration. Each pt's aberration profile was distinct. For instance, in osteosarcoma no 2 ps had the same profile. In other soft tissue sarcomas, aberrations involved *CDKN2A/B* loss or mutation (n=10; 22 %), *TP53* alterations (n=15; 33%), *CDK4* amplification (n=8; 17%), *MDM2* amplification (n=7; 15%), and *RB1* loss/mutation (n=6; 13%). In addition, novel aberrations: *KIAA1549-BRAF* fusion protein in a spindle cell sarcoma, CD30 + in osteosarcoma, and *PTPRD* mutation in Ewing's sarcoma were identified. Molecularly matched therapy are ongoing (Table ). **Conclusions:** Based on the uniqueness and distinct biology of sarcoma, we conclude that the established model for drug development in sarcoma of "one size fits all approach" does not fit the reality of sarcoma biology. New creative models for precision medicine with regulatory approval, establishment of levels of evidence, modification of reimbursement policies by health care payers and innovative dynamic ways to collect N of 1 clinical data in real time with open access are warranted.

| **Diagnosis** | **Aberration** | **Matched therapy** | **Response** |
|---|---|---|---|
| **RMS** | PIK3CA | PI3K inhibitor | SD(18 weeks) |
| **Spindle cell sarcoma** | *KIAA1549-BRAF* PTEN loss | RAF+mTOR | SD(26% decrease)(16 weeks) |
| **LMS** | PTEN loss | VEGF +mTOR | SD(16 weeks) |
| **LMS** | PIK3R1 | mTOR+HDAC | SD(15 weeks) |

**10596 General Poster Session (Board #303), Mon, 8:00 AM-11:45 AM**

**14-day continuous infusion ifosfamide in advanced refractory sarcomas.** *Presenting Author: Arun S. Singh, University of California Los Angeles Medical Center, Santa Monica, CA*

**Background:** Ifosfamide is commonly used to treat bone and soft tissue sarcomas (STS) and its efficacy appears to increase with doses >9g/m2/cycle. Due to the toxicity associated with bolus dosing, 14 day CIV outpatient dosing of this medication is being explored as a less toxic, convenient approach. In this study, we present the results of 51 patients who were treated with this regimen. **Methods:** 51 Patients with advanced/metastic bone and STS refractory to standard therapies received 1g/m2/day x 14 days of CIV ifosfamide/MESNA; the dosing was adjusted for tolerance/toxicity. 41 patients were from a retrospective cohort and 10 patients are from a prospectively collected study approved by the Western IRB. Grade 3/4 toxicities were recorded. Patients were assessed for objective response via RECIST 1.1. **Results:** 51 patients received this regimen over the course of 3 years. The most common histologies were high grade leiomyosarcoma (n=18), synovial sarcoma (n=5), HGUPS(n=5), and osteosarcoma (n=5). 63% of patients had 2 or more lines of previous therapy. The response of 6 patients could not be assessed due to death from disease progression, lack of follow up scans or discontinuation of therapy. 1/51 patients had a CR (2%), 11/51 had a PR (23.5%) and the CBR (CR+PR+SD) was 64.5%. The median PFS was 12 weeks (range: 2-120 weeks). Of grade 3/4 hematologic toxicities, 53% had neutropenia, 22% had anemia and 8% had thrombocytopenia. Of grade 3/4 non-hematologic toxicities, 6 patients (11.7%) had confusion, 2 had nausea/vomiting, 1 had CHF and 1 patient died while receiving treatment. No patients had hemorrhagic cystitis. **Conclusions:** 14 day CIV ifosfamide is a viable option for advanced sarcomas with a CBR of 64.5%. The median PFS of 12 weeks compares favorably to the previously reported data. The data in this study has fostered a prospective evaluation of CIV in advanced sarcomas.

**10597 General Poster Session (Board #304), Mon, 8:00 AM-11:45 AM**

**Modified isolated lung perfusion technique for allowance of prolonged perfusion without acute lung injury: A preclinical study with doxorubicin.** *Presenting Author: Pedro Augusto Reck dos Santos, Latner Thoracic Surgery Research Laboratories - University Health Network - Toronto Medical Discovery Tower - University of Toronto, Toronto, ON, Canada*

**Background:** Isolated lung perfusion (ILP) can enhance the treatment of lung metastases, allowing the localized delivery of drugs to the lungs, without systemic exposure. Previously, short-term ILP (± 30 minutes) resulted in variable efficacy and frequent toxicity. We developed a technique that minimizes perfusion-related injury to the lung and allows an extended perfusion time. Using our strategy, our objective is to demonstrate the feasibility and safety of ILP with doxorubicin (Dox). **Methods:** In pigs, left pulmonary artery and veins (PVs) were cannulated and clamped. Left lung ILP with a protective mode of ventilation/perfusion was performed for 4h. Dox 75 mg/m$^2$ alone or with ifosfamide (Ifos) 6 g/m$^2$ is a standard regimen currently used systemically for patients with metastatic sarcomas. Based on this, Dox 75mg/m$^2$ (group 1, n=4), 150 mg/m$^2$ (group 2, n=2), 225 mg/m$^2$ (group 3, n=2), and Dox 75mg/m$^2$ + Ifos 6 g/m$^2$(group 4, n=3) were administered at the start of ILP. After 4h ILP, cannulas were removed and blood reperfusion was allowed for more 4h. Lung physiology (Lphys) was assessed with peak airway pressure (Pawp), dynamic compliance (Cdyn), pulmonary vascular resistance (PVR), and PVs oxygenation (P/F ratio). Lung biopsies were obtained before, after ILP and after reperfusion for histological assessment of acute lung injury (ALI). Lung tissue levels of Dox were measured at the end of reperfusion and systemic levels of Dox were analyzed hourly. **Results:** In groups 1 and 4, Lphys was stable during 4h ILP period and reperfusion, without histologic ALI (p=0.12 and p=0.36). In group 2, P/F ratio dropped at reperfusion, and in group 3, severe ALI happened during ILP (increase of Pawp and PVR, and drop in Cdyn). In groups 1 and 4, mean tissue levels of Dox were 70.3 ug/g, homogeneously distributed in the lung (p=0.12). No Dox was detected systemically during the experiment. **Conclusions:** ILP with standard doses of chemotherapy (groups 1 and 4) was well tolerated using our ILP strategy for an extended period of time and without measurable ALI. In these groups, comparing to previous large animal studies, we found 2-3 x higher tissue levels of Dox, demonstrating the protective effect of our ILP strategy.

**10598 General Poster Session (Board #305), Mon, 8:00 AM-11:45 AM**

**Predictive value of BRCA1 haplotype for trabectedin efficacy in patients with advanced soft-tissue sarcoma.** *Presenting Author: Audrey Laroche, Intitut Bergonié, Bordeaux, France*

**Background:** Trabectedin (T) has shown objective response and disease stabilisation in 5%–10% and 30-40% of unselected patients with advanced soft tissue sarcoma (STS) failing prior anthracyclines and/or ifosfamide chemotherapy. Although the precise mechanism of action of T is not elucidated, this drug has been found to be more active in tumor cells with a deficient homologous recombination (HR) repair system. BRCA1 is a key player of the HER system. Our aim was to determine whether the BRCA1 single nucleotide polymorphims status was associated with clinical activity of T in advanced STS patients. **Methods:** We have analyzed single nucleotide polymorphisms of *BRCA1* in a cohort of 135 patients with advanced STS from nine major referral European centres for STS. All patients were treated between 1999 and 2011 in phase I-II clinical trials or in the context of a compassionate-use programme. T was given at different doses (0.5-3 mg/m$^2$) with the use of two different schedules: a 3-h infusion or a 24-h continuous infusion. BRCA1 haplotype was also assessed in two independent cohorts of patients: (i) localized STS (n=85); (ii) advanced STS managed with doxorubicin (n=44). **Results:** 734 cycles of T were administered, with a median of 3 cycles per patient (range 1–23). One complete response, 16 partial responses, and 29 disease stabilizations that lasted for >6 months were observed. The 6-months non-progression rate was 40.5% for patients who had at least 1 allele of the most frequent BRCA1 AAAG haplotype vs 16.5% for patients with a different haplotype; P = .01). This was also associated with a significant difference in terms of overall survival (P = .009). BRCA1 haplotype was not associated with outcome in the two independents cohorts of patients with localized STS or advanced STS treated with doxorubicin. **Conclusions**: BRCA1 haplotype may represent a predictive DNA-based biomarker for T efficacy in advanced STS patients. In particular, sarcoma patients without AAAG allele (26.5% of patients in our study) are not likely to have sustained benefit from T. Such a biomarker assessable form paraffin-embedded tumor material could be easily integrable into routine practice provided it is validated in a prospective setting.

**10599 General Poster Session (Board #306), Mon, 8:00 AM-11:45 AM**

**Low-dose gemcitabine doxorubicin and docetaxel combination in patients with advanced/unresectable/metastatic sarcoma who failed prior chemotherapy: Updated analysis.** *Presenting Author: Vivek Narasimhan, Sarcoma Oncology Center, Santa Monica, CA*

**Background:** Gemcitabine with Docetaxel is active in soft tissue sarcoma. Doxorubicin is a standard agent for sarcoma with proven efficacy. The combination of Gemcitabine, Docetaxel and Doxorubicin has been studied, and is well tolerated and active in breast cancer and non-small cell lung cancer. This study assesses the safety profile and efficacy of Gemcitabine, Doxorubicin, and Docetaxel regimen in patients with advanced, metastatic and/or unresectable sarcoma. **Methods:** 31 patients with advanced unresectable/metastatic sarcomas who progressed through standard chemotherapy were enrolled with consent. Patients were treated with Gemcitabine 400 mg/m2, Doxorubicin 20 mg/m2, and Docetaxel 20 mg/m2 on days 1 and 8 of a 21 day cycle. Disease was assessed with RECIST 1.1 and median Progression Free Survival(PFS) and Response rates(RR) were calculated. Toxicity evaluation was done using NCI CTCAE 4.2. **Results:** All subjects had advanced metastatic disease and were treated with a median of 2 prior regimens(range1-6). The sarcoma subtypes were Leiomyosarcoma(29%), Dedifferentiated Liposarcoma(13%), Myxoid Liposarcoma(13%), Angiosarcoma(6%), Synovial Sarcoma(6%), Pleiomorphic Undifferentiated Sarcoma(6%) and other(27%). 31% patients were treated with prior Gemcitabine and Taxotere and 67% with prior Anthracycline. The median age was 53(range25-72). 31 patients were enrolled and 26 were evaluable for response. A partial response was observed in one patient and stable disease in 24 patients with a median PFS of 3.5 months. Grade 3 or 4 cytopenias were observed in 45% of patients(7neutropenia, 3Anemia, and 5thrombocytopenia). One patient was taken off study due to toxicity and no significant grade 3 or 4 non-hematologic toxicities were seen. **Conclusions:** The combination of Gemcitabine, Doxorubicin and Docetaxel is well tolerated with manageable toxicity profile. Though response rates were low, this heavily pretreated population demonstrated durable stable disease even when rechallenged with prior used agents. The role of this low dose combination is not well defined but should be considered as an option in the appropriate setting.

**TPS10600 General Poster Session (Board #307A), Mon, 8:00 AM-11:45 AM**

**Phase 1 dose escalation trial of intravenous radium 223 dichloride alpha-particle therapy in osteosarcoma.** *Presenting Author: Vivek Subbiah, Department of Investigational Cancer Therapeutics (Phase I Program), University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Prognosis of patients with osteoblastic metastases from osteosarcoma is extremely poor. Given the heterogeneity in the biology of osteosarcoma, a novel approach is needed to overcome the current therapeutic plateau. Preclinical studies in rodents with alpha particle $^{223}RaCl_2$ ($^{223}Ra$) showed avid skeletal deposition, and relative sparing of the bone marrow. Experience with $^{223}Ra$ in phase I, II and III trials in men with metastatic prostate cancer confirmed excellent activity against bone metastases and a low toxicity profile (i.e., a high therapeutic index) and has been US FDA approved for prostate cancer. Because of the unique physical properties of $^{223}Ra$, this agent is anticipated to be a highly effective and better-tolerated treatment for bone-forming sarcoma. We hypothesize that can be safely administered to osteosarcoma patients, and early response and / or resistance signals can be assessed by correlative imaging studies and biomarkers. **Methods:** We are conducting an investigator initiated, single institution, phase I, dose-escalation trial of $^{223}Ra$ in recurrent or metastatic osteosarcoma patients $>$ 15 yrs and $>$40 kg. To be eligible the patient must have recurrent osteosarcoma with indicator lesion that has uptake of $^{99m}Tc$-MDP on bone scan. The primary objective is to determine the MTD of monthly $^{223}Ra$ in recurrent osteosarcoma pts. The study design is a 3+3 Phase 1 dose escalation with expansion at highest safe dose (N=6). Comparison of safety and toxicity of 50, 75, and 100 kBq $^{223}Ra$ /kg will be made.The secondary objectives are to analyze change in objective measurements of alkaline phosphatase and bone turnover markers at baseline, before dose 4 (mid study) and at end of study (after dose 6) vs change in SUV of PET- scans (18FDG and /or 18FNa) and of SPECT CT for $^{99m}Tc$-MDP. Changes in uptake will be analyzed for dose response effects (between groups) and pre vs mid study and end of study (within group). The first dose cohort of the Phase 1 trial has been completed and the second cohort is being planned. The rationale and implementation of this novel radiopharmaceutical therapeutic approach for osteoblastic metastases in osteosarcoma patients will be discussed. Clinical trial information: NCT01833520.

**TPS10601 General Poster Session (Board #307B), Mon, 8:00 AM-11:45 AM**

**A phase I/II study of sunitinib in young patients with advanced gastrointestinal stromal tumor.** *Presenting Author: Arnauld Verschuur, Hôpital d'enfants de La Timone, Marseille, France*

**Background:** Gastrointestinal stromal tumor (GIST) in young patients (pts) is a rare disease with distinct features from GIST in adults. Most notably, >85% of adults have tumors arising from receptor tyrosine kinase (RTK) mutations, typically in the *KIT* and *PDGFRA* genes, whereas such mutations occur in <15% of young GIST pts, for whom succinate dehydrogenase dysfunction is emerging as a central oncogenic mechanism instead. Sunitinib is an oral multitargeted RTK inhibitor approved for treatment of imatinib-resistant/intolerant GIST. With an $IC_{50}$ of 245 nmol/L, sunitinib has a high in vitro activity against wild-type *KIT* compared with imatinib ($IC_{50}$of 3,132 nmol/L). It is therefore hypothesized that sunitinib will be more active than imatinib in young GIST pts. This is supported by an expanded-access study, but with few pts and some limitations in data collection. A phase I study of sunitinib in pediatric pts with solid tumors, previously treated with multiple regimens of systemic chemotherapy, found that the MTD was half the effective dose in adult pts. It is not known if this will be reflective of the MTD in young GIST pts and/or if sunitinib will be effective at this dose. **Methods:** A single-arm, multinational, multicenter, phase I/II trial evaluating the pharmacokinetics, safety, and preliminary antitumor activity of sunitinib in ptsages 6 to <21 yrs with advanced, unresectable or recurrent GIST is open in North America, Europe, and Asia with 26 sites currently participating. Pts must have a histological diagnosis of GIST, measurable disease by RECIST, and imatinib-resistant/intolerant GIST or the non-mutant *KIT* genotype of GIST or not have access to imatinib in their country. Pediatric pts (<18 yrs) will receive sunitinib at a starting dose of 15 mg/m$^2$/day on Schedule 4/2 (4 wks on treatment, 2 wks off) in repeated 6-wk cycles, with dose escalation permitted after cycle 1 based on tolerance and real-time pharmacokinetics; young adults will receive sunitinib 50 mg/day on Schedule 4/2. Thirty pts are planned, and 3 have been enrolled to date. This trial is currently enrolling. Contact Pfizer Oncology at 1-800-718-1021. Clinical trial information: NCT01396148.

**TPS10602 General Poster Session (Board #308A), Mon, 8:00 AM-11:45 AM**

**Rego-SARC: Activity and safety of regorafenib (RE) in patients with metastatic soft-tissue sarcoma (STS) previously treated with anthracyclin-based chemotherapy—A multinational, randomized, placebo-controlled phase II trial.** *Presenting Author: Stephanie Clisant, Centre Oscar Lambret, Lille, France*

**Background:** Angiogenesis plays a key role in sarcoma biology. RE, targeting VEGFR-2 and -3, and tumor cell signaling kinases (RET, KIT, PDGFR, and Raf), has recently been shown to be effective in imatinib and sunitinib-refractory GIST in a phase III trial [Demetri, Lancet 2013]. Furthermore, the Palette trial has shown that pazopanib, another anti-angiogenic agent, significantly improved the PFS without OS advantage in anthracycline-refractory STS [Van Der Graaf, Lancet 2012]. **Methods:** We are conducting a multinational (France, Austria and Germany) double-blind placebo-controlled randomized (1/1) phase II trial to assess the activity and safety of RE in doxorubicin-refractory STS (ClinicalTrials.gov: NCT01900743). Key eligibility criteria are: measurable disease, age ≥18, less than 4 previous lines of CT, metastatic disease not amenable to surgical resection. Applied stratification criteria are: histological types (liposarcoma, leiomyosarcoma, synovial s., and others), countries and previous use of pazopanib. The primary endpoint is PFS according to central radiological review. Each stratum defined by histology will be separately analyzed. Statistical assumptions are: PFS0=1.6 and PFS1=4.6 months; 1-sided $\alpha$=0.1; $\beta$=0.05 with a total sample size of 192 pts. Tumor assessment is done monthly during the 4 first months, and every 3 months thereafter. After central radiological confirmation of tumor progression, an optional cross-over is proposed. Secondary endpoints are: toxicity (NCI-CTC AE V4.0); TTP; growth modulation index in pts receiving RE after randomization (GMI=TTP with RE/TTP with the prior treatment), 3 and 6 months PFS-Rates, best RR, OS. The exploratory translational research program will further characterize the nature of the genetic change by exploring the mutational status of the tumor samples using the Ion AmpliSeq Cancer Panel. In addition tissue-micro arrays (TMA) from FFPE material will be generated to allow a large-scale evaluation of molecular aberrations and downstream effects on pathway activation. The study is enrolling since June 2013. Clinical trial information: ClinicalTrials.gov: NCT01900743.

**TPS10603 General Poster Session (Board #308B), Mon, 8:00 AM-11:45 AM**

**SARC023: Phase I/II trial of ganetespib in combination with sirolimus for refractory sarcomas and malignant peripheral nerve sheath tumors (MPNST).** *Presenting Author: AeRang Kim, Center for Cancer and Blood Disorders, Children's National Medical Center, Washington, DC*

**Background:** Combination treatments of Hsp90 inhibitors with the mTOR inhibitor rapamycin produce dramatic tumor shrinkage in a genetically engineered MPNST mouse model of human MPNST (DeRaedt *et al. Cancer Cell* 2011). Previously, targeted agents have not resulted in substantial tumor regression in these models. Ganetespib is a potent small molecule inhibitor of Hsp90 that enhances endoplasmic reticulum stress with a favorable safety profile and promising activity in a variety of cancers. Sirolimus is a commercially available mTOR inhibitor, which has been tolerated in combination with multiple cytotoxic and targeted agents. These agents have also demonstrated activity in a variety of pre-clinical bone and soft tissue sarcoma models. **Methods:** SARC023 is a multi-institutional SARC sponsored, Department of Defense funded open label phase I/II trial of ganetespib in combination with sirolimus in patients with refractory sarcoma including MPNST (NCT02008877). The primary objective of the phase I component is to determine the safety, tolerability, and recommended dose of this combination. Eligibility includes individuals ≥ 18 years of age with unresectable or metastatic MPNST who have progressed after ≥1 prior regimens of chemotherapy. The Phase I component is also open to patients with other refractory or relapsed sarcomas. Ganetespib is administered intravenously over one hour on days 1, 8, and 15 every 28 days. Sirolimus is administered orally once daily continuously (28 days = 1 cycle). Patients receive treatment until disease progression or unacceptable toxicity for a maximum of 13 cycles. Upon determination of the recommended dosing, the phase II primary objective will be to determine the clinical benefit rate (CR, PR, or stable disease ≥ 4 months using WHO criteria) of this combination for patients with refractory MPNST. Secondary objectives include determination of the pharmacokinetic profile, correlative studies evaluating pharmacodynamic parameters of Hsp and mTOR inhibition in tumor tissue and peripheral blood mononuclear cells, patient reported pain outcomes, and measurement of tumor size changes using volumetric MRI analysis. Clinical trial information: NCT02008877.

**TPS10604 General Poster Session (Board #309A), Mon, 8:00 AM-11:45 AM**

**A phase II study of tivozanib in patients with metastatic and nonresectable soft-tissue sarcomas.** *Presenting Author: Lauren Elizabeth Nye, Northwestern University, Feinberg School of Medicine, Chicago, IL*

**Background:** Despite the multi-modality approach, many patients with early stage soft tissue sarcomas will develop recurrent or metastatic disease. Complete responses to chemotherapy for metastatic sarcomas are rare and do not translate to improved overall survival (OS). Given the lack of efficacy with current chemotherapy, investigational studies are needed to identify new antitumor agents. Angiogenesis plays an important role in cancer progression. Most tumors overexpress vascular endothelial growth factor receptors (VEGFRs), which allow the tumor to grow and metastasize. VEGFR1, VEGFR2 and VEGFR3 are high affinity receptor tyrosine kinases localized in the endothelium of tumor vasculature and are involved in tumor angiogenesis. VEGFR tyrosine kinase inhibitors (TKI) block phosphorylation of the VEGFR and inhibit activation of angiogenesis and, indirectly, tumor growth. Previous phase II data with a VEGFR TKI demonstrated improved progression-free survival (PFS) in patients with relapsed or refractory soft tissue sarcoma. Tivozanib is a potent and highly selective VEGFR TKI with activity against all three VEGFRs and thus a potential novel agent in the treatment of metastatic sarcoma. **Methods:** A total of 54 patients with metastatic sarcoma who have failed one previous therapy will be enrolled. Key inclusion criteria include diagnosis of metastatic and/or locally advanced or recurrent disease and measurable disease. Patients with alveolar soft-part sarcoma, chondrosarcoma, dermatofibrosarcoma, Ewing sarcoma, GIST, Kaposi sarcoma, mixed mesodermal tumor/carcinosarcoma, osteosarcoma, low grade sarcomas, rhabdomyosarcoma, interdigitating dendritic sarcoma and giant cell tumor of bone are ineligible. Eligible patients will receive tivozanib 1.5mg oral daily for 21 days in a 28 day cycle. The primary endpoint is PFS. Secondary objectives include overall response rate, clinical benefit rate, OS, toxicity and correlation of clinical outcome with antibodies for VEGFR1 and VEGFR2. Enrollment began in 03/2013. As of 01/2014, 22 of 54 patients have been enrolled. Clinical trial information: NCT01782313.

**11000 Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**A novel "diapeutic" molecular imaging agent for combined oncologic diagnosis and therapy in a broad spectrum of human cancers: Preliminary clinical experience with CLR1404.** *Presenting Author: Perry J. Pickhardt, University of Wisconsin, Madison, WI*

**Background:** Extensive preclinical investigation into CLR1404, an akylphosphocholine analog, has demonstrated highly selective uptake and prolonged retention within a variety of human cancer preclinical models. Radioiodine labeling using $^{124}$I and $^{131}$I may allow for combined oncologic imaging and treatment in humans, respectively, potentially bridging the gap between cancer imaging and therapy. We report preliminary imaging experience with this "diapeutic" agent in early phase human trials. **Methods:** Prospectiveimaging studies with $^{124}$I-CLR1404 PET/CT (n=14) and $^{131}$I-CLR1404 SPECT/CT (n=9) in 22 enrolled patients (mean age, 61 years; M:F 12:10) with proven metastatic cancer were analyzed and compared with $^{18}$FDG PET/CT and other imaging studies. Underlying primary cancer types included bronchogenic (n=7), colorectal (n=4), prostate (n=3), triple-negative breast (n=2), esophageal (n=2), head and neck (n=2), pancreatic (n=1), and melanoma (n=1). **Results:** There is preferential uptake of $^{124}$I- and $^{131}$I-CLR1404 within a variety of metastatic foci in all cancer subtypes. Persistent retention within sites of disease coupled with progressive washout of background activity favored more delayed imaging phases, days-weeks after injection. Distinct advantages in oncologic imaging over FDG PET include greater conspicuity of brain metastases (FDG false-negatives) and lack of uptake in areas of post-treatment false-positive FDG activity. CLR1404 uptake was also evident in nodal, skeletal, pulmonary, hepatic, and other sites of active metastatic disease. **Conclusions:** Selective tumor uptake with prolonged retention of CLR1404 was demonstrated within a broad spectrum of historically difficult-to-treat metastatic cancers. This novel molecular imaging agent appears to have distinct advantages over FDG for oncologic PET imaging. Combined diagnosis and therapy using same molecule (ie, a "diapeutic" approach with $^{124}$I and $^{131}$I labeling) could lead to truly personalized care by ensuring pre-treatment tumor-specific uptake, providing patient-specific dose planning, and enabling treatment-specific imaging surveillance.

**11001 Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**PET/CT with 89Zr-trastuzumab and 18F-FDG to individualize treatment with trastuzumab emtansine (T-DM1) in metastatic HER2-positive breast cancer (mBC).** *Presenting Author: Geraldine Gebhart, Institut Jules Bordet – Université Libre de Bruxelles, Brussels, Belgium*

**Background:** So far, no biomarker beyond HER2 status by immunohistochemistry (IHC) or in situ hybridization (ISH), has been validated to predict treatment efficacy of T-DM1, a novel antibody-drug conjugate targeting HER2. Zephir is a multicenter study designed to explore the role of molecular imaging in identifying patients with HER2 positive mBC (pretreated with any number of treatment lines) unlikely to benefit from T-DM1. Here we report the results of a planned interim analysis. **Methods:** Fifty-two (of 105 foreseen) patients with HER2 positive BC (IHC 3+ or FISH ≥ 2.2) underwent one pre-treatment HER2 PET/CT (4 days after administration of 37 MBq zirconium-89-trastuzumab), and 3 serial FDG PET/CT: at baseline, before the 2nd cycle (early FDG), and after 3 cycles of T-DM1 (late FDG). Central standardization and validation of acquisition parameters were performed. A patient-based imaging analysis was conducted by two independent reviewers and discordances were revised by a third investigator. HER2 PET/CT was considered negative if all or the major part of the metastatic tumor load showed no or minimal tracer uptake (≤ local background). FDG PET/CT response was classified as negative if all or the major part of metastatic tumor load showed no significant metabolic response (cut-offs set at 15% for early and 30% for late FDG PET/CT). Negative and positive predictive values (NPV and PPV) of HER2 PET/CT, early FDG response, and their combination for the prediction of late FDG PET/CT response were assessed. **Results:** HER2 PET/CT was scored negative in 17 (32%) patients, reflecting substantial imaging heterogeneity between patients considered as HER2 positive. PPV and NPV of HER2 PET/CT, early FDG PET/CT and their combination are summarized in the Table. **Conclusions:** Pre-treatment HER2 imaging and early FDG response assessment after 1 cycle seem very promising in identifying patients unlikely to show a metabolic response after 3 cycles of T-DM1. Clinical trial information: NCT01565200.

| | | | Late FDG PET | | | |
|---|---|---|---|---|---|---|
| | Classification | N patients | R | NR | PPV | NPV |
| **HER2 PET** | + | 34 | 26 | 8 | 76% | |
| | - | 17 | 4 | 13 | | 76% |
| **Early FDG PET** | R | 26 | 26 | 0 | 100% | |
| | NR | 26 | 5 | 21 | | 81% |
| **HER2 PET / Early FDG PET** | + / R | 23 | 23 | 0 | 100% | |
| | - / NR | 14 | 1 | 13 | | 92% |

Abbreviations: R, metabolic response; NR, metabolic nonresponse.

**11002 Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Detection of metastases in breast cancer: Is whole body PET/MR better than PET/CT?** *Presenting Author: Komal L. Jhaveri, New York University School of Medicine, New York, NY*

**Background:** Whole body (WB)PET/CT is commonly utilized in breast cancer (BC) patients (pts). Limitations include assessment of treatment response in bone metastases (mets), high physiologic uptake in brain and liver, and cumulative radiation exposure. The site of mets can have prognostic and therapeutic implications. PET/MR, an exciting new hybrid technology, delivers less radiation than PET/CT. Our aim was to compare the differences in metastatic lesion detection using PET/CT and PET/MR in all BC subtypes. **Methods:** Pts who had WB PET/CT for staging and assessment of treatment response also had WB PET/MR after a single 18-FDG injection. PET/MR and PET/CT images were each read by a radiologist blinded to prior exams or reports. The number of mets per organ was recorded. 2 experienced radiologists unblinded to imaging and pathology reports served as the gold standard. Clinical data were obtained. Trial accrual is ongoing. **Results:** 48 pts underwent PET/CT and PET/MR (28 MBC, 5 neoadjuvant & 15 adjuvant setting). Median age was 48; range 31-79 with 31 ER+/HER2-, 9 ER+/HER2+, 2 ER-/HER+, 5 ER-/HER2-, 1 unknown. 11 pts had no evidence of mets. In remaining 37 pts, PET/MR and/or PET/CT detected bone, liver, or brain mets in 23, 9 and 5 pts, respectively; some patients had ≥1 metastatic site. PET/MR accurately detected 1 bone (ER+/HER2), 3 liver (ER+/HER2-) and 5 brain lesions (2 ER+/HER2-, 2ER-/HER2+, 1ER+/HER2+) in 8 unique pts that were not identified on PET/CT. 2 liver and 2 brain mets identified on PET/MR were previously unknown. PET/MR accurately reported treated bone lesions in 10 pts. Per organ system, there were more false neg and false pos with PET/CT (Table). **Conclusions:** Our preliminary data suggest that PET/MR may be more sensitive and specific than PET/CT in detecting mets in breast cancer. Prospective studies of PET/MR are warranted to determine whether early detection of mets, including occult brain mets in HER2+ pts, impacts survival.

| Organ (N)[a] | # Pts with concordant PET/CT & PET/MR findings | # Pts with false (+) on PET/CT | # Pts with false (-) on PET/CT |
|---|---|---|---|
| **Bone (23)** [b] | 10 | 9 | 2 |
| **Lung (5)** | 2 | 2 | 1 |
| **Pleura (5)** | 4 | 1 | 0 |
| **Nodes (axilla + other) (19)** | 9 | 6 | 4 |
| **Liver (9)** | 5 | 1 | 3 |
| **Brain (5)** | 0 | 0 | 5 |

[a]Some pts had ≥1 metastatic site [b] In 2 pts, neither modality accurately detected the # lesions.

**11003 Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**A pilot laboratory study comparing the 21-gene assay and PAM50-ROR.** *Presenting Author: Che Prasad, Marin Medical Laboratories, Novato, CA*

**Background:** The Onco*type* DX 21-gene Recurrence Score assay was developed in endocrine-treated patients (pts) and validated as a predictor of 10-yr distant recurrence risk and chemotherapy benefit in ER+ early-stage invasive breast cancer. The Prosigna assay (ROR) which uses 46 of the PAM50 genes, was validated on centrally processed samples as a prognostic assay only in endocrine treated, post-menopausal pts. To date no direct comparison data on paired samples from the same patients for these two assays has been reported and yet it's frequently believed that these assays are interchangeable. We performed a pilot study comparing test results from the two assays obtained from the same tumor blocks. **Methods:** Sequential breast cancer tumors from Marin Medical Laboratories with sufficient tumor material were tested with the standard 21-gene Recurrence Score assay. 40 cases stratified by the Recurrence Score (20 low, 10 intermediate and 10 high) were sent to an independent laboratory where the Prosigna assay for ROR and intrinsic subtype was performed with the operators blinded to the Recurrence Score results. Descriptive statistics were calculated for the results obtained from the two assays. **Results:** Of the 40 pts, 3 were excluded due to low RNA signal in the Prosigna assay and 4 were ER(-) by RT-PCR. Of the 33 remaining cases, 24 were ductal, 7 lobular and 2 other; 27 were N- and 6 were N+. The Spearman rank correlation between Recurrence Score and ROR was 0.40 (95% CI 0.06 – 0.65). Risk group assignment (low/intermediate/high) between Recurrence Score and ROR was in agreement in 56% (15/27) of N(-) pts. Prosigna classified 19 as luminal A, 12 as luminal B, 2 as HER2 enriched and 0 as basal. In both the luminal A and B groups there was a wide range of Recurrence Score results. **Conclusions:** Consistent with other comparisons between expression-based assays, it should not be assumed that these assays are interchangeable. While additional data from a larger independent analysis is needed, this pilot suggests that there is only a modest agreement between the Recurrence Score and ROR, with almost half of N(-), ER+ pts classified differently.

**11004 Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Genomic heterogeneity in primary breast cancer: Clinical implications.** *Presenting Author: Lucy Rebecca Connolly, Wellcome Trust Sanger Institute, Camridge, United Kingdom*

**Background:** The targeting of new cancer therapeutics will be driven by genomic analysis of an individual's tumor. It is questionable that standard sampling approaches that utilize slices from single 'tissue blocks' or clinical biopsies would always reflect the full spectrum of clinically relevant changes in the breast tumor landscape. **Methods:** We explore the diversity between multiple samples (n=294) from 49 patient's primary breast tumors. Using a combination of targeted gene screens (n=285) and/or whole genome sequencing (n=25) mutation catalogues were compiled for each tumor. **Results:** To assess geographical heterogeneity within primary tumors we obtained multiple spatially separated samples (7-17) from 13 patients' primary surgical specimens. Somatic point mutation and insertion/deletion analysis identified branching heterogeneity in 11/13 surgical samples (including ER positive, triple negative and HER2+ subtypes). In 4 cases, potentially 'druggable' targets such as PIK3CA mutations occur in a single sampled region – indicating frequent sub-clonality, and spatial confinement, of cancer driver mutations. We observe divergent and convergent evolution involving cancer drivers within individual tumors. We exploit the resolution of whole genome sequencing to demonstrate that even when homogeneity of driver mutations is observed, mutational processes such as kataegis continue to operate independently in spatially distinct regions. The analysis is extended to clinical samples: Pre-treatment biopsies and post-surgical blocks from 36 patients who underwent neo-adjuvant chemotherapy were analyzed. Initial findings reveal genomic heterogeneity within cases of both complete response (n=10) and residual disease (n=26), but interestingly, sub-clonal driver mutations so far appear to be limited to those with residual disease. Our ongoing analysis incorporates copy number analysis, and explores the relationship between chemotherapy response and heterogeneity and compares the genomic landscape pre and post neo-adjuvant chemotherapy. **Conclusions:** Current sampling approaches can be expected to under-report clinically actionable genomic events in a significant proportion of breast cancers.

**11005 Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Met heterogeneity evaluation by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) in nonsquamous non-small cell lung cancer (nsNSCLC).** *Presenting Author: Edurne Arriola, Hospital del Mar, Barcelona, Spain*

**Background:** Molecular selection of patients who may benefit from Met inhibitors is being based on immunohistochemistry (IHC) with no consensus in the field. We sought to evaluate the association between *MET* gene copy number (GCN) and protein expression in NSCLC samples. Moreover, we wanted to analyze the heterogeneity within the same tumor specimen and its implications in Met evaluation. **Methods:** First, surgical cases from patients with nsNSCLC were included in a tissue microarray (TMA) representing 2 distinct morphologic areas of the tumor (2 consecutive sections). Second, biopsies from newly diagnosed patients were analyzed. Met expression was assessed by IHC (Ventana) using H-scores and MetMAb criteria and *MET* GCN by FISH (*MET* and CEP7 probes from Vysis). Association between GCN and protein expression and their correlation with clinico-pathologic and molecular information (*KRAS, EGFR)* was investigated. Additionally, heterogeneity of *MET*GCN and protein expression within different tumor cores and within consecutive sections was assessed. **Results:** One hundred and twenty-seven samples (120 patients) were analyzed. Ninety percent were adenocarcinomas, 35% grade 3, 19% *KRAS* and 11% *EGFR* mutant. Median age was 66 years, 70% males, and 53% current smokers. Median Met H-score was 140 and according to MetMAb criteria, 48% were Met high. High Met expression was associated with advanced stage (p=0.001). No association was observed with *KRAS/EGFR* mutations. *MET* amplification was observed in 8 cases (6.3%). No association was observed between *MET* GCN and protein expression. Met IHC score was high (H-score 400) in amplified cases with *MET*/CEP7 ratio >2, but not in those with *MET* GCN>5. For Met IHC, intraclass correlation coefficient (ICC) was 0.8 between consecutive tumor sections and 0.4 between different tumor cores. For *MET*FISH, ICC was 0.5 and 0.7, respectively. For amplified cases, 4 out of 12 cores were negative by FISH. **Conclusions:** The definition of Met positivity in the clinical setting is challenging, due to tumor heterogeneity. Met IHC does not accurately identify Met driven tumors. More precise criteria are needed for defining "Met dependence".

**11006 Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Emergence of new *ALK* mutations at relapse of neuroblastoma.** *Presenting Author: Gudrun Schleiermacher, Department of Pediatric Oncology and INSERM U830, Institut Curie, Paris, France*

**Background:** The *ALK* receptor tyrosine kinase is activated by point mutations in neuroblastoma and constitutes a potent therapeutic target in this disease. **Methods:** To evaluate the role of *ALK* mutations in neuroblastoma progression or relapse, we searched for *ALK* mutations in a large series of 54 paired diagnostic–relapse neuroblastoma samples using Sanger sequencing. When an *ALK* mutation was observed in one sample, deep sequencing was used to seek for a minor mutated component in the other sample. With a coverage of > 100,000, the background variability was 0.034% per base at each position, resulting in a sensitivity to detect low frequency mutations in 0.15%. **Results:** Among the paired samples, all 9 *ALK*-mutated cases at diagnosis demonstrated the same mutation at relapse by Sanger sequencing. Nevertheless, in one case, the mutation was detected in only one of several nodules at relapse. In contrast, in 5 cases, the mutation appeared relapse-specific. Among these, 4 cases could be further investigated by deep sequencing. In two cases no evidence of the mutation was observed at diagnosis. In one case, the mutation occurring at relapse could be identified at a sub-clonal level at diagnosis, whereas in another case, two different mutations resulting in identical amino acid changes could be detected at diagnosis and relapse. Further evidence of clonal evolution of *ALK*-mutated cells was provided by the observation of a minor *ALK*-mutated cell population in a tumour from which a cell line with *ALK* mutation in all cells was derived. **Conclusions:** These results indicate that, in neuroblastoma, *ALK* mutations newly detected at the time of relapse can be present in a subclone at the time of diagnosis with subsequent clonal expansion at relapse. With the advent of targeted therapy using *ALK* inhibitors, precise knowledge of the *ALK* status is mandatory. Our observation of a significant spatio-temporal variation of *ALK* mutations is of utmost importance in clinical practice, highlighting the potential of NGS and the importance of serial samplings for therapeutic decisions.

**11007 Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**A new nationwide genomic screening system in Japan for the development of targeted therapies against advanced non-small lung cancers with rare driver mutations.** *Presenting Author: Shingo Matsumoto, Division of Translational Research, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Kashiwa, Japan*

**Background:** A variety of targetable driver mutations other than *EGFR* mutations and *ALK*fusions occur in 1%-2% of NSCLCs. Efficient screening systems for these rare mutations are necessary for the successful development of targeted therapies. **Methods:** In February 2013, a new nationwide genomic screening system (LC-SCRUM-Japan) was established in Japan to screen advanced non-squamous NSCLCs without *EGFR* mutations for primarily *ALK/RET/ROS1*fusions. In November 2013, this system was amended to further screen for other driver mutations in fusion-negative cancers after the primary screening. Ten nanograms of genomic DNA extracted from biopsy or cytology specimens were subjected to the Ion Torrent AmpliSeq Cancer Hotspot Panel, version 2, and Ion Torrent next-generation sequencing, enabling the simultaneous analysis of ~2800 hotspot mutations in 50 cancer-related genes. **Results:** As of January 31, 2014, a total of 158 institutions were participating and 507 patients were enrolled in LC-SCRUM-Japan. Among the 148 cases that were enrolled after the protocol amendment, *ALK/RET/ROS1* fusions were detected in 1 (1%)/7 (5%)/8 (5%) cases, respectively, and 107 cases without fusions were transferred to the multiplex mutation screening. In the mutation screening, a total of 121 mutations were detected in 79 cases (74%), including 46 mutations in driver oncogenes in a mutually exclusive manner (23 *KRAS* mutations [21%], 7 *BRAF* mutations [7%], 5 *ERBB2* mutations [5%], 2 *PIK3CA* mutations [2%] and 1 *NRAS* mutation [1%]). In addition, 43 *TP53* mutations, 5 *CDKN2A* mutations, 4 *MLH1* mutations, 2 *PTEN* mutations, 1 *IDH1* mutation, 1 *IDH2* mutation, 1 *FBWX7* mutation, 1 *SMAD4* mutation and 1 *STK11* mutation were detected. Among them, a case with a *BRAF* V600E mutation was enrolled in a global phase II study of a BRAF inhibitor, dabrafenib (NCT01336634). **Conclusions:** This screening system enabled rare fusions and mutations in driver oncogenes, especially *RET, ROS1, KRAS, BRAF* and *ERBB2*, to be detected precisely and more frequently in limited amounts of samples from advanced NSCLCs, thereby contributing to the enrollment of patients in clinical trials for targeted therapies.

**11008 Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

**Comprehensive genomic profiling of solid tumors from 677 adolescents and young adults for revealing a distinct spectrum of targetable genomic alterations.** *Presenting Author: Deborah Morosini, Foundation Medicine, Inc., Cambridge, MA*

**Background**: Adolescent and young adult (AYA, age 15-39) cancers (CA) pose unique clincial challenges, yet genomic alterations (GA) in AYA CA have not been widely profiled. To identify potential therapeutic targets, we profiled a consecutive series of 677 AYA solid tumors, and describe a case of matching GA to targeted therapy. **Methods:** Tumor DNA extracted from FFPE tissue underwent library construction and hybrid capture for all exons of 236 cancer-related genes and 47 introns of 19 genes frequently rearranged in cancers and was sequenced to an average depth of >700x. Sequence data were assessed for base substitutions, in/dels, copy number alterations, and rearrangements. Actionable alterations were defined as those for which approved or experimental targeted therapies could be identified. **Results:** Across 30 AYA tumor types profiled, the most common were breast (BC) (15%), sarcoma (14%), brain (13%), colorectal (CRC)(9%), unknown primary (9%) and lung (LC)(6%). An average of 3.4 GAs per sample was found (range 0-22). Potentially actionable GAs were found in 71% of cases, including 93% of brain, 87% of BC, 85% of CRC and 75% of LC. Initial comparison reveals that in 44 AYA LCs, 20% had *ALK* fusions vs. 4% in older adults (age >39). Of 23 GBM cases, 48% had loss of function of *ATRX* and 39% had *IDH1* mutations, whereas *ATRX/IDH1* mutations were each present in 2-3% of our older GBM cohort. In one case, a 19 yr old female with LC was admitted to hospice having failed standard of care chemotherapy. Prior testing was negative for *EGFR*, *ALK* and *ROS1*. Genomic profiling revealed a novel *ALK* rearrangement and she began crizotinib therapy. Within 5 days she was discharged and continues to improve after 2 mos of therapy. **Conclusions:** Comprehensive genomic profiling can be optimized to accurately detect all classes of genomic alteration across AYA CA. These data highlight differences in this population and demonstrate the feasibility of identifying clinically meaningful alterations that can potentially guide targeted treatment decisions.

**11009 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

**Effect of multiparametric MRI of the breast on diagnostic accuracy.** *Presenting Author: Katja Pinker-Domenig, Medical University Vienna, Department of Biomedical Imaging and Image-guided Therapy, Division of Molecular and Gender Imaging, Vienna, Austria*

**Background:** Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) of the breast has been the mainstay of breast MRI with an excellent sensitivity but limited specificity. Available data suggests that the use of other functional MRI parameters such as diffusion-weighted imaging (DWI) and proton MR spectroscopic imaging ($^1$H-MRSI) may provide additional specificity. The aim of this study was to evaluate if multiparametric MRI using DCE-MRI, DWI and $^1$H-MRSI improves diagnostic accuracy in breast cancer diagnosis cancer in comparison to DCE-MRI alone and MP MRI with two parameters. **Methods:** One hundred and thirteen female patients (mean age, 52; range, 22–86) with an imaging abnormality (BI-RADS 0, 4-5) were included in this prospective IRB-approved study. Written informed consent was obtained in all patients. MP MRI of the breast at 3Tesla with DCE-MRI, DWI and 3D-$^1$H-MRSI was performed. The likelihood of malignancy was assessed for DCE-MRI and MP MRI with two (DCE MRI and DWI) and three (DCE MRI DWI and 3D$^1$H-MRSI) parameters separately. Histopathology was used as the standard of reference. Appropriate statistical tests were used to assess sensitivity, specificity and diagnostic accuracy for each assessment combination. **Results:** There were 74 malignant and 39 benign breast lesions. MP MR with three MRI parameters yielded significantly higher AUCs (0.936) in comparison to DCE-MRI alone (0.814) ($p<0.001$). MP MRI with just two parameters at 3T did not yield higher AUCs (0.808) than DCE-MRI alone (0.814). MP MRI with three parameters resulted in elimination of false-negative lesions and significantly reduced the false-positives ($p= 0.002$). **Conclusions:** MP MRI with three parameters increases the diagnostic accuracy in breast cancer diagnosis compared to DCE-MRI alone and MP MRI with two parameters.

**11010 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

**Exploratory biomarker analysis of a phase I study of AZD4547, an inhibitor of fibroblast growth factor receptor (FGFR), in patients with advanced solid tumors.** *Presenting Author: Elaine Kilgour, AstraZeneca Oncology Innovative Medicines, Macclesfield, United Kingdom*

**Background:** AZD4547 is a selective inhibitor of FGFR 1, 2, and 3, with activity in patient-derived explant models with FGFR gene amplification. Study 1C1 assessed safety and clinical activity of AZD4547 (80 mg bid continuous dosing), in patients with advanced solid tumors, prospectively selected for amplification of FGFR 1 or 2. FGFR gene amplification status was determined using fluorescent in situ hybridization (FISH) analysis of archival tumor tissue. **Methods:** Analysis of FFPE diagnostic tumor samples included FGFR expression by IHC, expression analysis of ~200 pathway related genes by Nanostring and targeted Next Generation Sequencing (NGS) of a 287 gene panel at Foundation Medicine. **Results:** Of 21 patients dosed with AZD4547, seven had high *FGFR* amplification (ratio FGFR: Centromeric probe $\geq$ 3.0) and three of these, a squamous NSCLC, breast and bladder cancer patients, had target lesion shrinkage or prolonged ($\geq$24 weeks) disease stabilization. NGS analysis of tumor from a partial response squamous NSCLC patient, confirmed high *FGFR1* amplification together with amplification of 11q13 genes FGF3/4/19 and CCND1. A breast cancer patient, with 25% reduction in target lesions, was highly *FGFR1* amplified by NGS and expressed FGFR1 protein. Four patients with high *FGFR* gene amplification by FISH had little sign of efficacy. Of these, one patient was not confirmed *FGFR* amplified by NGS analysis, likely due to tumor heterogeneity. The other three patient tumors had an additional Receptor Tyrosine Kinase (RTK) amplification (*IGF1R*, *HER2* or *EGFR)*, with accompanying high expression. Two out of three bladder cancer patients experienced prolonged disease stabilization, both with marked FGFR1 and FGFR3 expression, one with high *FGFR1*amplification while an FGFR3 ligand binding domain mutation was found in tumor from the other. **Conclusions:** In this AZD4547 Phase I study, evidence of FGFR pathway expression was observed in tumor samples from advanced cancer patients with signs of efficacy. Co-amplification of RTKs may confer resistance to AZD4547. FGFR1/3 expression, amplification and mutation are potential selection markers for bladder cancer patients. Clinical trial information: NCT00979134.

**11011 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

**Clinical outcome with correlation to disseminated tumor cell (DTC) status after DTC-driven secondary adjuvant treatment with docetaxel in early breast cancer (BrCa).** *Presenting Author: Bjorn Naume, Oslo University Hospital, 0424 Oslo, Norway*

**Background:** Presence of DTCs in bone marrow (BM) predicts reduced survival in early BrCa. The present study explores the use of DTCs to identify adjuvant (adj) insufficiently treated patients (pts) to be offered secondary adj treatment (Tx), and as a surrogate marker for Tx response. **Methods:** In this prospective trial, 1,121 early BrCa pts were enrolled after completion of 6 cycles of adj FEC chemotherapy from Oct 2003-08. BM aspiration was performed 8-12 weeks after FEC (BM1), followed by a second BM aspiration 6 months (mo) later (BM2). Presence of DTCs in BM was determined by immunocytochemistry using pan-cytokeratin mAbs. If $\geq$1 DTCs were present at BM2, 6 cycles (mean 5.8; range 3-6) of docetaxel (D)(100 mg/m$^2$, 3qw) was administered, followed by DTC analysis 1 mo and 13 mo after last D infusion (post-Tx). The primary endpoint was disease free survival (DFS). Log-rank statistics and Cox proportional-hazard model were used to compare outcome in pts treated with D with no DTCs after Tx to pts with DTC persistence, and in all pts according to primary tumor factors and DTC status. **Results:** Of 1,067 pts with available FU information (median 80.6 mo; end of FU Nov 2012) and a DTC result at BM2, 8.5% were DTC pos at BM1 and 7.2% at BM2. DTC pos pts at BM2 had higher pT- and pN-stage compared to BM2 neg pts ($p=0.035$ and $p=0.098$). Of 72 D-treated pts analyzed for DTCs after Tx, 15 (21%) had persistent DTCs. Pts with remaining DTCs had markedly reduced DFS (47% with relapse) compared to pts with no DTCs post-Tx (HR 6.9, 95% CI 2.2-21.7). Only 8.8% of D-treated pts with no DTCs post-Tx relapsed, compared to 12.7% of pts in the favorable group with no DTCs both at BM1 and BM2 ($p=0.378$, log rank). Separate analyses of pts with DTC neg status at BM2, showed that only ER neg pts with DTC pos status at BM1 had reduced survival, compared to those with no DTCs at BM1 ($p=0.029$). **Conclusions:** DTC status detects high-risk pts after FEC chemotherapy and DTC monitoring status after secondary Tx with D correlated strongly with survival. The results indicate that D contributes to improved prognosis for high-risk pts and emphasize the potential for DTC analysis as a surrogate marker for treatment effect in adj BrCa. Clinical trial information: NCT00248703.

**11012 Poster Highlights Session (Board #1), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Detection of *BRAF* mutations in urine and plasma cell-free DNA: Application to the diagnosis and management of histiocytic disorder patients.** *Presenting Author: Omar Ibrahim Abdel-Wahab, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** Histiocytosis patients (pts) have a high frequency of *BRAF*V600E mutations and respond to RAF inhibition but low tumor content and stromal contamination make detection in tissue biopsies challenging. Quantitative assessment of *BRAF*V600E mutations in tumor derived cell-free (cf) DNA may provide a convenient and reliable means of detecting this established biomarker and monitoring response to RAF targeted therapy. Here we compare the results of urine and plasma cfDNA *BRAF*V600E testing to tissue biopsy mutation testing in a large series of histiocytosis pts. **Methods:** Quantification of *BRAF*V600E was performed in cfDNA using droplet digital (dd) PCR (Trovagene, San Diego, CA). *BRAF*V600E analysis in tumor tissue was conducted using a variety of highly sensitive methodologies including locked nucleic acid and next-generation sequencing in CLIA-certified labs. Concordance between mutational analysis in tissue, plasma, and urine was determined. **Results:** 22 histiocytosis pts underwent cfDNA mutational analysis (18 Erdheim Chester Disease, 4 Langerhans Cell Histiocytosis). 20 pts also had CLIA-certified *BRAF*V600E mutational analysis in tissue (10 mutant, 6 wildtype, 4 test failure). All 10 *BRAF*-mutant pts based on tissue testing had a concordant positive cfDNA result in urine. Similarly, all 6 *BRAF*-wildtype pts based on tissue testing had a concordant negative cfDNA result in urine. 95% CI for concordance was 79-100%. Urine cfDNA was positive in 2 additional pts where tissue testing was unsuccessful. Plasma cfDNA testing did not identify *BRAF*V600E mutant pts who were not also positive by urine testing. **Conclusions:** Detection of actionable *BRAF* mutations by ddPCR in cfDNA is feasible and was completely concordant with CLIA-certified tumor mutation testing. Moreover, the ability to detect *BRAF* mutations in the urine of pts with repeated tumor tissue testing failure is potentially practice changing and demonstrates the clinical utility of cfDNA technologies. Mutations in cfDNA should be further investigated for longitudinal assessment of RAF-targeted therapy in pts with histiocytoses.

**11013 Poster Highlights Session (Board #2), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Molecular and genomic characterization of invasive circulating tumor cells (iCTCs) from men with metastatic castration-resistant prostate cancer (mCRPC).** *Presenting Author: Terence W. Friedlander, University of California, San Francisco, San Francisco, CA*

**Background:** Molecular characterization and genomic analysis of CTCs may allow for a better understanding of the mechanisms of resistance to therapies in metastatic castration-resistant prostate cancer (mCRPC). The Vitatex VitaAssay platform captures invasive CTCs (iCTCs) in a cell surface marker-independent fashion based on their ability to invade a fluorescently-labeled cell-adhesion matrix (CAM), allowing for the analysis of multiple CTC subpopulations. Here we sought to estimate epithelial, mesenchymal, and stem-like iCTC subpopulation diversity in men with CRPC starting abiraterone acetate therapy, to compare the genomic profiles of iCTCs to matched metastatic biopsies, and to explore the potential for 2D and 3D CTC culture. **Methods:** iCTCs were isolated from men with mCRPC using the CAM platform, and paired metastatic biopsies were performed. iCTCs were defined as CAM+/CD45-/CD14-/DAPI+, mesenchymal iCTCs as vimentin+/CAM+/CD45-/CD14-/DAPI+, and stem-like iCTCs as CD44+/CAM+/CD45-/CD14-/DAPI+. iCTCs were enumerated and purified using FACS. Agilent array comparative genomic hybridization (aCGH) of iCTCs and paired biopsies was performed, and to explore the potential for ex-vivo cell expansion and spheroid formation, iCTCs were cultured separately in CAM and in matrigel for up to 10 days. **Results:** iCTCs were isolated using the CAM platform from 42 men, of whom seven have undergone paired metastatic biopsy. The median baseline iCTC count per 7.5ml was 46 (range 0-444). In a subset of 17 subjects the median baseline CD44+ iCTC count per 7.5ml was 75 (range 0-1,410), and in a subset of 5 subjects the median vimentin+ CTC count per 7.5ml was 10 (range 1-17). AR amplification is detectable in iCTCs, iCTC aCGH profiles resemble paired soft tissue biopsy, and iCTC spheroids were observed. **Conclusions:** Multiple CRPC iCTC subpopulations are identifiable from men starting abiraterone. iCTCs resemble metastatic CRPC tissue and can be expanded in vitro. Further enumeration, genomic profiling, and clinical correlation of serial iCTCs taken from men with mCRPC is underway, and may shed light on mechanisms of abiraterone resistance.

**11014 Poster Highlights Session (Board #3), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Monitoring *EGFR* T790M with plasma DNA in lung cancer patients treated with EGFR tyrosine kinase inhibitor in prospective observational study.** *Presenting Author: Naoko Sueoka-Aragane, Department of Internal Medicine, Faculty of Medicine, Saga University, Saga, Japan*

**Background:** Use of plasma DNA to detect mutations has spread widely as a form of liquid biopsy. The gatekeeper T790M mutation of *EGFR* has been observed in half of lung cancer patients who acquired resistance to EGFR tyrosine kinase inhibitor (EGFR-TKI). We recently developed a novel sensitive, fully-automated monitoring system, MBP-QP (mutation-biased PCR and quenching probe), to detect T790M using plasma DNA. To determine the usefulness of the MBP-QP method for monitoring T790M during treatment with EGFR-TKI, a prospective clinical study was performed. **Methods:** This was a prospective, multicenter, observational study involving lung adenocarcinoma patients carrying *EGFR* activating mutations, such as L858R and exon 19 deletions, who were treated with EGFR-TKI. The primary objective was to determine whether T790M could be detected using plasma DNA at the time of progressive disease (PD). The secondary objective was to assess correspondence between T790M measured using plasma and that using cancer specimens. The association between detection of T790M and effect of EGFR-TKI was also investigated as an exploratory objective. **Results:** Ninety non-small cell lung cancer patients treated with EGFR-TKI were enrolled from seven hospitals in Japan: 92.1% had adenocarcinoma, 62% at stage IV, and 29% had postoperative recurrent disease. According to the investigators' evaluations, T790M was detected in 26% (15/58) of the patients who acquired resistance to EGFR-TKI. A central review showed that the frequency of T790M positives among the patients with PD was 22% (12/55). When EGFR-TKI was discontinued because of PD, T790M was detected in 33% (17/52), whereas any patients who were discontinued for other reasons such as adverse effects did not show T790M positivity. Eight re-biopsy specimens were obtained at the time of occurrence of PD, and the concordance rate was 63%. **Conclusions:** T790M was detected in plasma DNA at the time of PD occurrence. Compared to the frequency using re-biopsy reported by other papers, liquid biopsy covered approximately half of the total patients with PD. The relationship between T790M positivity and detailed characteristics of progression was analyzed. Clinical trial information: UMIN000005131.

**11015 Poster Highlights Session (Board #4), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Circulating tumor DNA (ctDNA) as a marker of recurrence risk in stage II colon cancer (CC).** *Presenting Author: Jeanne Tie, Western Hospital, Melbourne, Australia*

**Background:** Markers that better define recurrence risk for patients (pts) with stage II CC are urgently required, potentially defining a subset that would most benefit from adjuvant chemotherapy (CTX) and intensive surveillance. An alternative strategy to standard analyses of the resected surgical specimen is to directly examine plasma for evidence of residual disease. Recently, ctDNA has shown promise as a blood biomarker in advanced colorectal cancer; here we explore the potential of this marker in stage II CC. **Methods:** In this prospective study, plasma samples are being collected at 4-10 weeks post-op in 250 stage II CC pts, with serial 3 monthly samples on a subset of 175 pts. Adjuvant CTX is at clinician discretion, blinded to ctDNA analysis. Surveillance includes 3 monthly CEA and 6 monthly CT imaging for 2 years. All samples were sent to Johns Hopkins Kimmel Cancer Center, where tumor tissue was analyzed for hotspot mutations in *TP53, APC, KRAS, NRAS, BRAF, PIK3CA, CTNNB1, SMAD4*, and *FBXW7* using a massively parallel sequencing platform (Safe-SeqS). The identified mutation was queried and quantified in plasma using the same platform, blinded to clinical data. **Results:** Preliminary data is available on 78 of the 190 pts enrolled to date. Median age is 66 years, 25/78 (32%) received adjuvant CTX. At least 1 mutation was found in all tumors, with matching ctDNA detectable in 6/78 (7.7%) plasma samples. 10 (12.8%) recurrences have occurred at a median follow-up of 507 days, including 5 of 6 pts with detectable ctDNA and 5 of 72 with no detectable ctDNA (Table). Pts with detectable ctDNA had a shorter recurrence-free survival (median 234 days vs undefined, HR 23.09, log-rank $p < 0.0001$). In an exploratory analysis of the correlation between ctDNA and clinicopathologic features, detectable ctDNA maintained prognostic significance, including for T3 tumors (HR for time to recurrence 80.55, log-rank $p < 0.0001$). **Conclusions:** Early data suggests ctDNA is a promising marker of recurrence risk in stage II CC. Preliminary analyses suggests this may be independent of clinicopathologic features.

| | Recurrence | No recurrence | Total |
|---|---|---|---|
| **Post-op ctDNA positive** | 5 | 1 | 6 |
| **Post-op ctDNA negative** | 5 | 67 | 72 |
| **Total** | 10 | 68 | 78 |

Fisher's exact $P < 0.0001$. RR = 12 (95% CI 4.79 – 30.06).

**11016 Poster Highlights Session (Board #5), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Noninvasive and ultrasensitive quantitation of circulating tumor DNA by hybrid capture and deep sequencing.** *Presenting Author: Scott Victor Bratman, Stanford University, Stanford, CA*

**Background:** No validated biomarkers exist for minimal residual disease (MRD) detection in non-small cell lung cancer (NSCLC). We aimed to design a next-generation sequencing-based method for quantifying circulating tumor-derived DNA in NSCLC and other cancers. **Methods:** We developed CAPP-Seq (Cancer Personalized Profiling by deep Sequencing), a novel method for noninvasive cancer burden measurement. Our strategy leverages affinity capture to enrich recurrently mutated genomic regions from tumor DNA and plasma cfDNA. After benchmarking sensitivity, we analyzed a set of NSCLC tumors and corresponding serial plasma samples collected before and after radiation therapy, chemotherapy, and/or surgery. **Results:** We show that CAPP-Seq detects multiple cancer-specific somatic mutation types within NSCLC DNA, including single nucleotide variants, insertions/deletions, and rearrangements. Benchmarking analyses demonstrate that CAPP-Seq accurately enumerates mutations within cfDNA at a fractional abundance of ≥0.02%. Applying CAPP-Seq to tumor/normal genomic DNA pairs from 17 NSCLC patients uncovered a median of 6 mutations per patient (range, 1-28). Plasma samples (35) from 13 patients were profiled by CAPP-Seq. The abundance of patient-specific cancer markers within plasma cfDNA was readily measured by CAPP-Seq in both early- and late-stage NSCLC. Importantly, circulating tumor DNA responded appropriately to diverse therapies, becoming undetectable in 7 patients (including after surgery, chemoradiation, and targeted therapy) and declining but remaining detectable in others. CAPP-Seq measurements correlated with tumor volume ($R2 = 0.97$) and allowed for detection of resistance mutations in patients being treated with targeted therapies. **Conclusions:** We describe a novel NGS-based approach to MRD testing in cancer patients. CAPP-Seq could have utility for monitoring disease burden and response to therapy, early detection of relapse, and risk stratification in early-stage NSCLC following surgery or stereotactic body radiation therapy. Ultimately, we envision CAPP-Seq becoming a routine clinical assay for measuring tumor burden in diverse cancers from plasma and other body fluids.

**11017 Poster Highlights Session (Board #6), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Gene expression profiles of primary tumors versus circulating tumor cells in metastatic breast cancer.** *Presenting Author: Wendy Onstenk, Erasmus MC Cancer Institute, Department of Medical Oncology and Cancer Genomics Netherlands, Rotterdam, Netherlands*

**Background:** Before considering circulating tumor cells (CTCs) as a liquid biopsy in metastatic breast cancer (MBC), the degree of molecular discrepancy between primary tumors (PTs) and CTCs has to be established. **Methods:** In 69 MBC patients with ≥1 CTC before start of first-line systemic treatment, our previously described panel of 55 tumor-associated gene transcripts was measured by quantitative reverse transcription polymerase chain reaction in both formalin fixed paraffin embedded PTs and CellSearch-enriched CTCs. From 11 patients, a lymph node metastasis (LN), obtained at the time of primary tumor resection, was available for comparison with PTs and CTCs. A Compare Batches normalization was used to correct for batch effects. Overall gene expression profiles and the expression of therapeutic targets *ESR1*/ER and *ERBB2*/HER2 were compared. Associations with clinical outcome (time-to-treatment switch, start first- to second-line treatment) were exploratory. **Results:** In 55% of patients, PT and CTC profiles did not cluster. Patients with non-clustering profiles more often had synchronous metastases (42% versus 3%, $\chi^2$ $P = .001$), and ER-positive tumors (68.4% versus 38.7%, $\chi^2$ $P = .03$) compared to patients with clustering profiles. Discrepant expression of ER and HER2 was found in 26% and 25% of patients, respectively. Whereas ER was equally lost and gained in CTCs compared to PTs (12% versus 15%, McNemar $P=.82$), HER2 was more often lost than gained (21% versus 5%, McNemar $P=.02$). Patients with concordant ER-positive expression in PTs and CTCs had the best prognosis, those with discordant expression performed worse, and prognosis for concordant ER-negative patients was worst (Log-rank test for trend $P < .001$). A similar pattern was observed for HER2, although this was not statistically significant ($P = .10$). In all 11 patients, LN profiles clustered with the PT profiles; in 2 patients CTCs mismatched with both PT and LN. **Conclusions:** Gene expression profiles of PTs and CTCs at time of MBC differ in a substantial proportion of patients. Expression of ER and HER2 is often discrepant between PTs and CTCs, which had prognostic implications in this patient cohort and may thus be of clinical relevance.

**11018 Poster Highlights Session (Board #7), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**BRCA1-like copy number profiles to predict benefit of high-dose alkylating chemotherapy in high-risk breast cancer (BC): Results from randomized WSG AM-01 trial.** *Presenting Author: Philip C. Schouten, Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands*

**Background:** DNA copy number profiles identify patients with a defect in BRCA1 associated with a homologous recombination DNA repair defect. We previously showed that patients with a BRCA1-like profile benefit from high-dose (HD) and tandem HD chemotherapy (CT) (carboplatin/thiotepa/cyclophosphamide; ifosfamide/epirubicin/carboplatin). WSG AM-01 trial reported superiority of tandem HD vs. dose-dense CT in high-risk BC patients. Subgroup analysis attributed this effect to triple-negative BC. **Methods:** Phase III WSG AM-01 trial randomized 403 patients with >9 positive lymph nodes to 2xEC q2w followed by tandem HD (epirubicin/cyclophosphamide, thiotepa) or DD 4xEC --> 3xCMF q2w CT. Tumor CN profiles from 98 patients were generated with high-throughput sequencing and classified as BRCA1-like or non-BRCA1-like. Correlations with prognostic factors were assessed and Cox regression was done to investigate predictive/prognostic impact of BRCA1-like status on event free survival (EFS). **Results:** 17 of 94 (18%; HD/DD: 10 (19%)/7 (17%)) patients had BRCA1-like profiles. BRCA1-like status associated with high tumor grade (p=0.005) and triple-negative status (p<0.001). In multivariate Cox analysis for EFS, only age <50 years entered (HR=1.9, p=0.02) as a main effect. In subgroup analysis, only BRCA1-like status predicted for efficacy of HD. HR=0.26 (95% CI: 0.07-0.94, p=0.04) for BRCA1-like vs. 0.76 (95% CI: 0.43-1.34; p: 0.35) for non-BRCA1 like. In exploratory Cox interaction analysis (backward elimination) with BRCA1-like status, therapy and their interaction, the model retained BRCA1 status (HR=2.25; 95% CI: 1.07-5.94) and the predictive interaction BRCA1*therapy (HR=0.22; 95% CI: 0.06-0.79). **Conclusions:** Retrospective analysis suggests that superiority of rapidly cycled tandem HD alkylating over standard dose-dense CT in high-risk BC is substantially attributable to BRCA1-like (rather than TN) status. Comparing with other studies, this effect seems less drug-specific and indicates rather higher sensitivity of BRCA1-like tumors to any HD alkylating CT. The results will be validated in the prospective WSG ADAPT TN trial.

**11019 Poster Highlights Session (Board #8), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Prognostic and predictive significance of PAM50 intrinsic subtypes in the NCIC CTG MA.21 phase III chemotherapy trial.** *Presenting Author: Karen A. Gelmon, British Columbia Cancer Agency, Vancouver, BC, Canada*

**Background:** Breast cancer intrinsic subtypes defined by the 50-gene PAM50 test were reported to be prognostic and predictive in endocrine therapy trials. MA21 randomized 2,104 patients to receive dose intense cyclophosphamide, epirubicin and flurouracil (CEF); dose dense, dose intense epirubicin, cyclophosphamide and paclitaxel (EC/T); or 3-weekly doxorubicin, cyclophosphamide and paclitaxel (AC/T). We previously reported that AC/T had reduced relapse free survival (RFS) compared to both CEF and EC/T. Here, we investigated the prognostic and predictive (taxane versus not) significance of PAM50 in MA.21. **Methods:** Patients were ≤60 years old with node-positive or high-risk node-negative breast cancer. Median follow-up was 8 years. Intrinsic subtypes (luminal A, luminal B, basal-like, HER2E) were determined with FFPE extracted total RNA by Nanostring PAM50. Univariate assessment was with a stratified log-rank test. Effects of intrinsic subtypes and baseline patient characteristics on relapse-free survival (RFS) were investigated with stratified step-wise Cox multivariate regression, adding a factor if p<0.05. **Results:** The 1,094 cases completing PAM50 intrinsic subtyping were not significantly (p<0.05) different compared to those who did not in terms of treatment and stratification factors. 27% were classified as luminal A; 23% luminal B; 32% basal-like; and 18% HER2E. Intrinsic subtypes had a significant (p<0.001) univariate association with RFS. In multivariate analyses, intrinsic subtype had a significant prognostic effect on RFS (p= 0.001). Compared with luminal A, the hazard ratios (HR) were: luminal B =1.47 (95% CI = 0.93-2.30, p=0.10); basal-like= 1.95 (CI = 1.10-3.47, p=0.02); and HER2E = 2.66 (95% CI = 1.63-4.34, p<0.001). The interaction term between intrinsic subtype and treatment was not significant (p>0.05). **Conclusions:** Intrinsic subtype defined by the Nanostring PAM50 test had a significant prognostic effect on RFS for breast cancer patients treated with CEF, EC/T and AC/T. Subtype was not predictive of outcome amongst these chemotherapy regimens. Clinical trial information: NCT00014222.

**11020 Poster Highlights Session (Board #9), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Biomarker modulation in patients (pts) receiving TRC105 (T) and bevacizumab (B) in a phase Ib clinical trial.** *Presenting Author: Yingmiao Liu, Duke University Medical Center, Durham, NC*

**Background:** Endoglin (END; CD105) is a membrane-bound cell surface receptor expressed on proliferating endothelial cells implicated in resistance to VEGF inhibition. T, an anti-End monoclonal antibody, potentiates anti-VEGF therapy in *in vitro* and *in vivo* models. The combination of T plus B was well tolerated and was active in pts who progressed on prior B treatment. **Methods:** Pts with advanced refractory solid tumors were treated with escalating doses of T plus B. Pts received 1 week of B monotherapy prior to the addition of T. Thirty-eight biomarkers related to tumor growth, angiogenesis, and inflammation were analyzed using an optimized multiplex ELISA platform. Samples from 38 pts were collected at baseline (BL), 1 week (C1D8), 2 week (C1D15), 4 week (C2D1), and end of study (EOS). Biomarker concentrations on study were compared to baseline using the Wilcoxon signed rank test with statistical significance assumed at $p<0.05$. **Results:** After 1 week of B monotherapy (C1D8), PlGF was elevated and ANG-2, soluble END (sEND), TSP2, and VEGFR1 were decreased. Following the addition of T, only Ang-2 remained significantly decreased, while the following analytes were significantly elevated at C1D15, C2D1 and EOS: CRP, sEND, E-Selectin, IL-6, PAI-1 (active and total), P-Selectin, SDF-1, TGF-b1, and VCAM-1. Increases in sEND and PlGF are consistent with observations from pts treated with either T or B alone, respectively. The inflammatory markers, CRP and IL-6, and TGFb-regulated proteins, PAI-1 active and sEND, all exhibited greater than a 5-fold increase on average at EOS. Interestingly, the elevation of the END ligand, TGFb1, in response to T plus B treatment, has not been observed in pts treated with either agent alone. **Conclusions:** Treatment of pts with either T or B alone is associated with modulation of multiple angiogenic and inflammatory biomarkers. However, the combination of both agents led to increases in many inflammatory and TGFb-related proteins that persisted throughout the study. The differences across the biomarker patterns from pts treated with T plus B suggest increased bioactivity for the combination and support the role of T potentiating anti-VEGF therapies in pts.

**11021 Poster Highlights Session (Board #10), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Enhancing the prognostic power of the Nottingham tumor grading system.** *Presenting Author: Ritu Aneja, Georgia State University, Atlanta, GA*

**Background:** The terms "actively proliferating cell" and "mitotically dividing cell" are often used synonymously in breast clinical pathology. Mitotic and Ki-67 indices (MI and KI, respectively) are evaluated in different fields and at different scales, despite their mutual non-exclusivity. Pathology-centric view regards Ki-67-positive cells as "actively dividing", leading to the mistaken view that an increase in KI reflects an increased proportion of mitotic cells. Since MI is an equally-weighted component of the Nottingham grading system (NGS), we examined contribution of mitotic scores to the prognostic value of tumor grade and evaluated if a modified score called Ki-67–adjusted mitotic score (KAMS), could replace MI in NGS to re-stratify GII patients and strengthen the prognostic power of tumor grade. **Methods:** In a retrospective study of 2,200 breast carcinoma patient records from Northside Hospital, Atlanta, GA, KAMS was calculated by transforming monotonic ordinal MI into percent mitotic cells and dividing it by KI. Grade wise trends in KAMS were evaluated and survival stratification was done via Kaplan-Meier estimator. An adjustment principle based on each patient's KAMS and mitotic score was applied to the MI component of the Nottingham sum to re-stratify Grade II patients. **Results:** Average KAMS decreased significantly ($p< 0.0001$) from 0.153 to 0.132 to 0.085 for Nottingham grades GI, GII and GIII, respectively. KAMS was then used to stratify GII patients into two groups whose survival probabilities were significantly different ($p= .01$): "above-average KAMS" group had 96.3% survival while the "below-average KAMS" group had an 88.7% survival. Thus, low KAMS predicts poor prognosis for high-grade patients. While nuclear grade contributes majorly, MI contributed minimally to the prognostic value of tumor grade. Thus, replacing MI with KAMS within NGS re-stratified Grade II patients who were either (i) adjusted into GI (23% of original GII), or (ii) were adjusted into GIII (62% of original GII). **Conclusions:** KAMS decreases with Nottingham grade. KAMS-based survival stratification of GII and GIII patients show that low KAMS is associated with poor prognosis. Replacement of MI with KAMS within NGS better stratifies GII patients.

**11022 Poster Highlights Session (Board #11), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Prognostic and predictive blood-based biomarkers of overall survival (OS) in patients (pts) with advanced colorectal cancer (CRC) treated with cetuximab (C): Results from CALGB 80203 (Alliance).** *Presenting Author: Ace Joseph Hatch, Duke University Medical Center, Durham, NC*

**Background:** Previously, we identified potential predictive biomarkers of C sensitivity related to EGFR signaling from archived tumor tissue from CALGB 80203. Due to the fact that blood-based markers are more convenient and can be monitored over the course of treatment, baseline plasma samples were also collected and five (EGF, HB-EGF, sEGFR, sHER2, sHER3) markers were evaluated in plasma. **Methods:** CALGB 80203 was a randomized (1:1) phase II trial of 238 pts with locally advanced or metastatic CRC comparing FOLFOX or FOLFIRI (chemo) vs. chemo plus C. Baseline EDTA plasma samples from 154 pts were analyzed for the five candidate markers; an ELISA for CD73 is currently being optimized for use. The levels of each analyte were correlated with the primary endpoint of OS using univariate Cox proportional hazards models. Potential predictive markers were identified using a treatment by marker interaction term in the Cox model and the markers with significant p-values are reported. Hazard ratios between treatment groups are reported for low or high marker levels dichotomized at the median. **Results:** Univariate analyses indicated that plasma levels of EGF and sHER3 were negative prognostic markers ($p<0.05$) that correlated with OS for the overall pt population. Across all pts (KRAS mutant and wild-type), sHER3 was identified as a potential predictive biomarker for C. Pts with higher sHER3 levels had significant OS benefit from C treatment (interaction $p=0.03$; HR=0.57, 95% CI 0.36-0.92). Low levels of EGF predicted for OS benefit from C in KRAS WT tumors (interaction $p<0.01$; HR=0.42, 95% CI 0.19-0.90) and lack of benefit in the KRAS mutant pts (interaction $p=0.03$; HR=2.69, 95% CI 1.04-6.94), but were not predictive for C across all pts. **Conclusions:** Blood-based profiling of EGFR axis members identified sHER3 and EGF as candidate predictors for benefit from C. These data are consistent with our findings using mRNA expression from archived tumor samples and suggest a role for receptor shedding in HER3 biology. If further validated, these markers may help guide the development and use of anti-EGFR therapies and combination regimens.

**11023 Poster Highlights Session (Board #12), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Relationship between RECIST response and variation of circulating tumor cells (CTC) for patients enrolled in phase I trials.** *Presenting Author: Christophe Massard, Gustave Roussy, University Paris Sud, Villejuif, France*

**Background:** Because CTC counting has been shown to be a marker independent of tumor type or treatment, it could represent a new parameter to improve evaluation of tumor response to drugs in phase I clinical trials. We hypothesized that early change of CTC counts could occur before detectable variation in tumor size evaluated by imaging using RECIST criteria. **Methods:** Consenting patients with advanced and metastatic cancer referred three phase I units (Gustave Roussy, Institiut Curie, Pitie Salpétrière) were enrolled prospectively in this study. CTCs from 7.5 mL of whole blood drawn before treatment initiation (baseline) and 4 weeks after starting experimental therapy were enumerated using the CellSearch system, and tumor response was assessed using RECIST Criteria at baseline and 2 months after treatment initiation. **Results:** Between March 2010 and May 2013, a total of 326 patients were enrolled in phase I trials across 3 centres, among which 215 were evaluable (48% were male, median age=57; main tumor types: lung (25), colon (54), bladder (14), breast (28)). At baseline we detected $\geq$ 1CTC/7.5 ml in 114/215 (53% ; median CTC count=4 (1-3,264)), and at week 4, we observed $\geq$ 1CTC/7.5 ml in 103/215 (48% ; median CTC count=3 (1-100)). Sensitivity and specificity of CTC variation to detect progressive disease were 41% (32-51%) and 80% (72-87%) respectively. At the first follow-up imaging visit, 10 (5%) of the 215 patients were classified as having partial response, with 9 of these patients having no CTC or a decrease in CTC count after therapy. In contrast of the 102 patients (47%) classified as having progressive disease, 22 patients (21%) had an increase of CTC. The remaining 103 patients (48%) were classified as having stable disease, 35 of them (33%) had a decrease in CTC count, possibly suggesting a therapeutic benefit despite the lack of criteria for objective response. **Conclusions:** Early CTC change following therapy does not correlate with RECIST response in patients with advanced cancer enrolled in phase I trials. However, our results suggest that this biomarker may still have some interest to identify stable diseases with a certain anti-tumor effect.

**11024 Poster Highlights Session (Board #13), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Recurrence score and quantitative ER expression to predict in late distant recurrence risk in ER+ BC after 5 years of tamoxifen.** *Presenting Author: Norman Wolmark, National Surgical Adjuvant Breast and Bowel Project; The Allegheny Cancer Center at Allegheny General Hospital, Pittsburgh, PA*

**Background:** Identification of molecular determinants predicting late recurrence (>5 yrs) in stage I and II breast cancer has become clinically important in light of data demonstrating a benefit for ten yrs of tamoxifen administration. Since the 21-gene Recurrence Score (RS) is commonly utilized in early stage BC, we wished to determine its utility in predicting distant recurrences beyond five yrs as a function of quantitative ER expression. **Methods:** The 21-gene RS was assessed in 1,065 chemo and tam-treated, ER+, node-positive pts from NSABP B-28 and 668 tam-treated, ER+, node-negative pts from NSABP B-14. Cox PH models, KM estimates and log rank statistics were used to assess the association of the RS with risk of DR by quantitative ER expression, using the 21-gene assay, in pts event-free after 5 yrs. We established an ER cut-point (high vs low) in B-28, and tested the cut-point in B-14, formally evaluating the interaction of RS and ER. **Results:** Median follow-up was 11.2 yrs (B-28) and 14.5 yrs (B-14). 832 B-28 pts and 564 B-14 pts were DR-free after 5 yrs. A reference normalized ER cut-point of 9.1 $C_T$was established in B-28 based on the association of the RS with DR after 5 yrs. Of the event-free pts at 5 yrs, 68% in B-28 and 88% in B-14 had ER>9.1. In B-28 the RS result was strongly associated with DR after 5 yrs in the higher ER expressing pts (log rank P=0.001), but not in the lower ER expressing pts (log rank P=0.87). It was confirmed in the B-14 data that RS was associated with DR after 5 yrs in higher ER pts (Table) but not in the lower ER pts (interaction P=0.03). **Conclusions:** For late recurrences (beyond 5 yrs), the RS is strongly prognostic in pts with higher quantitative ER expression (>9.1). The findings suggest that extending tamoxifen beyond 5 yrs may be most beneficial in pts with high (and intermediate) RS with higher quantitative ER expression and of limited benefit in pts with a low RS (>50% of population under study).

**DR Risk after 5 yrs in B-14 by RS risk group for pts with ER>9.1 $C_T$.**

| | | %DR KM estimate (95% CI) | |
|---|---|---|---|
| **RS risk group** | **N (%) pts** | **5 to 10 yrs %** | **5 to 15 yrs %** |
| **Low** | 289 (58%) | 4.7 (2.8 - 8.0) | 6.8 (4.4 - 10.6) |
| **Intermediate** | 111 (22%) | 4.1 (1.6 - 10.6) | 11.2 (6.2 - 19.9) |
| **High** | 97 (20%) | 12.6 (7.4 - 21.2) | 16.4 (10.2 - 25.7) |
| **Log rank *P*=0.01** | | | |

**11025 Poster Highlights Session (Board #14), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Return of individual research results: Policies and experiences of cancer genomic researchers.** *Presenting Author: Lynn G. Dressler, Mission Health, Fullerton Genetics Center, Asheville, NC*

**Background:** Although it is not the intent of the International Cancer Genomics Consortium (ICGC) or The Cancer Genome Atlas (TCGA) studies to return individual research results (RIRR), clinically relevant results will be discovered. Debate about RIRR are well described in the literature, however little information exists regarding researcher experiences and institutional policies. **Methods:** The ICGC Ethics and Policy Committee developed an anonymous survey that was distributed electronically or by hardcopy to genomic researchers participating in ICGC and TCGA, asking about perspectives, experience and policy relevant to RIRR. Analysis was limited to researchers conducting human cancer genomic research. **Results**: 111/164 (66%) surveys were eligible for analysis. Compared to non US researchers, US researchers were significantly less likely to report a responsibility to consider whether a research result would have clinical relevance for the subject (83% v 57%; p=0.011). Fifty-one percent of researchers reported finding clinically relevant results important for the subject to know. The 3 most common findings were susceptibility to cancer/other chronic disease (46%); pharmacogenomic (42%), and Mendelian Disease (20%). Forty percent reported returning results to physicians (40% at least 1X; 15% > 5X) or individual research subjects (28% at least 1x). Most (80%) agreed that a result should be validated before return, yet there was no agreement even on how to analytically validate results. Regarding institutional policy, 28% reported an RIRR policy existed, including 9% whose policy was not to return results; 12% reported no policy; and 50% did not know if a policy existed. 17% reported that the informed consent (IC) never addresses RIRR; 30% reported the IC always addresses RIRR and 30% did not know what the IC addressed. **Conclusions:** Regardless of study intent, clinically relevant research results are being found and returned to physicians and individual research subjects. A critical need exists to develop consistent approaches for validating research results; raise researcher awareness of institutional policies and develop practical guidance for researchers involved in international collaborations.

**11026 Poster Highlights Session (Board #15), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**The use of whole-genome sequencing in therapeutic for decision making in patients with advanced malignancies.** *Presenting Author: Howard John Lim, British Columbia Cancer Agency, Vancouver, BC, Canada*

**Background:** We used information obtained from whole genome and transcriptome sequencing to aid in therapeutic decision-making in patients (pts) with advanced cancers. **Methods:** Eligible pts with incurable cancers with limited or no standard options, had several samples analyzed: a fresh tumor biopsy; a blood sample for normal comparison; and archival tumor tissue when available. Samples underwent both the Ion Torrent AmpliSeq cancer panel analysis and comprehensive DNA (80X) and RNA sequencing followed by in-depth bioinformatic analysis to identify somatic mutations, copy number alterations, structural rearrangements, and corresponding gene expression changes that may be cancer "drivers" or provide informative/diagnosticor actionable targets. Aberrant pathways were matched to drug databases and manual literature reviews were performed to identify drugs that may be useful or potentially contraindicated. A report was generated and discussed in a multidisciplinary team. **Results:** Between July 2012 - January 2014, 65 pts had consented (including 4 pediatrics cases) and 56 have been sequenced: 18 breast, 8 lung; 4 colorectal, 3 squamous, 3 adrenal; 2 pancreas; 2 sarcomas, 2 neurofibroma, 2 mesothelioma, and 1 of each of nasopharynx, primary unknown, CLL-peripheral mantle cell, parotid, anal, appendix, peripheral T-cell, prostate, ovary, endometrial, glioma, and leiomyoma. The median number of lines of chemo prior to sequencing was 3. The AmpliSeq panel only yielded actionable targets in 40% of cases. The full genomic data was more comprehensive about driver pathways and was informative in 70% of cases. Clinical data is available on 30 pts. In 21 pts data was actionable. In 3 pts, the diagnosis was changed and 9 pts died before the results could be used. Treatments were delivered based on the results in 8 pts, 6 (75%) of these pts derived clinical benefit from treatment based on genomic therapy. **Conclusions:** Whole genome sequencing based therapeutic decision-making in the management of advanced cancer is feasible. The information is more comprehensive than panels and yields clinically actionable data not identified by panel sequencing. Further studies are needed to determine the utility of this technology.

**11027 Poster Highlights Session (Board #16), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Comprehensive molecular profiling of advanced gastric cancer (AGC) using NGS and immunohistochemistry (IHC).** *Presenting Author: Yasutoshi Kuboki, Division of Gastrointestinal Oncology/Gastroenterology, National Cancer Center Hospital East, Kashiwa, Japan*

**Background:** In advanced gastric cancer, most of clinical trials are designed based on IHC/*in situ* hybridization in tissue. However, NGS screening allowed us to comprehensively profile tumor gene status recently. Our goal is to profile both gene alterations and conventional biomarker in gastric cancer for potential molecular targeted therapy. **Methods:** Formalin-fixed, paraffin-embedded (FFPE) tumor samples from 121 patients with stage III/IV gastric cancer who underwent gastrectomy were examined for HER2, EGFR, c-MET and FGFR2 expression using IHC. In addition, genomic DNA was extracted from each FFPE sample and a total of 15,991 regions in 409 cancer-related genes were sequenced to detect mutations using the Ion *AmpliSeq* Library kit 2.0 and Comprehensive Cancer Panel. In addition, to evaluate copy number variation of a gene, relative reading depth to the reference (RRDR) of an individual gene was calculated. Amplification was defined as an RRDR greater than 2. **Results:** The most frequently mutated genes were *TP53* (36.4%). In addition, mutations in oncogenes such as *PIK3CA* (7.4%), *ROS1* (4.1%), *HER2* (4.1%), *MET* (1.7%) and *ALK* (1.7%) were detected. The most frequently amplified gene was *SRC* (20.7%). Amplification was also detected for other genes such as *HER2* (14.9%), *CCNE1* (13.2%), *CCND1* (9.1%), *EGFR* (7.4%), *KRAS* (7.4%), *MET* (6.6%), *RET* (3.3%) and *FGFR2* (2.5%). The rate of over-expression (IHC 3+) was as follows: HER2 (16.5%), EGFR (23.1%), MET (9.9%) and FGFR2 (14.0%). Most of the cases with HER2 over-expression had *HER2* amplification. On the other hand, in a few cases with EGFR/c-MET/FGFR2 over-expression, amplification of these genes was not detected. Over-expression cases with EGFR or FGFR2 had other various gene alterations such as *PIK3CA* mutations and/or *KRAS* alterations. In contrast, HER2 or c-MET over-expression cases were mutually exclusive with respect to *PIK3CA* mutations. **Conclusions:** We identified several possible candidate genes that could be targets for personalized therapy. Comprehensive analyses including IHC will be necessary to design the optimal therapy with which to treat the right population of patients in future clinical trials.

**11028 Poster Highlights Session (Board #17), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Impact of next-generation sequencing (NGS) on treatment decisions in the community oncology setting.** *Presenting Author: Lindsay Carol Overton, Oregon Health & Science University, Portland, OR*

**Background:** Mutational testing has become standard of care in melanoma, lung, and colorectal cancers. The advent of Next Generation Sequencing (NGS) and increasing availability of new targeted therapeutics raise the question of how broader use of testing will impact care in the community setting. **Methods:** We conducted a retrospective chart review of patients (pts) seen at a network of community oncology practices whose tumors were tested with NGS for actionable mutations in AKT1, ALK, BRAF, DDR2, EGFR, ERBB2, FGFR1/3, GNA11, GNAQ, MAP2K1, HRAS, KDR, KIT, KRAS, MET, NF1, NRAS, NTRK1/2/3, PIK3CA, PIK3R1, PTEN, RET, STK11, TSC1, and TSC2. Under IRB approval, data were collected on diagnosis, date of testing, treatments, mutational results, treatment outcomes, and survival. **Results:** 632 pts had NGS, of whom 360 harbored actionable mutations (57%). Of these, 301 were included for review: 59 were excluded based on disease stage or insufficient clinical data. There were 26 different cancer types; lung, colorectal and breast cancers represented over half. As of December 2013, 45% of pts had started new therapies after NGS results were available. Mutational testing guided treatment in 34% of these pts, with over half enrolling on clinical trials targeting specific mutations. A minority (6.6%) was treated off label with FDA approved medications targeting the mutations. **Conclusions:** When performed in a timely manner, NGS had a clinically meaningful impact on treatment planning in one third of pts. The availability of molecularly targeted clinical trials played a significant role in the importance of the testing. Our data provide an initial view of how NGS can impact treatment decision making in the community setting.

| | |
|---|---|
| **Total number pts** | 632 |
| **Patients with actionable mutations** | 57% (n=360) |
| **Eligible for analysis based on advanced stage and availability of clinical information** | 48% (n=301) |

**Were test results available before the latest treatment was started?**

| Yes (45%, n=136) | | | | | No (55%, n=165) | | | |
|---|---|---|---|---|---|---|---|---|
| **Did results guide subsequent therapy?** | | | | | **Treatment status?** | | | |
| **Yes (34%, n=34)** | | | **No (66%, n=102)** | | **Still on last treatment** | **Not on treatment** | **Hospice/died** | **Other** |
| **Clinical trial** | Standard of care | Off-label use | Patient alive? | | | | | |
| **52%** | 22% | 26% | Yes 76% | No 24% | 30% | 28% | 37% | 5% |

**11029 Poster Highlights Session (Board #18), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Next-generation sequencing (NGS)-based profiling of pancreatic acinar cell carcinoma for identification of a recurrent *SND1-BRAF* fusion.** *Presenting Author: Vincent A. Miller, Foundation Medicine, Inc., Cambridge, MA*

**Background:** Pancreatic acinar cell carcinoma (ACC) is a rare subtype of pancreatic cancer with a poor prognosis. Chemotherapy and radiation therapy have limited efficacy against these tumors, and novel treatment strategies are needed. Previous whole exome sequencing studies have classified these tumors as genomically heterogeneous with distinct genomic profiles from other pancreatic cancers (Jiao et al., 2013). To identify genomic alterations that could serve as potential therapeutic targets, we profiled a small set (n=3) of pancreatic ACC tumors. **Methods:** Extracted tumor DNA underwent hybrid capture for 3,769 exons from 236 cancer-related genes plus 47 introns of 19 genes frequently rearranged in cancer and was sequenced to an average median depth of 728x. Sequences were assessed for base substitutions, insertions and deletions, rearrangements, and copy number changes. We characterized signaling properties of confirmed molecular alterations by ectopic expression of engineered cDNAs in 293H cells. **Results:** We observed an average of two genomic alterations per tumor. A recurrent *SND1-BRAF* rearrangement was identified in two samples that lacked other known driver events. This fusion was similar in structure to other reported *BRAF* fusions, and preserves the serine-threonine kinase domain of the protein. In vitro studies of *SND1-BRAF* suggest that it activates MAPK signaling, which can be inhibited by trametinib and sorafenib. **Conclusions:** Although the number of samples in this study is small, fusions involving *BRAF* potentially occur at a high frequency in pancreatic ACC and may represent a novel therapeutic target in this disease. These alterations occur within intronic regions, and may be missed by sequencing methods that investigate exonic regions only. Preclinical data suggest that *SND1-BRAF* driven activation of MAPK signaling can be inhibited with existing targeted agents, suggesting that a subset of this virulent disease may be amenable to treatment with available therapies. NGS-based profiling of an expanded cohort of pancreatic ACC tumors is ongoing to determine the overall frequency of *BRAF* fusions in this disease.

**11030 Poster Highlights Session (Board #19), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Multi-institutional multiplexed genetic analysis in lung adenocarcinoma (AC): The Lung Cancer Mutation Consortium (LCMC I) experience.** *Presenting Author: Dara L. Aisner, University of Colorado Cancer Center, Aurora, CO*

**Background:** Molecular analysis of lung AC has become standard of care for therapy selection. LCMC I collectively enrolled 1102 patients from 14 institutions with the goal of performing molecular analysis to identify therapy options. Technical aspects of the genomic testing, specimen and clinical correlations are presented. **Methods:** Testing for mutations in 8 genes (*EGFR, KRAS, ERBB2, AKT1, BRAF, MEK1, NRAS, PIK3CA*), and analysis of *ALK* and *MET* by FISH, was performed at 6 labs. Proficiency testing was carried out with blinded samples. Statistical analyses were performed for analysis completion, specimen types, testing methodology, mutation findings and clinical variables. **Results:** Five methodologies (SNaPshot®, mass spectrometry, Sanger +/- PNA, sizing) were variably employed for detection of mutations, with analytic sensitivities of ~5% allele frequency. All sites passed proficiency testing. 1006 specimens had at least one mutation analysis completed, 733 specimens had full genotyping results. Mutation detection rates did not vary according to method of analysis. Higher rates of specimen inadequacy were seen in biopsy (36/136; 23%) and cytology (23/65; 36%) compared to surgical (13/268; 5%) specimens at the site that analyzed the most cases. Biopsy and cytology samples, when acceptable showed no difference in mutation or FISH assay completion or positivity rate. Multiple analyses are summarized in the table. Double mutations were seen in 3.8% of samples. **Conclusions:** Molecular analysis is possible in a multi-institutional setting with consistent results. Cytology and small biopsy specimens were commonly sufficient for multiplex testing, although sample insufficiency was a common reason for exclusion (53% of excluded cases), and contributed to lack of assay completion. Multiple associations were identified between specific mutations and clinicopathologic features.

| Gene marker (% +) | Associations found (All p<0.01) |
|---|---|
| ***EGFR* (22%)** | Female, never smoker, Asian, bone metastases |
| ***KRAS* (25%)** | Tobacco exposure, lack of bone metastases, non-Asian, older age at dx |
| ***ALK* (9%)** | Never smoker, younger age at dx, liver metastases |
| ***MET* amp (3%)** | Male |
| ***ERBB2* (2%)** | Never smoker |
| ***BRAF* (2%)** | None |

**11031 Poster Highlights Session (Board #20), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**A comprehensive analysis of molecular profiles across over 10,000 tumor and germ-line exomes across more than 20 tumor types: Novel mechanisms and targets for clinical treatment.** *Presenting Author: Shahrooz Rabizadeh, NantOmics LLC, Culver City, CA*

**Background:** Whereas the clinical world is familiar with genomic assays targeted to a limited number of mutations as a means to derive molecular insight to therapies, the power to deliver more comprehensive, non-assumptive, and stochastic molecular analysis is now available to guide treatment decision that is unbiased to traditional tissue-by-tissue assignment of therapeutics or a priori assumptions that a few hundred DNA mutations are drivers of the cancer. **Methods:** Over 10,000 tumor and germ line exomes and RNA-seq data representing over 5,000 patients across more than 20 tumor types were processed using Contrastor, a cancer genome differentiation algorithm designed to detect variants (germline and somatic), copy-number alterations (overall and allele-specific), and genomic rearrangements. RNA-seq data was used to confirm the presence of alterations in the transcript when available. Paradigm, an algorithm that integrates genomic and transcriptomics data and designed to identify key altered cell signaling pathways, was used to reveal shared pathways amongst independent tumor types. **Results:** Aggregating the top altered genes across tissues reveals very few genes are dominated with alterations present in single diseases. DNA repair and kinase signaling proteins appear to be the predominantly altered classes, with transcriptional proteins also highly altered (TP53, MLL, CREBBP). A surprising number of new targets for pharmaceutical discovery were uncovered, and particularly in patients with no clear therapeutic options based on the analysis of "actionable" genes. Despite patients having unique molecular profiles, Paradigm revealed shared pathways across tissue types driving tumor progression that are likely targets for therapeutic intervention. **Conclusions:** The vast landscape and ample number of mutations identified in this comprehensive analysis illustrates the complexity of cancer genomics and the need for transcriptomics driven pathway analysis to identify the focal points of therapeutic intervention.

**11032 Poster Highlights Session (Board #21), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Intratumor heterogeneity (ITH) of lung adenocarcinomas defined by multi-region whole exome sequencing (WES).** *Presenting Author: Jianjun Zhang, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Individual cancers are composed of populations of cells with distinct molecular and phenotypic features, a phenomenon termed ITH. ITH may have profound impacts on biopsy strategy, characterization of actionable targets, treatment planning, and drug resistance. The extent and architecture of ITH of lung cancers are largely unknown. **Methods:** We performed multi-region WES of 48 samples from 11 surgically resected lung adenocarcinomas and their matched peripheral blood leukocytes to an average of 267-fold sequencing depth. All tumor samples were analyzed for point mutations, insertions/deletions, and copy number alterations. All somatic variations were validated with targeted capture ultra-deep sequencing to an average of 869-fold sequencing depth. Sub-clonal analysis based on a Bayesian statistics approach process was performed in each tumor sample. Phylogenetic trees of these 11 tumors were constructed after clonal ordering. **Results:** 17,572 somatic point mutations, insertions, and deletions were identified and validated. The numbers of somatic alterations varied significantly among different patients and among different samples within the same tumor suggesting significant inter- and intra-tumor heterogeneity. Sub-clonal analysis suggested presence of multiple related populations in each sample with the distribution allele frequencies varying substantially across regions of the same tumor. The majority of known driver mutations (e.g., EGFR, KRAS) were present in all regions of the sampled tumors. There was no correlation with extent/structure of ITH and age, gender, tumor size, lymph node status, or smoking status. With a median follow-up of 2.5 years, 2 patients recurred. Of potential interest, these 2 patients had the most complex ITH architectures in their primary tumors. **Conclusions:** Different lung adenocarcinomas may have distinct ITH architectures. Although the sample size is very small, the fact that both patients who relapsed had complex ITH architectures suggests that complex ITH architectures may lead to unfavorable clinical outcomes. Studies on larger cohorts are needed to elucidate the clinical impacts of ITH.

**11033 Poster Highlights Session (Board #22), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**BRCAness in non-small cell lung cancer (NSCLC).** *Presenting Author: Saiama Naheed Waqar, Division of Oncology, Washington University School of Medicine, St. Louis, MO*

**Background:** Germline mutations in the *BRCA1* and *BRCA2* DNA repair genes confer susceptibility to breast and ovarian cancer, and are targets for PARP inhibitors. The term "BRCAness" broadly refers to somatic molecular defects in the cellular DNA repair machinery, resulting in a phenotype similar to that caused by BRCA germline mutations. We evaluated data from The Cancer Genome Atlas (TCGA) for molecular alterations in double strand DNA repair genes in NSCLC. **Methods:** We examined somatic molecular alterations in 20 homologous recombination (HR) and 16 Fanconi anemia (FA) genes in 230 lung adenocarcinoma (LUAD) and 178 squamous cell carcinoma (SQCC) samples from TCGA data using cBio portal. Alterations were classified into homozygous deletion, mutation, and amplification. Tendency towards co-occurrence and mutual exclusivity of mutations in these genes was described using odds ratios (OR) and calculated by Fisher's exact test using $\alpha = 0.05$. **Results:** Somatic molecular alterations involving at least 1 HR or FA gene were observed in 121 (53%) of LUAD and 90 (51%) of SQCC respectively. The most common homozygous deletions noted were in *RAD51* (3%) in LUAD and *XRCC1* (1%) in SQCC. Frequent somatic gene mutations in *BRCA2* (5%), *BRCA1* (3%), *RAD54B* (3%) and *BRIP1* (3%) were observed in LUAD, including the well-known nonsense S3376 and S2695 mutations in *BRCA2*. *BRCA1* and *RAD51D* mutations tended to co-occur (OR >10; p=0.03), while *BRCA2* mutations tended to co-occur with *FANCB* (OR >10; p=0.02) and *RAD54L* (OR >10; p=0.01) in LUAD. Commonly observed somatic mutations in SQCC included the following genes: *BRCA1* (6%), *BRCA2* (6%), *FANCA* (3%) and *PALB2* (3%), including the known Q94 and K1160 nonsense mutations in *BRCA1* and nonsense mutations Q499 and E187 in *BRCA2*. *BRCA1* and *PALB2* gene mutations tended to co-occur (OR>10; p=0.001) in SQCC. Amplifications were most commonly noted in *XRCC2*, *NBN*, *RBBP8* and *C19ORF40* in LUAD (2% each), and *FANCG*, *FANCL, C19ORF40* in SQCC (4% each). **Conclusions:** BRCAness is commonly observed in NSCLC and may be a target for PARP inhibition in molecularly selected patient populations.

**11034 Poster Highlights Session (Board #23), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Oncogenic ARAF as a new driver in lung adenocarcinoma.** *Presenting Author: Luiz H. Araujo, The Ohio State University Comprehensive Cancer Center, Columbus, OH*

**Background:** We recently identified a novel somatic mutation in ARAF in a lung adenocarcinoma from a patient that demonstrated a remarkable response to sorafenib. The S214C lies in a negative regulatory domain of ARAF, distinct from the catalytic domain mutations commonly found in BRAF. The aim herein was to evaluate the oncogenic potential and characterize the mechanism of ARAF S214C activation. **Methods:** ARAF constructs were generated and ectopically expressed in an immortalized bronchial epithelial cell line (BEAS-2B). We evaluated the acquisition of anchorage independence, MEK activation, and cell morphology. COS7 cells were used for co-immunoprecipitation (IP) and kinase assays. **Results:** Cells expressingARAF S214C substantially increased soft agar colony formation relative to vector, wild-type, kinase-dead (D429A), and double-mutant (S214C+D429A) variants. Accordingly, ARAF S214C cells exhibited increased phospho-MEK levels, suggesting that the transforming potential is dependent on its kinase activity. We also demonstrated that cells expressing ARAF S214C with an additional RAS-binding domain mutation (R52L) lacked MEK activation and failed to form colonies, showing that RAS binding is essential for activity. Interestingly, ARAF S214C cells acquired an elongated, fibroblast-like shape, characteristic of MEK-active cells. Conversely, none of other variants presented this morphology. To determine if either BRAF or RAF1 were necessary for ARAF S214C activity, we performed BRAF and RAF1 knockdowns. ARAF S214C-induced MEK activation was not reverted by the knockdowns, suggesting that BRAF and RAF1 are not required. Subsequently, COS7 cells were co-transfected with tagged constructs of ARAF and either BRAF or RAF1, followed by co-IP. We showed that ARAF S214C does not heterodimerize, unless stimulated with sorafenib. Importantly, sorafenib-induced heterodimers lacked kinase activity, compatible with the clinical response reported. **Conclusions:** ARAF S214C demonstrates the *in vitro* features of a driver oncogene, and also a distinct mechanism of action. This oncogenic process can be successfully suppressed by RAF inhibitors like sorafenib, and could represent a new target for personalized therapy in advanced lung adenocarcinoma.

**11035 Poster Highlights Session (Board #24), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Efficacy of crizotinib in ROS1-rearranged lung cancer: The European experience.** *Presenting Author: Julien Mazieres, Hôpital Larrey CHU Toulouse, Toulouse, France*

**Background:** ROS1 chromosomal rearrangement (ROS1+) was described as an oncogenic driver in approximately 1% of non-small cell lung cancers (NSCLC). Due to the structural analogy of ROS1 and ALK, crizotinib is a potent inhibitor of both targets. An expansion cohort of a phase I trial reported promising activity [Ou et al., ASCO 2013]. Here, we describe the characteristics and outcomes of ROS1+ NSCLC patients treated with crizotinib in a large European case series. **Methods:** We conducted a retrospective study among European clinicians screening ROS1+ NSCLC. Eligible patients had advanced NSCLC, known ROS1+ NSCLC diagnosed by FISH and received crizotinib for at least 1 week at the dose of 250 mg BID through national access program or an individual off-label use basis. Treatment response was performed according to RECIST criteria version 1.1. Informed consent and IRB approval were obtained according to local regulations. Data were analyzed centrally. **Results:** We identified 28 ROS1+ NSCLC patients treated with crizotinib. Our population was characterized by a median age of 58 yr (34 to 78 yr), a gender-ratio of 17 women and 11 men and a high proportion of never smokers (n = 19, 67.9%). All the patients had stage IV disease and were pretreated with none (n=2), one (n = 8), two (n = 5), three (n = 3) or more (n = 10) lines of chemotherapy before the administration of crizotinib. All tumors were adenocarcinomas including 4 with lepidic pattern. ROS1 rearrangement was the exclusive driver except for 2 tumors with concomitant KRAS mutation. Twenty-six patients were evaluable for response (the waterfall plot will be presented at the meeting). We observed 3 progressive diseases, 3 stable diseases and 20 objective responses including 4 complete responses (overall response rate 77%, disease control rate 88%). Crizotinib primary resistance was associated with concomitant KRAS mutation or progression in the brain. Crizotinib was generally well tolerated and no unexpected adverse effects were observed. **Conclusions:** These results confirm the high crizotinib activity in ROS1+ NSCLC. Further patients should be treated in ongoing clinical trials to test the long-term activity of ROS1 inhibitors.

**11036 Poster Highlights Session (Board #25), Mon, 8:00 AM-11:00 AM and 11:30 AM-12:45 PM**

**Identification of a lung cancer growth factor, LASEP1, as a serological and prognostic biomarker and a therapeutic target.** *Presenting Author: Atsushi Takano, Center for Antibody and Vaccine, Research Hospital, Institute of Medical Science, The University of Tokyo, Tokyo, Japan*

**Background:** Cancer-specific oncoantigens could be ideal targets for the development of novel diagnostic/prognostic biomarkers and/or therapies. **Methods:** To identify new oncoantigens, we screened up-regulated genes that encode secreted protein in 120 cases of non-small cell lung cancers (NSCLCs) by means of cDNA microarray containing 27,648 genes and examined clinicopathological significance of their protein expression by tissue microarray covering 374 NSCLCs. We further examined their growth/invasion effect on cancer cells by siRNA and Matrigel invasion assays. We also measured their protein concentration in serum by ELISA. **Results:** We identified *LASEP1* (Lung cancer Associated Serum Protein 1) as a candidate secreted protein. Immunohistochemical staining confirmed that positive staining of LASEP1 was observed in 210 (56%) of 374 NSCLCs. Multivariate analysis revealed that high level of LASEP1 expression was associated with poor prognosis for NSCLCs patients. The proportion of serum LASEP1-positive cases was 127 (38.6%) of 329 lung cancers, while 4 (3.9%) of 102 healthy volunteers were falsely diagnosed. Furthermore, suppression of *LASEP1* by siRNAs inhibited the growth of cancer cell through a significant increase in the number of cells at the G1 phase. In addition exogenous LASEP1 expression enhanced the growth and the cell mobility *in vitro*. LASEP1 interacts with its 50-kDa receptor (LASEPR) on the surface of cancer cells. siRNAs for *LASEPR* also inhibited the growth of cancer cells. The LASEP1-LASEPR interaction promoted the cell growth in an autocrine manner. The growth activity of the LASEP1-positive cells was neutralized by addition of originally developed anti-LASEP1 monoclonal antibodies into their culture media. The systemic administration of the anti-LASEP1 antibody to tumor-implanted mice significantly suppressed tumor growth without any adverse events. By gene expression analysis using microarray to determine down-stream genes of *LASEP1*, we identified *WHSC1* encoding an oncogenic histone methyltransferase as a LASEP1-target gene. **Conclusions:** LASEP1 was suggested to be a good candidate for the development of biomarkers and therapeutic target for lung cancer.

**11037 General Poster Session (Board #319), Sat, 1:15 PM-5:00 PM**

**Differences in circulating angiogenic biomarkers as prognosticator for outcome in bevacizumab-treated nonsquamous non-small cell lung cancer (NSCLC) patients.** *Presenting Author: Marta Batus, Rush University Medical Center, Chicago, IL*

**Background:** Trials evaluating role of bevacizumab in patients with advanced NSCLC have shown only modest impact in outcomes. The objective of this study was to evaluate predictive value of panel of circulating biomarkers important in cancer-induced angiogenesis in frontline treatment. **Methods:** Chemonaïve non-squamous patients were assigned to regimens of standard platinum-doublet chemotherapy either alone (CTx; n=20) or in combination with bevacizumab (CTx+bev; n=21). Paired pretreatment and post first cycle sera from each patient were evaluated using Human Angiogenesis Growth Factor Panel (EMD Millipore) which contains angiopoietin-2, BMP-9, EGF, endoglin, endothelin-1, FGF-1, FGF-2, follistatin, G-CSF, HB-EGF, HGF, IL-8, leptin, PLGF, VEGF-A, VEGF-C, and VEGF-D on a FlexMAP 3D system (Luminex Corp.). Serum pretreatment and differential (pre- vs. post-treatment) levels of each analyte were associated with progression-free survival (PFS) and overall survival (OS) and compared between regimens. Multivariate Cox PH analyses were used to identify interaction of markers with CTx/CTx+bev on PFS and OS. **Results:** Increasing levels of VEGF-A in first cycle of treatment were differentially associated (HR=4.98; $p<0.001$) with a worse PFS in the CTx+bev cohort versus CTX. Alternately, increasing levels of IL-8 were differentially associated with poor PFS and OS in CTx patients ($p=0.003$, 0.02, respectively). Increasing leptin levels were associated with a favorable OS in CTx+bev cohort, versus CTX (HR=0.36, $p=0.02$). Large increases in angiopoietin-2, HGF, follistatin, VEGF-C, and VEGF-D were associated with a poor OS ($p<0.05$), whereas large increases in FGF-1, and endothelin-1 were associated with more favorable OS ($p<0.01$). **Conclusions:** Significant relationship betweenchanging levels of angiogenic biomarkers and PFS/OS observed in our relatively small groups of patients suggests that further evaluation of angiogenic biomarkers in longitudinal studies is warranted to substantiate value of molecules for prognosticating and identifying patients more likely to benefit from frontline bevacizimab therapy.

**11038 General Poster Session (Board #320), Sat, 1:15 PM-5:00 PM**

**Biologic pathways associated with breast cancer metastases to the brain.** *Presenting Author: Vinay Varadan, Case Comprehensive Cancer Center, Cleveland, OH*

**Background**: Brain metastases (BM) associated with breast cancer are difficult to treat, with a median survival less than 1 year for these patients. While basal-like and HER2+ breast cancers are at higher risk of developing brain metastases, no effective treatments exist for these patients. Comprehensive characterization of the transcriptome of matched primary breast (PB) tumors and BM allows for discovery of pathways mediating BM in breast cancer to improve treatment for this deadly disease. **Methods**: Pathology records were searched for patients who underwent surgical resection of BM from PB and archival FFPE material was obtained along with clinical data from the medical record and tumor registry. TMA sections were stained with ER, PR and HER2 to confirm receptor status. Tumor DNA/RNA was extracted from macrodissected 2 mm cores from FFPE. Gene expression profiling was performed using Affymetrix HTA 2.0 arrays on 96 FFPE samples for whom sufficient RNA was available. PAM50 subtypes were derived and differential gene expression between BM and PB was estimated using the Mann-Whitney-Wilcoxon test followed by multiple testing correction. Pathway enrichment analysis was performed using the KEGG and NCI Pathway Interaction Databases. **Results**: Differential gene expression analysis between the 46 BM and 26 PB showed enrichment ($p<0.05$;FDR$<0.1$) of B1 and B3 integrin, IL8 and CXCL2/4, UPA/PAI, Osteopontin, RAC1, BMP, TGF$\beta$, PI3K and Ras pathways in KEGG and NCI-PID. The matched subset of 27 BM and PB samples showed persistent enrichment for all these pathways and showed differential expression of angiogenesis (PDGFR, c-MET, Angiopoetin) lymphangiogenesis (VEGFR-3) and HIF-1-alpha and Jak-STAT signaling pathways. Differential expression of non-genomic ER signaling was seen in both cohort-level and matched PB/BM pairs and Androgen receptor signaling was modulated in paired samples. A subset of BM showed upregulation of the Creighton AKT geneset, which was confirmed using a predefined AKT activity signature. **Conclusions**: Our study shows significant modulation of driver pathways in brain metastases when compared with matched primary breast tumors. Orthogonal validation of these findings using IHC and functional studies will be presented.

**11039 General Poster Session (Board #321), Sat, 1:15 PM-5:00 PM**

**Antitumor activity of MP0250, a bispecific VEGF- and HGF-targeting darpin, in patient-derived xenograft models.** *Presenting Author: Ulrike Fiedler, Molecular Partners AG, Zurich-Schlieren, Switzerland*

**Background:** The interplay of tumor cells and their microenvironment is crucial in the growth of solid tumors. Key mediators of such interaction are the VEGF/VEGFR and the HGF/cMet pathways, which drive tumor survival, growth, angiogenesis, invasion and metastasis. It is anticipated that simultaneous inhibition of the VEGF/VEGFR and HGF/cMet pathways will interfere with crucial steps of tumor growth as well as with the onset of treatment resistance. MP0250 is a bispecific DARPin targeting both pathways simultaneously by specifically neutralizing VEGF and HGF. Its low toxicity offers the potential for combination with chemotherapy and other targeted therapies. **Methods:** Antitumor activity of MP0250 was tested in kidney, liver, lung and gastric patient-derived xenograft (PDX) models and compared to standard of care (SoC) therapies. **Results:** MP0250 showed consistent antitumor activity in 6 out of 7 investigated models. Its potency was superior to SoC in renal and gastric carcinoma models, and similar to SoC in liver and one lung cancer (NSCLC) model. Of note, neither MP0250 nor SoC (5-FU) showed potency in one SCLC lung cancer model. Tumor regression was induced by MP0250 in one liver and one renal model with optimal T/C values of 6.9% and 8.9%. Tumor growth inhibition was recorded in the other liver and one lung model (T/C values of 37% and 26%) whereas moderate efficacy was observed in the second renal cancer model (T/C value of 56%). Interestingly, MP0250 increased the potency of the SoC drug paclitaxel in the gastric cancer model (T/C values: MP0250 37%; paclitaxel 46%, MP0250/paclitaxel 21%). No toxicity of MP0250 was observed as monotherapy or in combination with SoC. **Conclusions:** MP0250, a bispecific DARPin blocking HGF and VEGF, is a potent inhibitor of tumor growth in PDX models, often surpassing the efficacy of SoC therapy. In a gastric cancer model, MP0250 increased potency of SoC. These results indicate that MP0250 has the potential to be used as monotherapy in a range of solid tumors and, as a result of its good safety profile, the possibility exists that it may be also combined with SoC and other tumor targeting molecules, i.e. TKIs. A phase I clinical trial is in preparation.

**11040 General Poster Session (Board #322), Sat, 1:15 PM-5:00 PM**

**A Markov chain model of a longitudinal breast cancer data set.** *Presenting Author: Paul K. Newton, University of Southern California, Los Angeles, CA*

**Background:** Cancer cell migration patterns are critical for understanding metastases and clinical evolution. Breast cancer spreads from one organ system to another via hematogenous and lymphatic routes. Although patterns of spread may superficially seem random and unpredictable we explored the possibility that this is not the case. **Methods:** Based on a data set of 453 breast cancer patients from Memorial Sloan Kettering Cancer Center—all non-metastatic at time of diagnosis—we created a Markov chain model of metastasis. This describes the probabilities of metastasis occurring at a given anatomic site together with the probability of spread to additional sites, based on observations. **Results:** Using actual data, we have learned (i) how to create the Markov transition matrix governing the probabilities of cancer progression from site to site; (ii) how to create a systemic network diagram governing disease progression modeled as a random walk on a directed graph; (iii) how to classify metastatic sites as ″sponges″ that tend to only receive cancer cells or ″spreaders″ that receive and release them; (iv) how to model the time-scales of disease progression as a Weibull probability distribution function; (v) how to perform Monte Carlo simulations of disease progression; and (vi) how to interpret disease progression as an entropy-increasing stochastic process. **Conclusions:** We have found that the patterns of metastatic spread in breast cancer are not unpredictable. Furthermore, the novel concept of classifying organ sites as sponges or spreaders may motivate experiments seeking a biological basis for these phenomena. This model may also be useful in mapping the accumulation of genomic aberrations not only over time, but also over space.

**11041 General Poster Session (Board #323), Sat, 1:15 PM-5:00 PM**

**A pilot study for cellular detection of circulating tumor cells and disseminated tumor cells of patients with hepatocellular carcinoma.** *Presenting Author: Nozomi Minagawa, Gastroenterological Surgery 1, Hokkaido University Graduate School of Medicine, Sapporo, Japan*

**Background:** Circulating tumor cells (CTC) in peripheral blood (PB) and disseminated tumor cells (DTC) in bone marrow (BM) have been recently focused as predictive and prognostic markers in solid tumors. But hepatocellular carcinoma (HCC) usually lacks epithelial antigens, only a few reports described CTC or DTC at a cellular level. The aim of this study is to establish methodology for detecting CTC and DTC in HCC at a cellular level, and to analyze with clinicopathological findings. **Methods:** PB (n-36) and BM samples (n-20) were preoperatively collected from patients with HCC between October 2011 and July 2013. Mononuclear cells were collected by Ficoll gradient separation. CD45+ cell population was deleted through magnetic activated cell sorting system. Subsequently, double immunofluorescence for AFP, Arginase-1 or Hep-Par1 and CD45 was performed. PB samples from 20 healthy volunteers and BM samples from 3 patients with benign disease were used as controls. Our protocol has been approved by the ethical committee of Hokkaido University Hospital and written informed consent was obtained from all enrolled patients. **Results:** Positive rates of CTC and DTC were 63.8% (23/36) and 65.0% (13/20). No CTC or DTC was found in the control groups. Detection of CTC or DTC was closely correlated with preoperative tumor marker and portal invasion. Positive rates of preoperative AFP and PIVKA-II in $CTC^+$, $DTC^+$ patients were statistically higher than that of $CTC^+$ or $DTC^+$ patients (AFP:73.9%, 84.6% vs 38.4%, 28.6%,p=0.04, PIVKA-II: 86.9%, 92.3% vs 53.8%, 57.1%, p=0.02). Detection of CTC or DTC is also correlated portal invasion (60.8%, 61.5% vs 7.7%, 0%,p=0.04). There're higher risk of distant metastasis in $CTC^+$ or $DTC^+$ patients, compared with that of $CTC^-$ or $DTC^-$ patients (47.8%, 53.8% vs 7.7%, 0%, p=0.04).There're significant differences in the distant metastasis-free survival (p=0.01), but not in the overall survival and in the liver recurrence-free survival (p= 0.94, 0.05). **Conclusions:** Our protocol might provide highly specific detection of CTC, DTC from HCC patients. Detection of CTC or DTC might contribute to considering postoperative therapeutic strategies.

**11042 General Poster Session (Board #324), Sat, 1:15 PM-5:00 PM**

**Effect of exemestane plus everolimus on CTC counts and Ki-67 expression on CTCs in patients with advanced hormone receptor-positive, HER2-negative breast cancer.** *Presenting Author: Sofia Agelaki, Department of Medical Oncology, University General Hospital of Heraklion, Heraklion, Greece*

**Background:** The utility of CTCs in predicting patient (pt) outcome has been demonstrated in metastatic breast cancer treated with chemotherapy or endocrine therapy. In this trial we evaluated the prognostic impact of CTC assessment in pts treated with exemestane plus the targeted therapy everolimus. **Methods:** Forty pts with HER2-negative metastatic breast cancer received exemestane plus everolimus. Blood was drawn for CTC assessment by CellSearch System and immunofluorescence (IF) analysis (7.5 and 10 ml, respectively) on day 1 of cycles 1 (n=40), 2 (n=39), 4 (n=28), on each disease evaluation and on relapse, whichever occurred first. Cytospins ($10^6$cells) of peripheral blood mononuclear cells (PBMCs) from 31 of 40 pts were double stained with pancytokeratin (CK) along with Ki-67 antibodies. **Results:** Using CellSearch 25 (62.5%) pts had detectable CTCs (cut-off ≥ 1 CTC) at baseline, 12 (30.8%) post-$1^{st}$ and 9 (32.1%), post-third cycle. In 9 pts no CTCs were observed at any time point. CTCs ≥5 were identified in 10 (25%), 6 (15.4%) and 3 (10.7%) pts at baseline, post-firstand post-third cycles, respectively. Four (40%) pts with baseline counts of CTCs ≥5 turned to <5 post-first ycle. Total CTC counts declined from 332 at baseline (mean number/pt 8.3, range 0-103) to 90 (mean 2.3, range 0-34) and 46 (mean 1.64, range 0 - 16) post-first and -third cycles, respectively. Using IF, 7 (22.5%) pts had detectable CK(+) CTCs (cutoff ≥ 1 CTC) at baseline; 8 (25.8%) of 31 and 7 (28%) of 25 were CTC(+) post -first and -third cycles, respectively. Total CTC numbers were 197 at baseline (mean, 16.42, range, 0-192) and 58 (mean 1.87, range 0-34) and 336 (mean 13.44, range 0 - 290) post-first and -third cycle, respectively; the ratio of Ki-67(+)/CK(+) CTCs declined from 32% to 13.8% and 13.4%, post-first and -third cycle, respectively. **Conclusions:** Exemestane plus everolimus effectively decreases CTC counts and the population of Ki-67(+) CTCs in HER2-negative metastatic breast cancer. Correlations with patient characteristics and outcome will be presented.

**11043 General Poster Session (Board #325), Sat, 1:15 PM-5:00 PM**

**Tumorspheres cultured from circulating epithelial tumor cells (CETCs) as diagnostic marker in patients with solid cancers.** *Presenting Author: Katharina Pachmann, Transfusion Center Bayreuth, Bayreuth, Germany*

**Background:** Metastatic disease is a serious threat and the most common cause of *cancer*-associated death in patients with solid tumors. The presence of CETCs is closely related to tumor metastasis, but it is still unclear whether all CETCs are capable to proliferate and generate metastasis. Therefore we investigated their proliferative capacity by analyzing the frequency of tumorsphere formation with subsequent phenotypic characterization of the tumorspheres arising in patients with solid tumors. **Methods:** 37 patients with solid cancer and early metastatic disease and detectable CETCs were enrolled in the present study. 10 patients had breast, 10 colorectal, 10 prostate and 7 lung cancer. CETCs were determined using the maintrac method and the CETCs were cultured in suspension culture in the context of the other white blood cells allowing for epithelial sphere formation. Cell viability, stem cell marker expression and ALDH 1 activity was evaluated by fluorescence scanning microscope (Olympus Scan R). **Results:** Sphere formation was observed in 90 %, 90 %, 80 % and 85.7 % of patients with breast, colorectal, prostate and lung cancer, respectively. Among solid cancer patients the number of tumor spheres increased significantly with tumor progression, especially with development of distant metastasis. The selectivity for distant metastasis of the area under ROC curve for the number of tumorspheres was 0.72 ($p < 0.02$). Five or more tumorspheres grouped metastatic disease with a sensitivity and specificity of 88.2 % and 75 %, respectively. Analysis of surface marker expression profile of tumorspheres showed that tumorspheres cultured from CETCs had typical phenotype of cancer stem cells and tumorspheres in patients with breast cancer possessed a high enzymatic activity for ALDH 1 with the ALDEFLUOR assay. There was no sphere formation in 20 healthy donors. **Conclusions:** Here, we describe for the first time the identification of CETCs which are capable of forming tumorspheres with proliferative activity and stem cell characteristics. This may contribute to the design of tools for early detection of progression and treatment in solid cancer.

**11044 General Poster Session (Board #326), Sat, 1:15 PM-5:00 PM**

**Bisphosphonate treatment of primary breast cancer patients with disseminated tumor cells in the bone marrow.** *Presenting Author: Andreas D. Hartkopf, Department of Gynecology and Obstetrics, University of Tuebingen, Tuebingen, Germany*

**Background:** The role of the addition of bisphosphonates (BPs) to adjuvant breast cancer treatment is unclear. Recent trials have reported different results in terms of survival. In a large meta-analysis, menopausal status was found to predict efficacy of BPs. As BPs primarily target the skeletal system to modify disease progression, we aimed to investigate whether primary breast cancer (PBC) patients that harbor disseminated tumor cells (DTCs) in their bone marrow (BM) might benefit from adjuvant BPs. **Methods:** BM aspirates were collected from patients that underwent surgery for PBC at Tuebingen University Hospital, Germany between 01/2001 and 01/2013. DTCs were identified by immunocytochemistry (pancytokeratin antibody A45/B3) and cytomorphology. Patients with a DTC-positive BM were included into this retrospective analysis. The influence of BP therapy on disease free (DFS) and overall survival (OS) was analyzed in an univariate (log-rank test) and multivariate analysis (cox regression). **Results:** 794 patients were available for this retrospective analysis. In 329 (41%) of these patients, BPs were added to conventional adjuvant therapy. Univariate analysis revealed that there was a significant risk reduction in terms of DFS (hazard ratio (HR)=0.42 [95% confidence interval (CI): 0.25-0.69], $p<0.001$) and OS (HR=0.49 [95% CI: 0.30-0.82], $p=0.006$) in patients treated with BPs. In a subgroup analysis, BPs significantly enhanced DFS ($p=0.018$) but not OS ($p= 0.235$) in premenopausal patients; in postmenopausal patients BPs improved DFS ($p=0.014$) and OS ($p=0.009$). In a multivariate analysis, independent predictors of reduced DFS were BP treatment and nodal status and independent predictors of reduced OS were BP treatment, nodal status and PR status. **Conclusions:** Adjuvant BP therapy can improve survival in primary breast cancer patients that harbor DTCs in the BM. Whether the DTC status is predictive for BP treatment efficacy must be evaluated in prospective trials.

**11045 General Poster Session (Board #327), Sat, 1:15 PM-5:00 PM**

**Epithelial-to-mesenchymal (EMT) markers and nanomechanical signatures of circulating tumor cells (CTC) for prediction of men with castrate-sensitive versus castration-resistant prostate cancer (PCa).** *Presenting Author: Devalingam Mahalingam, Cancer Therapy and Research Center, The University of Texas Health Science Center at San Antonio, San Antonio, TX*

**Background:** Advance PCa patients (pts) on androgen-deprivation therapy (ADT) eventually develop castrate-resistance (CR) disease. Men failing to achieve PSA $\leq$ 4ng/mL after 7 months of ADT have the greatest risk of early death from advance PCa. The challenge is to distinguish indolent vs. aggressive cancer, castrate sensitive (CS) vs. CR early for better disease control. During PCa progression CTC shed from tumor into bloodstream is subject to physical forces, epigenetic modifications and EMT transition. Little is known if EMT transition and the nanomechanical signatures of CTC can predict sensitivity to ADT. **Methods:** We obtained CTCs from 29 pts with advance PCa. CTCs were isolated from pts blood (~15 ml) using microfiltration system (ScreenCell). We analyzed CS and CR PCa cell lines, and correlated CTCs from pts with CS or CR using high throughput microfluidic single-cell RT-PCR. CTCs from 18 pts were subjected to nanomechanical analysis with atomic force microscopy (AFM) using PeakForce QNM Catalyst (Bruker). Elasticity, deformation and adhesion were evaluated as elements of nanomechanical phenotype. **Results:** 20pts with CR and 9pts with CS advance PCa were enrolled. Median age 65 (47-91). Median PSA 40.77 (0.1-2368.31ng/ml). A median of 1.6 (0–15) CTC/ml were detected. Increased expression of EMT genes was found in CR PCa cells and CTCs compared to CS counterparts. IPA indicated that these EMT genes are closely related to AKT, $\beta$-catenin, Myc and NF$\kappa$B pathways. AFM show that CTCs of CR pts are $\geq$ 3 fold more elastic, ~5 fold more adherent and ~3 fold more deformable than CTCs of CS pts. Using Young modulus elasticity value $<$2.91 kPa, adhesion value $>$ 120 pN and deformation value of $>$ 412nm, combined analysis of all 3 parameters gives a $>$ 99% power of detecting a nanomechanical phenotype of CR PCa ($p=0.0002$). **Conclusions:** CTCs isolated from CR PCa pts often lose the typical features of prostate epithelial cells, display incremental EMT-related gene expression and have a distinct nanomechanical phenotype compared to CS PCa, and could serve as biomarker for early CR detection, treatment stratification and subsequent disease monitoring.

**11046 General Poster Session (Board #328), Sat, 1:15 PM-5:00 PM**

**Identification through genome-wide association study (GWAS) of single nucleotide polymorphisms (SNPs) associated with extreme phenotypes of tobacco-induced non-small cell lung cancer (NSCLC) risk.** *Presenting Author: Jose Luis Perez-Gracia, Department of Oncology. Clinica Universidad de Navarra, Pamplona, Spain*

**Background**: SNPs may modulate individual susceptibility to carcinogens. We used GWAS to identify SNPs associated with individuals presenting extreme phenotypes of sensitivity and resistance to develop tobacco induced NSCLC. We hypothesized that selection of extreme phenotypes would enrich the frequencies of alleles that contribute to the trait, thus increasing the power to identify them. **Methods:** From an identification cohort (n=3631) we selected caucasian heavy smokers that either developed NSCLC at an early age (cancer cohort) or that did not present NSCLC at an advanced age (cancer free cohort). We analyzed their genomic DNA using the array Illumina HumanOmni 2.5 Quad that includes over 2 million powerful markers selected from the 1000 Genomes Project, targeting genetic variation down to 1% minor allele frequency. **Results:** 96 patients (48 per cohort) were selected. Mean age for the cancer and cancer free cohorts was 49 (range 38-55) and 76 years (72-84). Mean tobacco consumption was 41 (range 18-99) and 68 pack-years (40-120). GWAS identified 8 SNPs differentially expressed by logistic regression and 54 SNP by Fisher´s test ($p<10^{-5}$). Odds-ratio ranged between 0.08-0.29 for protective SNP and 3.4-11.2 for SNP that increased NSCLC risk. Candidate SNPs were located within or in adjacent regions of genes related to: a) oncogenic and tumor-suppressor pathways: *CSMD1, FOXF1, MSX2, SOX11*; b) tobacco induced NSCLC: *ABCB5*; c) regulation of transcription: *DROSHA, HDAC9, KIAA0947*; d) regulators of inflammation through the NF-kappa pathway: pellino E3, *TRIM9*; e) previously linked to carcinogenesis and cancer prognosis: *ABHD6, GRIK1, RAB40B, SCN1A, SLC24A2, SLC25A26, ZFYVE26*; and f) not previously linked to cancer: *ACER3,* AP000946.2, *ATP10A, ATP10D,* CNTN5, *CYYR1*, LINC00572, *PDE10A, RP11-115D19.1, RP11-202D1.3, RP11-521E5.1, SYTL5, ZPBP*. **Conclusions:** We identified candidate SNPs potentially associated with the risk of developing tobacco induced NSCLC in individuals with extreme phenotypes. Validation of the most significant SNPs in an independent set of individuals with similar phenotypes is ongoing.

**11047 General Poster Session (Board #329), Sat, 1:15 PM-5:00 PM**

**Systematic review of a personalized strategy in cancer clinical trials leading to FDA approval.** *Presenting Author: Denis Leonardo Fontes Jardim, University of Campinas, Campinas, Brazil*

**Background:** Evidence for the hypothesis that personalization of therapy optimizes benefit is a subject of debate. We compared efficacy between US Food and Drug Administration (FDA) approved cancer treatments deploying a personalized strategy vs. those without a biomarker-based rationale. **Methods:** We reviewed registration trials (based on package inserts from Drugs@FDA) that evaluated new agents receiving FDA approval (Sept. 1998 to June 2013) for cancer. Pooled analysis of response rate (RR), progression-free survival (PFS) and overall survival (OS) for all trials and hazard ratios (HRs) for time-to-event endpoints for randomized trials were compared between personalized (defined as using a drug matched to a biomarker or in a population where $>$ 50% of patients harbor the cognate target) vs. non-personalized trials. **Results:** A total of 58 approved drugs were included (57 randomized [32% personalized] and 55 non-randomized trials [47% personalized]; N=38,104 patients). Personalized trials more often included oral drugs (68% vs. 35%, P=0.001), single agents (89% vs. 71%, P=0.036) and more frequently allowed crossover to experimental arms than non-personalized trials (67% vs. 28%, P=0.009). RR was significantly higher (49% vs. 25%, P$<$0.001) and PFS was longer (8.5 vs. 5.5 mos, P=0.001) with a personalized approach. In the multilinear regression analysis, personalized therapy was selected as an independent factor predicting a higher RR (P$<$0.001) and longer PFS (P=0.002). Median HR for PFS of experimental to control arms was 0.37 for personalized vs. 0.58 for non-personalized trials (P=0.003), indicating that, in randomized trials, the personalized experimental arm had significantly more improvement in PFS. Personalized trials also showed a longer OS (median= 18.2 vs. 13.5 mos, P=0.035 in the multilinear analysis), even though crossover was allowed more frequently in personalized trials. Median treatment-related mortality did not differ (0.4%, personalized vs. 1.0%, non-personalized, P=0.22). **Conclusions:** Personalized trials were associated with more pronounced clinical benefit, expressed by significantly higher RR and longer PFS and OS, despite the latter being confounded by more frequent crossover.

**11048 General Poster Session (Board #330), Sat, 1:15 PM-5:00 PM**

**Targeted next-generation sequencing (NGS) of carcinoma of unknown primary site (CUP): Actionable genomic alterations (GA) and new routes to targeted therapies.** *Presenting Author: Jeffrey S. Ross, Albany Medical College, Albany, NY*

**Background:** CUP comprises 3% of adult malignancy in the US. Evaluation for a primary site is often unrevealing and may involve invasive studies. We performed NGS to identify potential therapeutic targets not currently tested for in routine care of CUP patients. **Methods:** Hybridization capture of 3,769 exons from 236 cancer-related genes and 47 introns of 19 genes commonly rearranged in cancer was applied to ≥ 50ng of DNA extracted from 200 CUP FFPE specimens and sequenced to high, uniform median coverage (756X) and assessed for all 4 classes of GAs. Elligible CUP were uniformly negative for site-specific IHC, FISH or mRNA biomarkers. Actionable alterations were defined as those for which cancer drugs on the market or in registered clinical trials could be identified. **Results:** 63% of CUP were adenocarcinomas (ACUP) and 37% were non-adenocarcinomas (non-ACUP). 54% were female and 46% male (median age 59). IHC workup was performed on 95% and mRNA profiling on 3%. 841 GA were identified in 121 genes for an average of 4.21 GA/CUP. 192/200 (96%) CUP had at least 1 GA. 169 (85%) CUP had at least 1 actionable GA (2.00 actionable GA/CUP). The most common actionable GA were *KRAS* (25% ACUP, 12% non-ACUP), *CDKN2A* (19% ACUP and non-ACUP), *MCL1* (10% ACUP, 8% non-ACUP), *PTEN* (8% in both ACUP and non-ACUP), *PIK3CA* (8% in ACUP and 9% in non-ACUP), *BRAF* (6% in ACUP and 2% in non-ACUP) and *NF1* (5% in ACUP and 3% in non-ACUP),. Mutations and amplifications of *ERBB2* (*10%), EGFR* (8%) and BRAF (6%) were common in ACUP but not present in non-ACUP. 5 (3%) CUP had rearrangements involving *ERBB3*, *FGFR1* and *FGFR2.* The greater frequency of actionable GA in the RTK/RAS signaling pathway observed in 90 (72%) ACUP cases compared to the 29 (39%) of non-ACUP cases was significant ($p<0.0001$). **Conclusions:** 85% CUP patients had at least one actionable GA with the potential to impact therapy selection with GA in the RTK/RAS/MAPK pathway more frequent in ACUP tumors. Given the poor prognosis of CUP, comprehensive genomic profiling may identify targeted therapeutic approaches to improve outcomes for this disease while potentially reducing the often costly and time consuming search for anatomic site of origin.

**11049 General Poster Session (Board #331), Sat, 1:15 PM-5:00 PM**

**Noninvasive monitoring of dynamics of acquired EGFR-T790M mutation and discovery of its heterogeneity in patients with advanced NSCLC treated with EGFR-TKI.** *Presenting Author: Di Zheng, Shanghai Pulmonary Hospital, Department of Medical Oncology, Tongji University School of Medicine, Shanghai, China*

**Background:** EGFR-T790M mutation, a valuable target for next generation of EGFR-TKI, accounts for about half of acquired resistance to current EGFR-TKI therapy in EGFR sensitive mutation positive NSCLC patients. Noninvasive detection of EGFR-T790M in plasma circulating free DNA (cfDNA) has been proved to be feasible as re-biopsy of tumor tissue was challenging. However, clinical application of T790M plasma testing remains to be explored, particularly the rate and timing of detection, the status of co-existence with a sensitive mutation, and its potential impact on chemotherapy following EGFR-TKI resistance. **Methods:** A highly sensitive digital PCR method for EGFR mutation testing in plasma was developed and its high sensitivity and specificity were validated in testing cfDNA from EGFR-TKI-naïve NSCLC patients. This method was applied to detect T790M in plasma cfDNA from 66 post disease progression (PD) NSCLC patients, who developed acquired resistance to EGFR-TKI. Plasma samples before PD were available for some patients. **Results:** Overall, EGFR-T790M was detected in 36 out of 66 post-PD patients (54.5%). Among 10 of the 36 post-PD T790M+ patients, 5 (50%) were detected T790M+ during 1.5-3.5 months before PD. While T790M co-exists with a sensitive mutation in 30 of the 36 T790M+ patients (83.3%), T790M presents alone in 6 of the 36 patients (16.7%). Furthermore, dynamic quantitative changes of sensitive mutations and T790M in a few patients who received chemotherapy plus TKI after PD showed preliminary insight that, even in double mutant cases, T790M and sensitive mutant DNA might not always come from the same tumor cell populations, and the T790M heterogeneity status could affect outcome of chemotherapy following EGFR-TKI resistance. **Conclusions:** Noninvasive monitoring of plasma cfDNA could detect T790M with a positive rate similar to that reported in tumor tissue in advanced NSCLC patients treated with EGFR-TKI. T790M could be detected in plasma up to 3.5 months before clinical PD. T790M may present with or without EGFR sensitive mutation in tumor cells, and its heterogeneity status could affect outcome of chemotherapy following EGFR-TKI resistance.

**11050 General Poster Session (Board #332), Sat, 1:15 PM-5:00 PM**

**Clinical utility of the 12-gene DCIS score assay: Impact on treatment (Tx) recommendations.** *Presenting Author: Michael Alvarado, Helen Diller Family Comprehensive Cancer Center Carol Franc Buck Breast Care Clinic, San Francisco, CA*

**Background**: About 20% of breast cancers (BC) are DCIS. Local recurrence (LR) rates with surgery alone are 15-60%; about 50% are invasive. Radiation (XRT) reduces LR by 50% but has not impacted survival. Clinicians and patients (pts) must decide between multiple options including breast conserving surgery, mastectomy, partial or whole breast XRT, and hormonal manipulation. Traditional clinicopathologic (CP) factors provide an average LR risk derived from population studies. The validated Onco*type* DX 12-gene assay for DCIS gives additional, independent, individual estimates of 10-year risk of any LR and invasive LR. We report the first study to assess the impact of the DCIS Score result on XRT recommendations for pts with DCIS. Baseline (BL) characteristics are described here; final results on change in Tx recommendations from pre- to post-assay will be presented at the meeting. **Methods**: 11 U.S. sites enrolled pts with DCIS from 9/2012-1/2014. Pts with LCIS but no DCIS, invasive BC, or planned mastectomy were excluded. Data were prospectively collected on CP factors, physician estimates of LR risk, DCIS score, and Tx recommendation before and after the assay result was known. The study received IRB approval. **Results**: 110 pts had a mean age of 60.1 yrs (SD: 9.9); 75.5% were postmenopausal. Mean DCIS size was 13.5mm (SD: 15.8); 20% had nuclear grade of 1, 46.4% grade 2, and 33.6% grade 3. Necrosis was noted in 63.6% (focal in 29.1%). Median distance from closest margin was 3mm. ER and PR IHC tests were positive in 85.5% and 78.2%. Mean physician-assessed 10-yr risk of LR was 20.8% (range 6-40%) for any LR and 10.9% (3-25%) for invasive LR. Anti-estrogen Tx was recommended in 72.7%, aromatase inhibitor in 20.9%, XRT in 72.7%, and additional surgery in 18.2%. **Conclusions**: The DCIS Score use may reduce both under- and overtreatment; establishing its impact on treatment decisions is critical to understanding the utility of this genomic assay in clinical practice.The BL characteristics of the cohort, the LR risk estimate and the pre-assay Tx recommendations are consistent with current practices, including 73% recommended XRT. The full analysis will assess the clinical utility of incorporating the DCIS Score result into clinical practice.

**11051 General Poster Session (Board #333), Sat, 1:15 PM-5:00 PM**

**Targeted deep sequencing from circulating plasma DNA as a multipurpose biomarker in pts (pts) referred for phase I trials.** *Presenting Author: Jean-Sebastien Frenel, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*

**Background:** Plasma from pts with cancer contains cell free DNA (cfDNA) that can be interrogated by next generation sequencing (NGS). We assessed the use of plasma NGS as a multi-purpose biomarker in advanced cancer pts referred for Phase I trial participation. **Methods:** Between 12/2012 and 12/2013, the plasma of pts with known mutations in tumor biopsies completing at least 2 courses of investigational targeted drug therapy was collected monthly until disease progression. cfDNA was extracted and NGS performed on the PGM platform with the Ion AmpliSeq Cancer Hotspot Panel v2 starting from 10ng of DNA. This panel amplifies 207 amplicons covering 2,800 COSMIC mutations from 50 oncogenes and tumor suppressors. **Results:** The mean sequencing coverage across the experiments was 1,685x. Overall, 37 pts (colon (n=11), ovary (10), breast (7), bladder (2), kidney (2), glioblastoma (2), endometrium/melanoma/penile/lung (n=1) receiving inhibitors of the PI3K-AKT-mTOR pathway (n=23), MEK (n=7), PARP (n=3)) or others targets (n=4) were included. *TP53, KRAS* and *PIK3CA* were the most commonly mutated genes in tumor biopsies. At Phase I trial initiation (C1D1), 20 of 37 pts (54%) had at least one mutation identified in cfDNA. Pts with only nodal or peritoneal disease were less likely to have a mutation detected: 1/6 (17%) having a cfDNA mutation. Thirty-six different mutations were identified at C1D1 in 20 pts: *TP53* (n=15) with an allele frequency (AF) ranging from 2% to 57%; *KRAS* (n=6; AF 4-51%); *PIK3CA* (n=6; AF 5-58%); *APC* (n=4; AF=15-33%); *SMAD4, HRAS, FBXW7, CDKN2A, ATM* (n=1). Three mutations identified in cfDNA were not identified in tumor: *TP53* (Y220C; AF 4.5%), *ATM* (R337C; AF 18%), *TP53*(R342fs*2; AF 23%). In 15 pts, subsequent AF mutation monitoring showed that 75% (3/4) of pts with a >30% decrease in AF at C2D1 compared to baseline had stable disease or a partial response by RECIST after 2 cycles. Conversely 87.5% (7/8) of pts with an increasing AF >20% at C2D1 had progressive disease by RECIST after 2 cycles, while a stable AF at C2D1 ($-20\% < \Delta AF < +30\%$) was associated with SD in 2/3 pts. **Conclusions:** NGS of plasma is feasible even with low DNA input and may be of utility as a predictive and response biomarker.

**11052 General Poster Session (Board #334), Sat, 1:15 PM-5:00 PM**

**Prediction of recurrence with the Onco*type* DX recurrence score in node-positive, HR-positive, breast cancer patients treated with adjuvant chemotherapy: Results from PACS01 trial.** *Presenting Author: Frederique Madeleine Penault-Llorca, Centre Jean Perrin, Clermont-Ferrand, France*

**Background:** The Recurrence Score (RS) predicts outcome in node- and node+, ER+ pts treated with endocrine therapy and predicts chemotherapy benefit. We studied the prognostic impact of RS in node+, HR+ pts treated with adjuvant chemotherapy plus endocrine therapy in PACS01 **Methods:** PACS01 compared FECX6 with FECX3+ docetaxel X3(FEC-D) in 1999 pts. After a protocol amendment, HR-positive pts received 5 yrs of tam after chemo. The current study includes 530 pts from the PACS01 parent trial who were central IHC HR+ with sufficient tissue for Onco*type*DX. The primary objective was to estimate the association between RS and distant recurrence free interval (DRFI). Secondary endpoints included disease free survival (DFS) and overall survival (OS). Median follow-up time was 7.7 yrs **Results:** Of the 530 pts, 209 (39.4%) had low RS; 159 (30.0%) intermediate RS; and 162 (30.6%) high RS. 74.2% were treated with tam. In the primary analysis, RS was a significant predictor of DRFI (HR= 4.1 for a 50 point difference, $P<0.001$), DFS (HR=3.3, $P<0.001$) and OS (HR=5.0, $P<0.001$). In multivariate analyses, RS provided independent prognostic information beyond clinicopathologic factors including treatment, age, tumor size & grade, number of + nodes, surgery type and Ki-67 status ($P<0.001$). RS was a significant predictor of DRFI, DFS, and OS in both treatment arms ($P<0.001$). There was no statistically significant interaction between RS and treatment arm in predicting distant recurrence ($P=0.79$). **Conclusions:** The 21-gene RS maintains significant prognostic impact in HR+, node+ pts who have received FEC or FEC-D adjuvant chemotherapy. These findings emphasize the need to target pts with high residual risk for recurrence with additional therapies to overcome unfavorable biology, potential endocrine and/or chemotherapy resistance.

**Kaplan-Meier estimates of 5-yr DRFI, DFS, and OS.**

| End point (95%CI) | RS low n=209 | RS intermediate n=159 | RS high n=162 | Log-rank p-value |
|---|---|---|---|---|
| **DRFI %** | 93.7 (89.4-96.3) | 87.3 (81.0-91.6) | 69.3 (61.5-75.8) | p<0.001 |
| **DFS %** | 90.8 (86.0-94.1) | 84.9 (78.3-89.6) | 64.6 (56.7-71.4) | p<0.001 |
| **OS %** | 99.0 (96.2-99.8) | 95.6 (90.9-97.9) | 85.6 (79.1-90.2) | p<0.001 |

**11053 General Poster Session (Board #335), Sat, 1:15 PM-5:00 PM**

**Molecular abnormalities of 17 types of gastrointestinal cancer in an international cohort of 11,324 patients.** *Presenting Author: Gargi Dan Basu, Caris Life Sciences, Phoenix, AZ*

**Background:** Gastrointestinal cancers (GICs) are classified based on both organ and tissue of origin, but might be better classified based on their molecular profile. We performed a multiplatform biomarker analysis of the main 17 types of GICs to identify molecular abnormalities and their associations. **Methods:** We analyzed 11,324 cases of GIC (96% from USA) using gene sequencing (up to 44 different genes, Sanger, NGS), protein expression by immunohistochemistry (up to 28 gene products) and gene amplification by CISH or FISH (up to 8 genes). Further, we performed heat map analysis of the 70 molecular anomalies in 17 GIC sites. **Results:** Steroid receptor (ER, PR) expression was distinctively high in neuroendocrine cancers (CA) (10-40%) while AR expression was elevated in hepatocellular carcinoma (HCC) (20%). HER2 overexpression and amplification was distinctively elevated in gastric, GEJ, esophageal and gall bladder CA (up to 20%). Overexpression of TOP2a was noted in most of the GICs, reflecting their highly proliferative and aggressive nature. Overexpression of cMET (up to 82%) and EGFR amplification (up to 32%) was noted in a majority of GICs suggesting benefit from cMET and EGFR targeted therapies. HCC had a high frequency of CTNNB1 (19%, 11/58) and low frequency of ABL1 mutation (3%, 2/59). Distribution of APC mutations in GIC ranged from 10-73%. PIK3CA mutation and PTEN loss were frequent events (up to 15% and 89% respectively) in a majority of GIC, suggesting potential benefit of targeting the PI3K pathway. Based on the RAS/RAF and PI3K/PTEN/Akt/mTOR pathway alterations, colon and rectal CA share similar molecular signatures but gall bladder and biliary tract CA, as well as colon and appendix CA, are molecularly distinct. Small bowel and duodenal CA exhibited different molecular signatures based on APC, ATM, SMAD4 and p53 mutations. **Conclusions:** Molecular profiling of GICs might allow us to reconsider clinical trial design and disease management based on individual cancer molecular abnormalities. Protein expression and copy number alterations should be considered together with mutational analysis to refine cancer treatment in GI tract malignancies.

**11054 General Poster Session (Board #336), Sat, 1:15 PM-5:00 PM**

**Quantification of T790M mutation in *EGFR*-mutant lung adenocarcinoma with nanofluidic digital PCR arrays.** *Presenting Author: Kazutoshi Isobe, Department of Respiratory Medicine, Toho University Omori Medical Center, Tokyo, Japan*

**Background:** Patients with EGFR-mutant lung adenocarcinoma develop acquired resistance to EGFR-TKI (TKI) in 10-16 months. About 50% of patients with acquired resistance to TKI have T790M mutation (T790M). However, repeat biopsy to monitor mutation status is not practical. Digital PCR arrays limiting dilution of DNA and can detect single molecules, thus enabling extremely sensitive detection and quantification. We evaluated the usefulness of nanofluidic digital PCR arrays in EGFR-mutant lung adenocarcinoma. **Methods:** We enrolled 12 patients with primary lung adenocarcinoma and *EGFR* mutation (exon 19 deletion in 8; L858R in 4) at the pretreatment primary site who acquired resistance to gefitinib. Patients were divided into 2 groups according to T790M status after TKI resistance, as confirmed by rebiopsy. Nanofluidic digital PCR arrays (BioMark HD System, Fluidigm Japan K.K. Tokyo, Japan) were used to quantify T790M in genomic DNA from the pretreatment primary site and serum cell-free DNA (cfDNA) after TKI resistance. Numbers of mutant molecules were estimated by the number of positive chambers in the digital PCR chip and were corrected using the Poisson equation. We assessed the ratio of the number of positive T790M molecules to the number of positive exon 2 molecules. **Results:** The digital PCR array detected and quantified T790M (0.00-1.21%) in samples from the pretreatment primary site and serum cfDNA after TKI resistance. On digital PCR, the rebiopsy-positive T790M group (n=4) had a significantly higher quantified T790M at the pretreatment primary site than did the T790M-negative group (n=8) ($0.59\pm0.58\%$ vs $0.07\pm0.09\%$, $p < 0.001$). However, the results of analysis of serum cfDNA after TKI resistance did not significantly differ ($0.09\pm0.14\%$ vs $0.05\pm0.15\%$, respectively, $p = 0.41$). T790M at the pretreatment primary site as quantified by digital PCR significantly positively correlated with progression-free survival (PFS) after gefitinib therapy ($r = 0.71$, $p < 0.001$). **Conclusions:** Use of digital PCR to quantify T790M at the primary site of EGFR-mutant lung adenocarcinoma was useful for predicting T790M positivity in rebiopsies after TKI resistance and PFS after gefitinib therapy.

**11055 General Poster Session (Board #337), Sat, 1:15 PM-5:00 PM**

**Prognostic potential of *MDM2* 309T>G polymorphism in stage I lung adenocarcinoma.** *Presenting Author: Kimihiro Shimizu, Division of Thoracic and Visceral Organ Surgery, Gunma University Graduate School of Medicine, Maebashi, Japan*

**Background:** The MDM2 protein plays an important role in regulating cell proliferation and apoptosis by ubiquitination and proteosome-mediated degradation of p53. *c.309 (rs2279744)* polymorphism (*T>G*) in the *MDM2* intronic promoter has been reported as a susceptibility and/or prognostic factor in various cancers. The purpose of this study was to investigate the risk factors for worse survival in patients with pathological (p-) stage I lung adenocarcinoma. **Methods:** We retrospectively reviewed 179 stage I lung adenocarcinoma patients. Clinicopathological and genetic characteristics including *MDM2 SNP309, p53 codon72,* as well as *EGFR, KRAS,* and *p53* mutation were analyzed. Associations between these factors and survival outcome were analyzed by cox proportional hazards models. We further evaluated the associations of prognostic effects of *SNP309* and smoking status or gene mutation status by stratified analyses. **Results:** A significant association was found between pleural invasion or lymphatic invasion and *SNP309 TT* genotype (TT vs. TG+GG, p= .027, p= .008, respectively; $\chi 2$ test) Overall-survival (OS) of patients with *MDM2 TT* genotype was significantly shorter than that with *TG* genotype and *GG* genotype (p= .048 and p= .009, respectively by log-rank test). A multivariate analysis of OS showed that *MDM2* genotype (TT; Hazard Ratio [HR] =3.7, 95% confidential interval [CI] 1.5 to 9.2, p= .005) was an independently significant prognostic factor. Subgroup analysis also showed that *TT* genotype was especially associated with worse OS among smoker group (HR=6.75, 95%CI 1.90 to 24.0, p= .005), *EGFR* wild-type group (HR=3.75, 95%CI 1.22 to 11.6, p= .022), *p53* wild-type group (HR=7.00, 95%CI 2.30 to 21.3, p= .001), and *p53 codon72 RR+RP* group (HR=5.44, 95%CI 1.91 to 15.5, p= .002). **Conclusions:** Our findings suggest that *MDM2 TT* genotype is associated with worse OS among p-stage I lung adenocarcinoma patients, particularly in the smoker group, *EGFR* wild-type group, *p53* wild-type group, and *p53 codon72 RR+RP* group.

**11056 General Poster Session (Board #338), Sat, 1:15 PM-5:00 PM**

**Association of KRAS mutations in cell-free circulating tumor DNA with occurrence of resistance to TKIs in NSCLC.** *Presenting Author: Marzia Del Re, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy*

**Background:** EGFR activating mutations predict sensitivity to tyrosine kinase inhibitors (TKIs) in NSCLC. Although initial responses are commonly observed, patients inevitably progress as a consequence of acquired resistance. Secondary mutations in the EGFR domains (Gainor JF, Shaw AT. J Clin Oncol 2013;31:3987) or in cross-talking pathways (i.e., KRAS, Martin P, et al. J Thorac Oncol 2013;8:530) have been detected in biopsies of resistant cancers. However, the location of the tumor and the risk of complications are serious limitations to re-biopsies in NSCLC. Alternatively, detection of somatic mutations in circulating cell-free DNA (ccfDNA) in plasma could be instrumental to a better understanding of the dynamics of the genetic shift of tumors under stress conditions caused by drug treatments. **Methods:** Twenty-eight NSCLC patients displayed an activating EGFR mutation or ALK translocation in the primary tumor and received a TKI against EGFR (gefitinib or erlotinib, n= 25) or ALK (crizotinib, n= 3). Blood (5 ml) was collected after tumor progression and DNA was extracted from plasma using QIAamp circulating nucleic acid kit and tested for EGFR and KRAS mutations using Rotor-Gene Q PCR (Qiagen, Valencia, CA) or digital droplet PCR (Bio-Rad, Hercules, CA). **Results:** EGFR mutations of the primary tumor were confirmed in ccfDNA of 35.7% patients after progression under TKIs (L858R 7.1%, exon 19 insertions/deletions 28.6%). The EGFR T790M mutation was in 10.7% of patients' ccfDNA. Interestingly, 10 (35.7%) patients displayed a codon 12 KRAS mutation in ccfDNA, including all patients with ALK+ tumors, after TKI treatment. The KRAS mutations were not detectable in their primary tumor using conventional diagnostic approaches. Pre-treatment plasma samples were available in only two patients and KRAS mutations were not detected. **Conclusions:** The observation of KRAS mutations in plasma of patients with tumors carrying EGFR mutations or ALK rearrangements after TKI treatment suggests an important role of this oncogene in acquired resistance.

**11057 General Poster Session (Board #339), Sat, 1:15 PM-5:00 PM**

**Genomic characterization of metastatic cisplatin-resistant samples from urothelial cancer patients.** *Presenting Author: Yohann Loriot, Department of Cancer Medicine, INSERM U981, Gustave Roussy, Cancer Campus, Grand Paris, Villejuif, France*

**Background:** Although several studies have reported genomic characterisation of primary urothelial carcinoma (UC), little is known about the genomic alterations of the metastatic cisplatin-resistant tissues. We sought to define the prevalence and co-occurrence of actionable genomic alterations in patients with metastatic cisplatin-resistant lethal UC. **Methods:** Patients with metastatic UC, who progressed after at least one line of standard therapy, were enrolled in a prospective molecular screening trial (MOSCATO 01) at Gustave Roussy. CT-Scan or ultrasound-guided biopsies were performed in metastases to carry out a comprehensive molecular characterization. DNA was extracted from fresh tumor samples and analyzed by comparative genomic hybridization (CGH) (≥ 30% tumor cells required) and by Next Generation Sequencing (NGS) for up to 74 target genes (≥ 10% tumor cells required). Whole-exome sequencing (WES) was performed retrospectively in selected cases. **Results:** From December 2011 to December 2013, 30 heavily pretreated patients with metastatic UC were included in the MOSCATO 01 trial. Median age was 61 (37-73); All patients had been treated with platin-based chemotherapy with a median number of lines of 2.5 (1-5). Out of them, a tumor biopsy could be performed in 26 patients (87%). CGH and targeted exome sequencing profiles were assessed in 19 (73%) and 23 (88%) of them, respectively. A total of 19 patients (73% of biopsied patients) were profiled for both sequencing and CGH. WES was performed in 16 (62%) pairs of metastatic tissue and normal DNA (Integragen Inc, Hiseq platform). Our analyses identified potential therapeutic targets in 61 % of the tumours, including 31% with targets in the PI3K/AKT/mTOR pathway, 31% with targets in the FGF/FGFR pathway and 15% with targets in the RTK/MAPK pathway (including ERBB2). Others frequent aberrations were found in the chromatin regulatory genes (MLL gene family) and cell-cycle regulatory genes (E2F3, CDKN2A/B genes). **Conclusions:** Lethal platin-resistant UC exhibit high-level of genomic heterogeneity. The majority of these tumors harbour actionable genomic alterations that can be targeted with selective agents currently in clinical development or registered.

**11058 General Poster Session (Board #340), Sat, 1:15 PM-5:00 PM**

**Aromatase inhibitors in elderly patients with advanced breast cancer: An exploratory pharmacogenetic study.** *Presenting Author: Enrica Rumiato, Immunology and Molecular Oncology Unit, Istituto Oncologico Veneto IOV - IRCCS, Padova, Italy*

**Background**: Aromatase inhibitors (AIs) are the first choice for older patients (pts) with estrogen-receptor (ER) positive advanced breast cancer (BC). Yet, response is variable and difficult to predict. Some pts exhibit very good long-lasting response whereas others rapidly progress even after initial response. Factors such as tumor subtype (i.e., luminal A vs B) or BMI have been reported to correlate with response but so far no predictive marker is available. The aim of this study was to identify gene variants associated with AIs response in elderly pts with advanced BC. **Methods**: Genomic DNA from peripheral blood of 55 pts with locally advanced or metastatic breast cancer was analyzed with DMET Plus GeneChip array (Affymetrix, Santa Clara, CA), appropriateness of data was evaluated with DMET Console and statistically relevant variants were assessed with DMET-Analyzer. Median age was 79 years (IQR, 73-86), all patients had ER-positive HER-2 negative BC. Clinico-pathologic factors were evaluated for their impact on response. Bivariate analysis was used with the non-parametric tests Chi-square and Fisher's exact. **Results**: Pts had locally advanced (30 pts) and metastatic (25 pts) BC. All pts had ER positivity ≥70%, 31 pts had Ki67 <20%, 13 pts had grade 3 tumors. Median BMI was 26, median 17-ß-estradiol level was 80 pmol/L. Overall, 23 pts had complete or very good partial response, 28 pts partial response <50% or disease stabilization, 4 pts progressive disease as best response at 6 months. No significant correlation was observed between any of the baseline variables (tumor subtypes, BMI, Ki67, estradiol level) and response. None of the 11 aromatase gene (*CYP19A1*) polymorphisms present in the DMET array achieved the statistical significance. However, when considering only pts with locally advanced BC, the *ABCG1* rs3788007 and *UGT2A1*rs4148304 were associated with objective response. The association of these variants with response was confirmed when the analysis was extended to metastatic pts. **Conclusions**: This exploratory study indicates DMET array as a valid approach to discover new predictive gene variants in AIs-treated elderly pts with advanced BC. Our data need to be validated in a larger cohort.

**11059 General Poster Session (Board #341), Sat, 1:15 PM-5:00 PM**

**The FGFR landscape in cancer: An analysis of 4,869 cases.** *Presenting Author: Teresa L Helsten, University of California, San Diego, La Jolla, CA*

**Background**: Fibroblast growth factor receptors (FGFRs) are highly conserved tyrosine kinase receptors involved in development and carcinogenesis. Humans have 4 FGFRs. Germline FGFR mutations cause craniosynostosis and dwarfism. **Methods**: DNA extracted from 4869 formalin-fixed, paraffin embedded cancers was assayed by next generation sequencing (CLIA) (mostly FoundationOne, Cambridge, MA). Data were curated and interpreted by N-of-One (Lexington, MA). Histology was defined by ordering physicians. Our objective is to characterize the nature/frequencies of FGFR aberrancies in these cancers. **Results**: 356 aberrations were identified in 345 cases (7%; some harbored > 1 FGFR aberration). Aberrations in FGFR1 were most common (N = 170), with FGFR3 (N = 93), FGFR2 (N = 70), and FGFR4 (N = 23) less common. The most common abnormalities were amplifications in FGFR1 (N = 152), FGFR2 (N = 35), and FGFR3 (N = 24). The Table shows cancers with ≥ 75 cases. In urothelial tumors, 12% of aberrations were somatic mutations in FGFR3 (the same as those in dwarfism). In lung squamous cell carcinomas, FGFR1 was amplified in 9% and 3% harbored somatic FGFR3 mutations associated with dwarfism; in lung adenocarcinomas, only 4% were FGFR abnormal. **Conclusions**: Gene amplifications and activating missense mutations are frequent in cancer, suggesting that they may be actionable targets for the FGFR-targeting drugs already available.

| | | Frequency of aberrations (% of cases) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Cancer** | **N** | **All** | **FGFR1** | **FGFR2** | **FGFR3** | **FGFR4** | **Amplification** | **Mutation** | **Rearrangement** |
| **Urothelial** | 126 | 33.3 | 9.5 | 0.8 | 23.0 | 0 | 9.9 | 16.7 | 6.8 |
| **Breast** | 525 | 18.0 | 13.8 | 2.6 | 0.8 | 0.6 | 16.8 | 0.6 | 0.4 |
| **Endometrial** | 80 | 13.8 | 1.3 | 10.0 | 2.5 | 0 | 1.3 | 11.3 | 1.3 |
| **Ovarian** | 234 | 8.6 | 4.7 | 1.7 | 1.7 | 0.4 | 8.2 | 0.4 | 0 |
| **Adenocarcinoma unknown primary** | 267 | 8.2 | 1.9 | 2.6 | 3.4 | 0.4 | 4.9 | 1.9 | 1.5 |
| **Glioma** | 144 | 7.6 | 3.5 | 0 | 4.2 | 0 | 0.7 | 5.6 | 1.4 |
| **Cholangiocarcinoma** | 115 | 7.0 | 0.9 | 6.1 | 0 | 0 | 2.6 | 0.8 | 3.9 |
| **Gastric** | 163 | 6.8 | 1.8 | 3.9 | 1.2 | 0 | 4.9 | 0.6 | 1.2 |
| **Nonsmall cell lung** | 675 | 5.6 | 2.7 | 0.4 | 1.5 | 1.0 | 3.7 | 1.6 | 0.2 |
| **Esophageal** | 90 | 5.6 | 3.3 | 1.1 | 0 | 1.1 | 5.6 | 0 | 0 |
| **Pancreatic** | 175 | 4.6 | 1.1 | 1.1 | 2.3 | 0 | 2.5 | 1.0 | 1.1 |
| **Colorectal** | 294 | 4.4 | 2.4 | 0.7 | 0.7 | 0.3 | 3.1 | 1.4 | 0 |
| **Renal cell** | 92 | 4.4 | 2.2 | 0 | 1.1 | 1.1 | 3.5 | 0 | 0.9 |
| **Neuroendocrine** | 107 | 3.7 | 3.7 | 0 | 0 | 0 | 3.7 | 0 | 0 |
| **Sarcoma** | 190 | 3.7 | 2.1 | 0.5 | 1.1 | 0 | 1.6 | 2.1 | 0 |
| **Head and neck** | 215 | 2.3 | 0.5 | 0.9 | 0.5 | 0.5 | 0.9 | 1.4 | 0 |
| **Melanoma** | 134 | 1.5 | 0.8 | 0.8 | 0 | 0 | 0.8 | 0.8 | 0 |
| **Leiomyosarcoma** | 77 | 1.3 | 1.3 | 0 | 0 | 0 | 1.3 | 0 | 0 |

**11060 General Poster Session (Board #342), Sat, 1:15 PM-5:00 PM**

**Evaluation of PI3K-pathway–activation status in matched primary (P) and metastatic (M) ER+/HER2- breast cancer (BC) lesions according to PIK3CA-mutation status.** *Presenting Author: Debora Fumagalli, Jules Bordet Institute, Breast Cancer Translational Research Laboratory, Brussels, Belgium*

**Background:** Despite the high frequency of PIK3CA mutations (mut) in BC, their role in tumor progression is uncertain. We have previously shown that PIK3CA mut status was highly concordant between Ps and matched Ms in ER+/HER2- BCs (89%). We sought to evaluate the levels of PI3K pathway activation concordance in Ps and matched Ms. **Methods:** For a series of 119 P ER+/HER2- BCs and 31 matched Ms with known PIK3CA mut status, the expression of 400 genes was obtained with the Nanostring technology. The expression of a PI3K pathway activation gene signature (PIK3CA-GS by Loi S PNAS 2010) and of single genes (ESR1 and AURKA) was derived. For 97 of the Ps and 27 of the Ms, the copy number data of 40 genes was obtained with an EvaGreen qPCR assay. **Results:** 43% of all samples had a PIK3CA mut. The PIK3CA-GS was able to predict moderately samples' mut status (AUC 0.641, p 0.004). When considering only the Ps, 65% (36/55) of PIK3CA mut and 42% (27/64) of wild type (WT) samples had an expression of PIK3CA-GS higher than the median value, indicating PI3K activation status. The proportion of CCND1 amplified cases was moderately higher in WT compared to mut samples (p 0.06) while the proportion of FGFR1 (p 0.001) and ZNF703 ($p<0.001$) amplified cases was higher in GS low compared to GS high samples. When considering the 31 pairs, we observed a moderate correlation between PIK3CA-GS values in Ps and matched Ms (Spearman rho=0.50, $p<0.01$). In each pair, the expression level of the GS could change substantially: in 6 (19%) cases it went up, in 6 (19%) it went down and in 19 (61%) it remained the same. Compared to matched Ps, Ms looked biologically more aggressive with significantly higher levels of proliferation as measure by AURKA (p 0.04) and lower levels of ESR1 (p 0.01) despite maintaining an ER+ status at IHC. **Conclusions:** Despite the high concordance of PIK3CA genotype between Ps and matched Ms, activation of downstream signaling seems to vary. This suggests that, beside genotyping, additional investigations should be performed in each lesion to assess the level of pathway activation. Evaluation of downstream effectors using phosphorylated antibodies at IHC is ongoing (pAKT, pMTOR, pERK1/2, pS6).

**11061 General Poster Session (Board #343), Sat, 1:15 PM-5:00 PM**

**Prognostic and predictive role of circulating angiopoietin-2 in multiple solid tumors: An analysis of approximately 500 patients treated with lenvatinib across tumor types.** *Presenting Author: Ignace Vergote, Department of Oncology,University Hospitals Leuven and Katholieke Universiteit Leuven, Leuven, Belgium*

**Background:** Lenvatinib is an oral tyrosine kinase inhibitor targeting VEGFR1-3, FGFR1-4, RET, KIT, and PDGFR$\alpha$. Two phase 3 trials in differentiated thyroid cancer [DTC] and hepatocellular cancer [HCC] are ongoing. Baseline levels (BL) of circulating cytokines and angiogenic factors (CAFs) were evaluated across multiple phase 2 trials in 6 different types of solid tumors. **Methods:** BL serum or plasma samples from a total of approximately 500 patients were analyzed for about 50 CAFs using ELISA and multiplex assay platforms* in 5 phase 2 trials of lenvatinib for thyroid cancer (DTC and medullary thyroid cancer [MTC]), HCC, glioblastoma, endometrial cancer (EC), and melanoma (with or without BRAF V600E). Correlation with clinical outcomes (objective response rate [ORR], overall survival [OS]) was performed using Wilcoxon signed-rank test and univariate Cox proportional hazard model, respectively, whereas correlation with tumor size prior to lenvatinib treatment was performed using the Spearman's rank correlation test. **Results:** Among 50 CAFs, BL angiopoietin-2 (Ang-2) correlated with tumor size (p) in DTC (0.004), MTC (0.004), EC ($<0.001$), melanoma [WT ($<0.001$), MU ($<0.001$)] and HCC (0.046) among multiple phase 2 trials. BL Ang-2 levels showed consistent correlation with clinical outcomes per tumor types across trials and with OS (p/hazard ratio per standard deviation) in DTC (0.001/3.2), MTC ($<0.001$/3.2), EC ($<0.001$/1.8), and melanoma [WT (0.001/1.5), MU ($<0.001$/2.0)]. Correlation with ORR was observed only for a minor subset of analyzed CAFs; only BL Ang-2 levels correlated with ORR in $>1$ tumor type, specifically in DTC (0.034*), MTC (0.025) and EC (0.001). In EC, almost 50% of BL CAFs showed a significant correlation with tumor size, potentially suggestive of an EC-specific tumor micro-environment and the contribution of Ang-2 to tumor angiogenesis in EC. **Conclusions:** BL Ang-2 levels correlated with tumor size and OS across majority of solid tumors in multiple lenvatinib phase 2 trials. Only BL Ang-2 levels also correlated with ORR in a subset of tumors including EC. Clinical trial information: NCT00784303,NCT01111461,NCT01136967,NCT00946153, NCT01433991,.

**11062 General Poster Session (Board #344), Sat, 1:15 PM-5:00 PM**

**Prognostic ability of CD44 expression in ER-positive breast cancer.** *Presenting Author: Yesim Gokmen-Polar, Indiana University School of Medicine, Indianapolis, IN*

**Background:** CD44, a cell surface receptor, is implicated in both progression and suppression of metastatic cascade. CD44 has gained attention as a breast cancer stem cell marker and is considered a therapeutic target. However, loss of CD44 expression is also associated with high-grade tumors and metastasis. Earlier studies have been small, therefore, we analyzed the value of CD44 expression in larger gene expression datasets to clarify its prognostic and predictive ability in breast cancer. **Methods:** CD44 expression levels were analyzed based on ER-status, molecular subtypes and other clinico-pathological parameters using 11 publicly available Affymetrix datasets. Association of outcome was investigated for each patient cohort with distant metastasis free-survival (DMFS) as endpoint and 10 year censoring in the following subgroups: 1) all 1,881 tumors, 2) ER positive tumors (n=1,225), 3) ER-negative tumors (n=395), 4) systemically untreated patients (n=927), and 5) patients treated with tamoxifen alone (n=326). **Results:** Lower expression of CD44 was associated with ER positivity (P=0.01), and higher histological grade (grade 3)($P\leq0.00001$). Expression was highest in luminal A tumors with progressive decrease in basal, luminal B and HER2 subtypes respectively. In multivariate analysis, high CD44 expression correlated with higher DMFS in ERpos tumors [(P=0.004; HR= 0.7 (95%CI 0.55-0.9)], ERposLNneg tumors [(P=0.002; HR= 0.64 (95%CI 0.48-0.85)], grade 2 tumors [(P=0.02; HR=0.51 (95% CI 0.29-0.91)] and TAM treated tumors [(P=0.002; HR 0.1 (95% CI 0.03-034)], whereas low CD44 expression was associated with lower DMFS in TAM treated tumors [(P=0.02); HR= 2.21 (95% 1.12-4.38)]. Of all tumors, CD44 was most prognostic in ERpos and ERposLNneg groups ($P\leq0.001$) followed by HU_Luminal B and PAM50_HER2 enriched groups (P=0.02). Of eight gene modules analyzed, CD44 expression was negatively correlated with checkpoint genes, M-phase and immune response, while positively correlated with basal phenotype. **Conclusions:** The analysis provides relevance of the prognostic and predictive utility of CD44 in ER+LN- breast cancer. This also suggests the importance of patient stratification in the management of these patients and therapeutic strategies.

**11063 General Poster Session (Board #345), Sat, 1:15 PM-5:00 PM**

**INDUCT: A risk score to predict relapse in estrogen-receptor–positive breast cancer.** *Presenting Author: Steven Buechler, University of Notre Dame, South Bend, IN*

**Background:** Early stage ER+ breast cancer may be treated with hormone therapy and/or chemotherapy. Currently available prognostic tools (e.g. Oncotype DX, Mammaprint and ProSigna) assess the risk of recurrence and the benefit of hormone and chemotherapy. However, these tests do not outperform traditional parameters such as tumor size, grade and patient age. New assays are needed to improve the prediction of relapse in ER+ patients. **Methods:** A continuous risk score (INDUCT score) predictive for relapse was developed using integrative analysis of publicly available microarray datasets and FFPE- based qRT-PCR assay. The INDUCT score was validated in (1) Affymetrix datasets consisting of 5 independent patient cohorts and 2) in a cohort of METABRIC dataset. The INDUCT score was further compared to traditional clinico-pathological parameters as well as to current prognostic assays such as Oncotype DX, Mammaprint and Prosigna. **Results:** The continuous INDUCT score (0-100) was developed to predict relapse in patients with ER+, lymph-node negative (LN-) breast cancer. A low INDUCT score ($<42$) based the expression of five genes (*ESPL1*, *MKI67*, *SPAG5*, *PLK1* and *PGR*) identified a good prognosis group (8 year relapse-free survival probabilities $\geq 0.93$) of 68% patients in both Affymetrix and METABRIC datasets. Importantly, the high expression of more than two genes was needed to achieve a score greater than 42, suggesting that the combinatorial effect of these genes is required to promote metastasis. The INDUCT score is significant in both LN negative [$P=1.7\times10^{-4}$; HR=3.4 (95%CI 1.7-6.9)] and positive [$P=2.8\times10^{-5}$ ; HR=2.5 (95%CI 1.6-4.0)] patients and in the presence [$P=1.9\times10^{-5}$ ; HR=2.7 (95%CI 1.8-4.1)] or absence [$P=5.6\times10^{-4}$; HR=4.0 (95%CI 1.8-9.3)] of tamoxifen therapy INDUCT is not improved by the addition of clinico-pathological parameters in LN- breast cancer and exhibits superior prognostic and predictive ability than Oncotype DX, Mammaprint and ProSigna assays. **Conclusions:** The five-gene INDUCT score demonstrates superiority to the traditional parameters as well as current prognostic assays in predicting the likelihood of relapse. This may further improve personalized management for patients with ER+ breast cancer.

**11064 General Poster Session (Board #346), Sat, 1:15 PM-5:00 PM**

**Classifying endometrioid endometrial cancer by long noncoding RNA profiling: Indication of prognosis and therapy selection.** *Presenting Author: Yunyun Jiang, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** The Cancer Genome Atlas (TCGA) has recently reported an integrative analysis of endometrioid endometrial carcinoma (EEC) . However, the landscape of long non-coding RNAs (lncRNA) and its role in defining tumor subtypes with clinical relevance have not been addressed. **Methods:** Using TCGA molecular RNAseq profiles related to 304 primary endometrioid endometrial tumors (serous and mixed tumors were excluded), we performed genomic analysis of GENCODE lncRNAs. Furthermore, we established lncRNA expression-based subtypes with distinct signatures, and described global correlations of lncRNA expression-based subtypes with genomic aberrations and clinico-pathological tumor features. **Results:** Using stringent criteria, we identified 1,931 lncRNAs and predicted those that are potential drivers through integrative analysis. Unsupervised clustering of lncRNA expression revealed three robust subtypes, one of which displayed a worse overall survival as compared to the other two (Cluster C3, p=0.029). Pathological grade 3 tumors were enriched in this cluster (p<0.0001) in which microsatellite-unstable (MSI) and POLE ultramutated/hypermutated subgroups were also enriched (p<0.0001). In Cluster C3, integrative analysis with copy-number alteration and mutation revealed significant enrichment of KRAS mutation and STK11 loss, recently shown to dictate response to metformin. The coupled overexpression of lncRNA HOTAIR with EZH2 and exclusive enrichment of the EED polycomb gene targets in the same cluster indicate the association between the polycomb repressive complex 2 (PRC2) and aggressive disease, suggesting application of histone deacetylase inhibitor related therapies. Conversely, we found significant enrichment of CTNNB1 mutations in Cluster C2, suggesting WNT pathway related therapeutic methods. **Conclusions:** Our results revealed the application of systematic characterization of a large cohort of clinically annotated EEC with a poor prognosis cohort clearly identified. The application of lncRNA profiling can potentially be utilized as a tool for clinical outcome prediction and targeted therapy selection.

**11065 General Poster Session (Board #347), Sat, 1:15 PM-5:00 PM**

**Prediction of late relapse in patients with estrogen-receptor–positive breast cancer.** *Presenting Author: Steven Buechler, University of Notre Dame, South Bend, IN*

**Background:** Proliferation plays an important role in the prediction of early relapse of ER+ breast cancer. This constitutes the basis of almost all of the currently available prognostic tools including gene expression based signatures (e.g. Onco*type*DX, Mammaprint, and ProSigna). However, these tools are poor predictors of late relapses (greater than 8 years from initial diagnosis) and there is a dire need for a classifier that can accurately identify patients who remain at high risk of long-term relapse in spite of standard therapy. A better understanding of the mechanisms leading to late relapse could lead to improved strategies for management of these patients. **Methods:** Gene expression of 1,518 primary tumors from the METABRIC dataset, which contains long-term follow up for breast cancer specific survival (BCSS), was divided into training and validation sets balanced for late relapse cases. An innovative multistate gene methodology was used to identify predictors of late relapse in the training set and confirmed in validation set. **Results:** Analysis of the training set (n=382; 48 late relapse cases) identified 20 genes that were most predictive of late relapse. Late Relapse Score (LateR) was developed using these genes to optimally separate patients into low and high risk groups (P=0.002). In the validation set (n= 367; 47 late relapse cases), the LateR risk stratification (61% low risk) predicted late relapse (low LateR 0.87 (95%CI 0.80-0.95); high LateR 0.70 (95%CI 0.60-0.81); p=0.03). Furthermore, the combination of INDUCT score and LateR lead to more accurate prediction (p=0.002). In the LateR high risk group, pro-inflammatory cytokines are significantly up-regulated and genes involved in immune response are significantly down-regulated. **Conclusions:** Immune system plays a major role in the development of late relapse. LateR accurately predicts the likelihood of late relapse for patients with ER+ breast cancer. Together with the INDUCT test for early relapse, LateR provides a valuable tool for assessing the likelihood of relapse and might help the patient and their physicians make appropriate long-term treatment decisions.

**11066 General Poster Session (Board #348), Sat, 1:15 PM-5:00 PM**

**A 5-gene signature based on TLR4 signaling as predictive of risk of distant relapse in breast cancer treated with taxane-anthracycline neoadjuvant chemotherapy.** *Presenting Author: Joseph A. Pinto, División de Investigación, Oncosalud - Auna, Lima, Peru*

**Background:** TLR4 is typically activated by gram (-) bacterial lipopolysaccharide; however, recent reports describe that paclitaxel could trigger the TLR4 signaling pathway leading to chemotherapy resistance. Our purpose was to evaluate influence of genes involved in TLR4 signaling in the distant-recurrence free survival (DRFS) in breast cancer patients treated with neoadjuvant taxane- anthracycline chemotherapy. **Methods:** We retrieved normalized gene expression data from a public database (GSE25066) with 508 samples of breast cancer patients profiled with the U133A microarray and treated with neoadjuvant Taxane-Anthracycline chemotherapy. Division of discovery and validation sets was according to Hatzis et al (2011). Housekeeper-normalized transcript counts were log2 transformed and data were row z -score standardized. The intensity of each gene expression was transformed to an ordinal coding level according to the ranking of the gene expression level in each gene and was coded as 1, 2, 3,or 4, respectively. The gene expression was ranked ≤ 25th, > 25th and ≤ 50th, > 50th and ≤ 75th, or > 75th percentile for each gene expressions. **Results:** The signature was developed on the training set and a multivariate stepwise Cox analysis selected 5 genes independently associated with DRFS: IRAK1 (HR=1.32, p=0.025), IRF3 (HR=0.66, p=0.001), NFKB1 (HR=0.58, p<0.001), NEMO (HR=1.50, p=0.002), TRIM5 (HR=1.40, p=0.007). These 5 genes were combined into a linear score weighted according to the coefficients of the Cox model, (Risk Score= 0.279 IRAK1 - 0.421 IRF3 - 0.548 NFKB1 + 0.404 NEMO + 0.336 TRIM5). The linear score was highly associated with DFS (HR=2.8, 95%CI=1.7-4.7, p<0.001). Patients were classified as having a high-risk gene signature or a low-risk gene signature, with the 50th percentile (median=0.0082) of the risk score as the threshold value. The score resulted highly associated with DRFS also in the validation set (p=0.001) Five-gene signature was an independent prognostic factor for DFRS in the validation group. **Conclusions:** The 5-gene signature based in TLR4 signaling has a good discriminating ability.

**11067 General Poster Session (Board #349), Sat, 1:15 PM-5:00 PM**

**Genomic profiling of breast cancer in African American women.** *Presenting Author: Raquel Nunes, Washington Cancer Institute, MedStar Washington Hospital Center, Washington, DC*

**Background:** Molecular profiling of breast cancer (BC) identifies intrinsic subtypes with distinct gene expression and clinical characteristics. In the US, BC is less frequent in African-American females (AAF); however mortality is higher, particularly among younger women. **Methods:** Gene expression in tumors from AAF presenting with early stage or locally advanced BC was evaluated using the Symphony platform on fresh and paraffin-embedded tissue (Agendia inc), a microarray-based method which classifies tumors according to prognosis (MammaPrint, MP), molecular subtype (BluePrint, BP) and estrogen receptor (ER), progesterone receptor (PR) and Human Epidermal Growth Factor Receptor 2 (HER2) mRNA levels (TargetPrint, TP). Genomic information is correlated with clinical and pathologic characteristics and Oncotype DX recurrence score (RS) when available. Patients (pts) will be followed for 5 years. **Results:** Results are available in 88 pts, with 12 pending for an accrual goal of 100. Median age 60 years (range 22-98), 37 stage I, 36 stage II, 15 stage III disease. 67% of pts had High Risk (HR) MP. Age ≤ 40 and grade were significantly associated with HR MP (p=0.022 and < 0.0001, respectively), while stage was not. 20 cancers were triple negative (TN) by IHC;18 of these were Basal-type and 1 HER2-type (1 not evaluable). In the 10 cases ER positive by IHC but negative by TP, 5 were Basal-type and 5 were HER2-type. Of the 12 pts HER2 positive by IHC/FISH, 4 were Luminal-type and 1 was Basal-type; none of these was HER2 positive by TP. 24 pts had Oncotype RS results: 2 were HR both by Oncotype and MP; 5 had intermediate RS, 3 were HR by MP; 17 had a low RS, 8 of which were HR by MP and Luminal-type by BP. **Conclusions:** AAF with stage I to III BC often present with High Risk disease, particularly at younger ages and irrespective of stage. Molecular subtyping confirmed the biologic heterogeneity in TN, HER2 positive and ER positive tumors. Oncotype RS and MP offered different prognostic information. Follow up will be needed to determine correlation with outcome. Funding: MP, BP and TP test provided by Agendia. Biostatistical support by GHUTTCS-CTSA.

| | MP | | ER/PR positive | | HER2 positive | |
|---|---|---|---|---|---|---|
| BP | Low risk (n=29/32%) | High risk (n=59/67%) | IHC | TP | IHC/FISH | TP |
| Luminal | 29 | 25 | 54 | 54 | 4 | 0 |
| Basal | 0 | 25 | 5 | 0 | 1 | 0 |
| HER2 | 0 | 8 | 5 | 0 | 7 | 7 |

**11068 General Poster Session (Board #350), Sat, 1:15 PM-5:00 PM**

**Incidence of inconsistent driver mutations between multiple lung ground-glass nodules in patients with non-small cell lung cancer.** *Presenting Author: Shengxiang Ren, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China*

**Background:** Intertumor heterogeneity had been observed in various kinds of malignant tumors including non-small cell lung cancer. Comparing with extra-pulmonary metastasis, patients with multiple pulmonary nodules have a significantly higher rate of heterogeneity. The aim of this study was to compare the known driver mutations distribution among non-small cell lung cancer(NSCLC) patients with multiple intrapulmonary ground-glass nodules(GGNs). **Methods:** 35 consecutively resected lung cancer patients with multiple lung GGNs at a single institution (Tongji University, Shanghai, China) were analyzed for mutations in EGFR, KRAS, HER2, BRAF and PIK3CA together with genes fusion in ALK, ROS1 and RET. **Results:** The median age was 60 years old, male/female:12/23, never smoker/smoker: 25/10, PS 0/1: 22/13. Totally, 72 lesions were included into this analysis, including 9 of adenocarcinoma in situ, 9 minimal invasive adenocarcinoma and 54 invasive adenocarcinoma. Among them, 33 (45.8 %) tumors harbored EGFR mutations, including 13 were deletions in exon 19, 18 were L858R missense changes, and two were 19 deletion together with L858R mutations. 5 (6.9 %) harbored EML4-ALK fusions, 4 (5.6%)had HER2 mutations, 3(4.2%)had KRAS mutations, 1 had ROS1 fusion and BRAF mutation respectively. A majority of the mutations were mutually exclusive, except 1 both with EGFR mutation and ALK fusion. The discordant frequency rate of the driver mutation distribution was 68.6%(24/35) in the whole population, while it was 80%(24/30) in the patients harbored at least one of the detected driver mutations. In one of the 2 cases who had 3 resected lung lesions, exon21 L858R point mutation, exon 19 deletion, and L858R point mutation together with ALK fusion were found in the 3 tumor samples separately. **Conclusions:** The high incidence of inconsistent driver mutations distribution between multiple intrapulmonary nodules in this study suggested that these GGNs might arise as independent events and contributed to the higher rate of heterogeneity in intrapulmonary nodules. Patients with multiple GGNs should be given a separate staging and treatment strategy.

**11069 General Poster Session (Board #351), Sat, 1:15 PM-5:00 PM**

***TP53*-mutation status by gene-expression signature (*TP53* signature) and prediction of efficacy of neoadjuvant chemotherapy (NAC) and recurrence after surgery in breast cancer.** *Presenting Author: Shin Takahashi, Tohoku University, Sendai, Japan*

**Background:** *TP53* mutation is an independent poor prognostic factor in breast cancer. We have reported that status of the *TP53* mutation is predictable by expression profile of 33 genes ('TP53 signature') in breast cancer and that the TP53 signature can predict overall survival and recurrent free survival of early breast cancer (Cancer Sci. 99: 324-32, 2008). The aim of this study is to determine whether the TP53 signature can also predict both the efficacy of NAC and the recurrence after surgery in breast cancer. **Methods:** An open-access data of the NAC cohort (E-GEOD-25066) that contains 508 patients with HER2 negative breast cancer is used. Among the genes previously used TP53 signature, 20 up-regulated and 5 down-regulated genes in breast cancer with *TP53* mutation were selected and the *TP53* status was determined by the ratio of the sum of expression values of 20 up-regulated genes to that of the 5 down-regulated genes. If the ratio (5 down-regulated genes / 20 up-regulated genes) was less than 0.325, the tumor was determined as a*TP53* mutant. If it was greater than or equal to 0.325, the tumor was determined a*TP53* wild-type. **Results:** Fifty percent (255 of 508) of tumors was determined as a *TP53* mutant. The pathological CR (pCR) rate is significantly higher in *TP53* mutant tumor than in *TP53* wild-type tumor (34.7% vs 5.4%). In Stage I and II patients (n=280), recurrence free survival (RFS) was significantly better in patients leading to pCR than in patients not leading to pCR (P=0.047), supporting the previous reports. Patients with *TP53* wild-type tumor showed better RFS than patients with *TP53* mutant tumor (P=0.0018). Patients with *TP53*mutant tumor not leading to pCR showed significantly worse RFS than the other patients (P<0.001). **Conclusions:** TP53 signature has the ability to predict the efficacy of NAC and recurrence after surgery in breast cancer. The TP53 signature was especially useful to predict the recurrence in combination with pCR status. Our data suggests that patients with *TP53* mutant tumor not leading to pCR after NAC may need adjuvant chemotherapy after surgery to improve prognosis of these patients.

**11070 General Poster Session (Board #352), Sat, 1:15 PM-5:00 PM**

**Whole-genome sequencing (WGS) to identify *H. pylori* and its impact on the gastric microbiome.** *Presenting Author: Manish A. Shah, Weill Cornell Medical College, New York Presbyterian Hospital, New York, NY*

**Background:** Although *H. pylori* is a WHO class I carcinogen for gastric cancer (GC), nearly all infected patients do not develop GC, and *H. pylori* eradication does not reduce GC risk. We used WGS to examine the hypothesis that changes in the gastric microbiome associated with *H. pylori* infection may play a role in GC development. **Methods:** Patients (pts) undergoing upper endoscopy were categorized as follows: (1) active *H. pylori* infection (*H. pylori* identified on biopsy or positive CLOtest), (2) prior *H. pylori* infection (previous *H. pylori* treatment or ELISA IgG positive), and (3) GC. Endoscopic biopsies from 3 locations in the antrum/body were freshly frozen for WGS (50bp paired-end) on a HiSeq2000 platform at ~10X coverage. We developed a custom computational pipeline algorithm that successively removes human sequences, with remaining un-mapped reads aligned to ~1,400 unique bacteria genomes. Bacterial species were validated by PCR. **Results:** 15 pts have enrolled: active *H. pylori* infection (n=6), prior *H. pylori* infection (n=5), and GC (n=4), with WGS performed in 10 thus far. A total of 16 microbial species are identified (Table). *H. pylori* was identified in all patients regardless of *H. pylori* infection state (i.e. active v. prior), as well as in the GC cohort. **Conclusions:** Multiple bacterial species are identified in gastric mucosa. *H. pylori* is identified in all pts, including previously treated pts. *H. pylori* treatment fails to eradicate *H. pylori*, thus possibly explaining why *H. pylori* treatment fails to reduce cancer risk. This is the first demonstration of detailed unbiased microbiome detection performed from gastric endoscopic biopsy samples using WGS.

**Gastric microbiome identified using WGS.**

| | Active | Active | Prior | Prior | Prior | GC |
|---|---|---|---|---|---|---|
| **Bacterial species** | 05-An | 08-An | 07-An | 09-An | 10-An | 11-An |
| **Helicobacter_acinonychis** | 3 | 15,306 | 9 | 1,421 | 14,817 | 47 |
| **Helicobacter_cetorum** | 0 | 873 | 0 | 87 | 753 | 0 |
| **Helicobacter_pylori** | 19 | 81,762 | 43 | 10,914 | 245,231 | 815 |
| **Lactobacillus_gasseri** | 0 | 0 | 0 | 1 | 89 | 322 |
| **Lactococcus_lactis** | 0 | 0 | 0 | 2 | 906 | 0 |
| **Propionibacterium_acnes** | 208 | 41 | 292 | 46 | 87 | 69 |
| **Staphylococcus_warneri** | 13 | 450 | 0 | 2 | 4 | 6 |
| **Streptococcus_thermophilus** | 3 | 0 | 2 | 1 | 461 | 4 |

Values are the number of read counts mapped to the respective bacteria species. Top 8 species are shown in subset of pts.

**11071 General Poster Session (Board #353), Sat, 1:15 PM-5:00 PM**

**Concomitant mutation and amplification of the ERBB2 (HER2) gene in human tumors.** *Presenting Author: Tobias Grob, Institute of Pathology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

**Background:** Amplification of the ERBB2 (HER2) gene is a well-known genetic aberration in many tumor entities. Up to 20% of breast and gastric cancer show ERBB2 gene amplification and anti-HER2 targeting therapies are well established for these tumors. In other tumor entities such as lung cancer, colorectal cancer and bladder cancer the fraction of ERBB2 amplified tumors is considerably lower. In contrast to breast cancer, these tumors show heterogeneity of ERBB2 amplification in a substantial proportion. Oncogenic EGFR mutation with subsequent EGFR amplification is a common phenomenon in lung cancer. In analogy, primary ERBB2 mutation could explain the observed heterogeneity of ERBB2 amplification in some tumors. **Methods:** 100 tumors showing ERBB2 amplification by fluorescence in situ hybridization were examined for ERBB2 mutation: 50 breast cancer samples, including 10 cases with borderline gene amplification, 10 cases with heterogeneous gene amplification and 11 samples of metastatic lesions as well as 15 colorectal carcinomas, 12 gastric carcinomas, 12 non-small cell lung cancers and 10 urothelial carcinomas. Tumor DNA was extracted and examined for mutations in the tyrosine kinase domain (exons 18-23) of the ERBB2 gene by Sanger sequencing. **Results:** ERBB2 mutation was found in two metastatic lesions of breast cancer, two lung cancers and two colorectal cancers. In five of these cases short in-frame insertions in exon 20 were found. In one case of a breast cancer lung metastasis a missense mutation in exon 19 (p.L755S) was detected. The semi-quantitative chromatograms show an overrepresentation of the mutations indicating a selective amplification of the mutated allele. **Conclusions:** In certain tumor entities the heterogeneity of ERBB2 amplification indicates a late genetic event. The finding of a concomitant mutation in ERBB2 amplified tumors might explain the heterogeneity in some of these tumors. The effect of a primary oncogenic ERBB2 mutation might be increased by selective amplification of the mutated allele resulting in an additional growth advantage. If ERBB2 amplified tumors with a primary ERBB2 mutation also benefit from an HER2 targeted therapy needs to be elucidated.

**11072 General Poster Session (Board #354), Sat, 1:15 PM-5:00 PM**

**A tool to predict post-transcriptional instability related to the dysregulation of the SETD2 histone methyltransferase in renal cell carcinoma (RCC).** *Presenting Author: Mia D. Champion, Mayo Clinic, Scottsdale, AZ*

**Background:** Recent studies report that dysregulation of the SETD2 histone methyltransferase in (RCC) decreases global histone 3 lysine 36 trimethylation (H3K36me3), resulting in mis-regulation of alternative splicing of associated exons. It remains unclear how disruptions of chromatin-based modifications contribute to tumorigenesis and can be leveraged to develop more potent treatment strategies. **Methods:** We performed ChIP-, RNA-, and exome- sequencing on matched human RCCs (SETD2 wt /mutant), and RCC cell lines. These datasets were used to develop a tool, ChIP-RNA-seqPRO, to identify regions of dysregulated epigenomic modifications and altered transcript splicing present in the tumor, but absent in a normal sample. The tool provides annotations relevant to post-transcriptional processing and known disease associations (e.g. cancer-associated RNA editing sites). In addition, ChIP-RNA-seqPRO calculates a Modification Association Score (MAS) from changes in ChIP-seq peak distribution, transcript splicing, and associated sequence repeats and variations in order to predict post-transcriptional instability that is correlated with the clinically aggressive tumor phenotype and identify novel therapeutic targets. **Results:** In addition to identifying novel, tumor-unique predicted transcript isoforms and regions of chromatin modification alteration, we have also identified tumor-unique RNA variations shared between samples. Greater than 40% of these sites are known RNA editing sites also identified in other cancers. In addition, gene lists with applied MAScores were analyzed for pathway enrichment. Pathways associated with predicted post-transcriptional instability in SETD2-deficient RCC included regulation of Hypoxia-Inducible Factor (HIF), MAPkinase associated signaling pathways, and the p73 transcription factor network (p-value $< 0.05$). **Conclusions:** Our findings demonstrate the utility of our methods in profiling the regulatory association between epigenomic modification and post-transcriptional processing, and offer unprecedented insight into how the instability of these processes drives the progression of RCC.

**11073 General Poster Session (Board #355), Sat, 1:15 PM-5:00 PM**

**GBM cell microvesicles carrying gDNA oncogenic sequences cross the BBB and reach the peripheral blood.** *Presenting Author: Esther Holgado, Hospital de Madrid, Madrid, Spain*

**Background:** Glioblastoma (GBM) is the most common primary malignant brain tumor in adults accounting for 60-75% of astrocytic tumors. It corresponds to WHO grade IV. Microvesicles (MVs) are vesicles that can be found in body fluids from patients with different types of cancer. These MV can be classified into apoptotic breakdown (up to several $\mu$m), plasma membrane blebbing (100 to 1,000 nm), and exosomes (less than 100 nm) released by fusion of endosomal-derived multivesicular bodies They play a crucial role in tumor progression since they can mediate intercellular communication, inflammation, angiogenesis and coagulation. We have identified, for the first time, the presence of genomic DNA sequences corresponding to oncogenes from all three types of MVs. These three types of MVs can cross the bbb and reach the peripheral blood where gDNA sequences might be used as biomarkers to stratify patients and evaluate response to treatment. **Methods:** GBM-initiating cells were isolated from surgical samples and cultured. A collection of primers targeting specifically human gDNA were designed and validated. Using a modification of the protocol proposed by Skog group we isolated apoptotic, blebbing, and exosomes. Afterwards, we isolated total gDNA from supernatant of cells and mice plasma with brain tumor. This gDNA was used as a template for de detection of gDNA oncogene sequences. Finally, we confirmed the presence of such sequences within all three type of MVs isolated from peripheral blood of GBM patients. **Results:** We found gDNA oncogene sequences within all three types of MVs. We demonstrated that MVs secreted by tumor cells into the brain can cross the bbb and reach the peripheral blood, were they contribute to the total number of circulating MVs y mice model. gDNA oncogenic sequences can be also detected in all three types of MVs isolated from peripheral blood of GBM patients. **Conclusions:** gDNA sequences can be introduced into apoptotic and blebbing MVs, and exosomes. These three types of MVs can cross the bbb and reach the peripheral blood where they can be detected by using low invasive procedures. The presence of gDNA will be useful for the detection of specific mutations, and/or epigenetic changes in the producer tumor cell.

**11074 General Poster Session (Board #356), Sat, 1:15 PM-5:00 PM**

**Variation in the *ESR-1* gene as a prognostic marker in early breast cancer survival.** *Presenting Author: Danny Houtsma, Department of Clinical Oncology, Leiden University Medical Center, Leiden, Netherlands*

**Background:** Variation in the genes coding for the estrogen receptor (ESR-1), CYP2c19 and UGTB15 is associated with worse outcome in tamoxifen treated early breast cancer patients. It is unclear whether this variation is a predictive marker for tamoxifen efficay or if it is a prognostic marker for breast cancer outcome. The aim of this study was to examine if SNP's in these genes are also associated with survival in early breast cancer patients treated with adjuvant exemestane as to explore a prognostic potential of these markers. **Methods:** Patients of whom tissue was available were selected from the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial. DNA was isolated from tumor samples. The following 4 SNPs were genotyped using Taqman assays: rs9340799 and rs2234693 in the ESR-1 gene, rs1902023 in the UGTB15 gene and rs4244285in the CYP2c19 gene. Primary endpoint was relapse-free survival (RFS) and secondary endpoint was overall survival (OS). A Kaplan-Meier analysis was performed and Cox proportional hazards models assessed survival differences. Analyses were adjusted for age at diagnosis, tumor size, nodal status, histological grade, surgery, adjuvant radiotherapy and chemotherapy. **Results:** 807 patients were included in the analyses and genotypes were obtained in 84%-96% of the samples. No association was found with the primary endpoint of relapse free survival with any of the four SNPS. However, the rs2234693 variant in ESR1 was associated with worse overall survival with an odds ratio of 1,4 ($P = 0.016$) consistent with a prognostic rather than a predictive drug response effect. **Conclusions:** Variation in the ESR-1 gene is related to overall survival in early breast cancer patients. Variation in the ESR-1 gene may be used as a prognostic marker of early breast cancer survival regardless of which endocrine treatment is used.

**11075 General Poster Session (Board #357), Sat, 1:15 PM-5:00 PM**

**Whole-genome bisulfite sequencing of a complex karyotype AML and identification of regulatory aberrations distinct from normal karyotype AML.** *Presenting Author: Stephen Capone, University of Southern California, Los Angeles, CA*

**Background:** We characterized the methylome and transcriptome of blasts from a 20 year old man with a metastatic mediastinal immature teratoma who developed a complex karyotype acute myeloid leukemia (CK-AML) while on treatment. We performed low-input whole genome bisulfite sequencing (WGBS), RNA sequencing (RNAseq), and HumanMethylation450 (HM450) assays. RNAseq and (when present) matching HM450 results from normal CD34+ cells (N=6), normal karyotype (NK-AML, N=10) and CK-AML blasts (N=10) were compared. **Methods:** We purified patient bone marrow blasts and CD34+ cells from healthy volunteers (N=6) by fluorescence assisted cell sorting (FACS). We prepared 200ng (HM450) and 50ng (WGBS) of DNA, the latter by EpiGnome Methyl-Seq Kit (Epicentre). Sequencing on a HiSeq 2,000 yielded ~60 million mapped 50bp reads per sample. WGBS alignment and SNP calls were by BWA and Bis-SNP. 5ng RNA generated ~30 million mapped reads per sample, which we aligned with STAR. HM450 and RNAseq data from McNerney's (Blood, 2013) and TCGA NK- and CK-AML samples were also reprocessed. **Results:** The patient's blasts homozygously expressed mutant *TP53* (R282W), *TP53INP1*, *NCKAP1L*, *UBR4*, and *IL17RB*. HM450 data revealed copy number aberrations and a signature common to TCGA CK-AMLs. Focal hypermethylation overlapped Polycomb repressor complex binding sites in CD34+ cells and, in contrast to NK-AML, affected *HOXA* and *HOXB* clusters. Megabase-scale blocks of hypomethylation overlapped those seen in B-cell immortalization (Hansen, 2013) and IMR90 senescence (Cruickshanks, 2013). Non-coding RNAs (e.g. *HOTAIRM1*) distinguished CK-AML from NK-AML and normal CD34+ cells. **Conclusions:** This is the first characterization of an AML methylome using WGBS. The methylome of the CK-AML patient shows changes associated with senescence and transformed cells: genome-scale hypomethylation, focal hypermethylation, and promiscuous transcription. Genome-wide DNA methylation changes in the patient's blasts broadly parallel those seen with immortalization and senescence in other cell types. The genetic and epigenetic heterogeneity observed in CK-AML may nonetheless contribute to its malignant evolution and poor outcomes.

**11076 General Poster Session (Board #358), Sat, 1:15 PM-5:00 PM**

**Next-generation sequencing (NGS) as part of pathologic diagnostic armamentarium.** *Presenting Author: Lorna Rodriguez-Rodriguez, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

**Background:** Because genomic alterations inform tumor biology, treatment decisions, and new research opportunities, we established a Molecular Tumor Board. Cases with NGS results from a CLIA certified assay are presented and therapeutic strategies are suggested when appropriate. Cases called for re-consideration of final pathologic diagnosis are presented as example of the utility of NGS in aiding final diagnosis and recommending treatment of unusual cases. **Methods:** NGS on formalin-fixed, paraffin embedded tumors (N=101 patients) was done using hybridization-captured, adaptor ligation–based libraries to high, uniform coverage for 3,230 exons of 182 cancer-related genes plus 37 introns from 14 genes frequently rearranged in cancer. Data curation was performed by Precision Medicine physicians at Rutgers Cancer Institute of New Jersey. Cases were presented formally at the Molecular Tumor Board where systems biologists, oncologists, pathologists, and scientists discussed de-identified data. **Results:** Five cases had ambiguous diagnoses: three gynecologic malignancies, a brain tumor of unknown origin (presented in detail elsewhere), and a presumed lung carcinoma with concomitant pancreatic cancer. One case had two tumor foci sharing almost all of the genomic alterations and were more similar to those found in sarcoma than in GIST, the final diagnosis was metastatic ovarian carcinosarcoma. In another, a presumed recurrence of ovarian cancer had alterations that were more consistent with pancreatic primary. By tumor board recommendations, the patient underwent endoscopic biopsy of the pancreas that uncovered a primary pancreatic cancer. In two cases, mutational analysis revealing shared mutations between two tumor foci overcame diagnostic dilemma of new primary versus metastasis. **Conclusions:** NGS assays are useful to identify actionable genomic changes and challenge pathologic diagnosis, translating into patient benefit. Genomic alteration signatures should be validated for tumors that are rare, difficult to diagnose or unusually recalcitrant to treatment. NGS should become part of the pathologic armamentarium for tumor diagnosis.

**11077 General Poster Session (Board #359), Sat, 1:15 PM-5:00 PM**

**Inferring clonal composition from multiple sections of a breast cancer.** *Presenting Author: C. Anthony Blau, Center for Cancer Innovation, University of Washington, Seattle, WA*

**Background:** Cancers arise from successive rounds of mutation and selection, generating clonal populations that vary in size, mutational content and drug responsiveness. Ascertaining the clonal composition of a tumor is therefore important both for prognosis and therapy. **Methods:** Mutation counts and frequencies resulting from next-generation sequencing (NGS) potentially reflect a tumor's clonal composition; however, deconvolving NGS data to infer a tumor's clonal structure presents a major challenge. We propose a generative model for NGS data derived from multiple subsections of a single tumor, and we describe an expectation-maximization procedure for estimating the clonal genotypes and relative frequencies using this model. **Results:** We demonstrate, via simulation, the validity of the approach, and then use our algorithm to assess the clonal composition of a primary breast cancer and associated metastatic lymph node. After dividing the tumor into subsections, we perform exome sequencing for each subsection to assess mutational content, followed by deep sequencing to precisely count normal and variant alleles within each subsection. By quantifying the frequencies of 17 somatic variants, we demonstrate that our algorithm predicts clonal relationships that are both phylogenetically and spatially plausible. **Conclusions:** Applying this method to larger numbers of tumors should cast light on the clonal evolution of cancers in space and time.

**11078 General Poster Session (Board #360), Sat, 1:15 PM-5:00 PM**

**Pathway-based signature analysis of RNA-seq data to reveal new targetable avenues for metastatic castration-resistant prostate cancer (mCRPC) patients (pts): Preliminary results from the SU2C/PCF/AACR West Coast Prostate Cancer Dream Team (WCDT).** *Presenting Author: Adrian Bivol, Department of Biomolecular Engineering, University of California, Santa Cruz, Santa Cruz, CA*

**Background:** The mechanisms of resistance to agents such as abiraterone or enzalutamide in pts with mCRPC are poorly understood, and progressive mCRPC has been challenging to biopsy and characterize on a molecular basis because of its bone tropism. As part of the WCDT project, which aims to identify genetic pathways underlying primary and acquired resistance to these agents, RNA-sequencing following laser capture microdissection of mCRPC biopsies was undertaken, along with a panel of 37 mutated cancer genes. Interpreting these data is challenging as few computational approaches exist that can leverage external data (e.g. TCGA) to shed light on pathways that drive cancer progression in an individual patient. **Methods:** RNA-seq and mutation data from mCRPC biopsies is interpreted by mapping onto a comprehensive pathway database connecting a tumor sample with genetic regulatory logic. Pathway mapping occurs either prior to inferring predictive signatures using the PARADIGM engine, or after differential gene expression analysis. Topological analysis reveals possible drug targets within the inferred networks. **Results:** 60 of 300 planned mCRPC pts have undergone a metastasis bx, RNA-seq data from 9 samples has been analyzed. PARADIGM-based signatures revealed expected neurotransmitter pathways discriminating neuroendocrine from non-NE samples. Gene expression-based signatures mapped onto pathways revealed RB1, Reelin, and VEGF signaling characteristic of liver metastases compared to mets from other tissues. Finally, gene expression-based signatures uncovered several pathways enriched in Abiraterone naive compared to resistant samples (FDR $<$ 5%). **Conclusions:** Significant pathways can be inferred and potential drug targets identified on very small cohorts with this approach. Methods that harness existing datasets using pathway-guided descriptions may raise the interpretability of omics datasets collected in personalized medicine settings.

**11079 General Poster Session (Board #361), Sat, 1:15 PM-5:00 PM**

**A national platform for molecular diagnostics: Results of the Cancer Research U.K. Stratified Medicine Programme.** *Presenting Author: Emily Shaw, Cancer Research UK, London, United Kingdom*

**Background:** Increasing demand for testing multiple markers for targeted therapies requires a platform to incorporate molecular diagnostics in the normal pathway of care. This programme was planned to demonstrate the applicability of a nationwide platform of testing, linked to healthcare records in a central database. **Methods:** From 8/2011 to 6/2013, patients with breast, colorectal, prostate, lung or ovarian cancer, or melanoma, were approached at 26 hospitals for consent to centralised molecular testing of routine biopsies. Formalin-fixed paraffin-embedded sections were forwarded with peripheral blood samples to 3 technical hubs for analysis of a small panel of abnormalities by Sanger sequencing, pyrosequencing or similar mathods, and fluorescent in-situ hybridisation for chromosomal structural changes. Results were transmitted directly to clinical centers for inclusion in medical records. A routine clinical dataset was collected from all patients using the national cancer registration system. **Results:** 10,754 patients (98% of those approached) consented to analysis of material, with 9010 samples sent for analysis. Of 1,889 lung cancers, 35% had at least one abnormality, only 0.65% had more than one. kRAS was most often mutated (26%), followed by EGFR (8.3%), Alk rearrangement (1.9%) and BRAF (1%). In 1634 colorectal cancers, 47% had one abnormality, 30% two and 3% three. Commonest abnormalities were mutated TP53 (25%), double mutated TP53 and kRAS ( 17%), kRAS only (17%) and BRAF (5%). In 535 melanomas there were 42% BRAF mutants, 22% NRAS mutant and only 2.4% with double abnormalities. There was heterogeneity between the laboratories in turnaround time and failure rate, especially for non-standard analyses. A multiplex next-generation sequencing (NGS) panel was piloted for samples collected in the last 3 months of the programme, showing high levels of concordance in comparison to conventional sequencing. **Conclusions:** A broad system of molecular diagnostics is feasible and highly acceptable to patients. The efficiency is improved with NGS analysis, and the system is now being used to support prescreening of patients with lung cancer for entry into a multiarm study of novel therapeutics.

**11080 General Poster Session (Board #362), Sat, 1:15 PM-5:00 PM**

**FGFR and FGF ligand overexpression in lung cancer: Implications for targeted therapy.** *Presenting Author: Krishna Maddula, HTG Molecular Diagnostics, Tucson, AZ*

**Background:** Fibroblast growth factor receptors (FGFR) have been shown to be frequently dysregulated in non-small cell lung cell carcinoma (NSCLC). To determine the impact of dysregulation of FGFR pathway in NSCLC, we profiled 100 samples using a sensitive gene expression assay for FGFR and its ligands. **Methods:** FGFR and FGF gene expression in formalin fixed paraffin embedded (FFPE) samples was performed using a sensitive quantitative nuclease protection assay. This gene expression panel includes all four FGFRs, all 22 FGF ligands and known FGF interacting proteins KLOTHO and KLOTHO beta. Using this array we profiled 100 NSCLC samples (45 squamous, 55 non-squamous). **Results:** Gene expression analysis of the FGFR family in lung cancer showed overexpression by 3X over median levels of FGFR2 and FGFR3 predominantly in squamous subtype (28% and 19% respectively), FGFR4 overexpresion mainly in non-squamous subtype (25%) and FGFR1 overexpression evenly distributed between squamous and non-squamous subtypes (9 %). There were rare instances of joint overexpression of more than one FGFR, FGFR 1 and 2 together (6%), FGFR 1 and 3 together (2%) and FGFR 3 and 4 together (2%). Overexpression of FGFs was seen in ~35% of all NSCLC samples with FGF19 overexpression being the most common, with increases seen in 20 % of all NSCLC samples. **Conclusions:** We report for the first time a sensitive and comprehensive FGF and FGFR gene expression analysis of 100 lung cancers. Our expression profiling did not confirm frequent overexpression of FGFR1 in squamous NSCLC in contradiction to frequent gene amplification at this locus suggesting that DNA amplification may not result in transcriptional alteration in many cases. Additionally, we detected frequent overexpression of FGFR2 and 3 in squamous NSCLC and FGFR4 overexpression in adenocarcinoma subtype of NSCLC. The receptor overexpression is frequently associated with overexpression of FGF ligands suggesting a paracrine effect. Expression profiling data support frequent FGFR pathway dysregulation in lung cancer and highlight that gene expression profiling is an important modality for identifying potential responders to novel anti-FGFR therapies.

**11081 General Poster Session (Board #363), Sat, 1:15 PM-5:00 PM**

**Effects of concomitant therapies on $\gamma\delta$ T-cell responses to zoledronate in patients with advanced prostate cancer.** *Presenting Author: Deborah Enting, Department of Immunobiology, King's College London, London, United Kingdom*

**Background:** $\gamma\delta$ T cells have attracted interest as a biological tool for cancer therapy owing to demonstrated tumour cytocidal potential in vitro, and their correlation with improved outcome in patients with malignancies. They are also not MHC-restricted, offering opportunities beyond individual-specific therapies. Indeed, clinical trials with bisphosphonate-activated $\gamma\delta$ T-cell-based immunotherapy are ongoing. However any clinical adoption of $\gamma\delta$ immunotherapy will need to be in the context of other therapies ('standard-of-care'). The influence of concomitant therapies such as chemotherapy on the effector function of $\gamma\delta$ T cells remains largely unexplored. **Methods:** We developed an immunomonitoring protocol to determine the $\gamma\delta$ T cell response to zoledronate (ZOL) in the context of hormonal therapy with or without docetaxel chemotherapy in patients with advanced prostate cancer. Blood samples were collected prior to ZOL and chemotherapy and 6 days later, with a second collection cycle after 4 weeks. Phenotypic and functional analyses were performed on purified peripheral blood mononuclear cells from each of the four successive collection points. **Results:** Many patients receiving ZOL show a markedly low percentage of $\gamma\delta$ T cells. Moreover, the percentage of NKG2D$^+$ $\gamma\delta$ T cells is significantly reduced in both treatment groups, although the majority of patients experienced a conspicuous boost in this compartment after ZOL treatment. However, this 'bounce-back' effect was lost in patients who have received ZOL long term. **Conclusions:** Thus, ZOL modulates $\gamma\delta$ T cell phenotypes *in vivo* but repeated long term ZOL treatment could lead to exhaustion of this immune compartment. This observation could have important clinical implications with regards to the duration of bisphosphonate treatment, which currently is undetermined. Furthermore, in the form of an interventional clinical trial, we are now assessing whether adjuvant IL-2 therapy can prolong the activation potential of $\gamma\delta$ T cells in the context of ZOL, offering a simple immune-enhancement potential that might usefully be adopted for particular cohorts of patients.

**11082 General Poster Session (Board #364), Sat, 1:15 PM-5:00 PM**

**Effect of lymphoid tissue inducer cells on lymphatic tumor cell invasion via activation of the RANKL/RANK axis within triple-negative breast cancers.** *Presenting Author: Sheeba Irshad, Breakthrough Breast Cancer Research Unit, London, United Kingdom*

**Background:** Inflammation and infiltration of the tumor tissue by host immune cells have been shown to promote tumor cell invasion and metastasis. The exact molecular mechanisms mediating tumor cell entry and persistence within the lymphatics remains unclear. We previously reported the novel identification of retinoic acid receptor related orphan receptor (ROR)gt$^+$lymphoid tissue inducer cells (LTIs) within breast cancer tumor microenvironments. The presence of these cells was shown to be associated with a high expression of a lymphoid chemokine gene signature; correlating also with an increased lymphatic vessel density and tumor invasion into lymphatic vessels. Here we report on the mechanistic relationship between LTi cells and tumor cell invasion. **Methods:** Both *in vitro* and *in vivo* experiments were carried out to further investigate the correlations observed within our human dataset. **Results:** We report the temporal sequence of LTi cell recruitment into first the primary tumors and then into the draining lymph nodes during tumour progression within a triple negative breast cancer (4T1.2) mouse model. These changes were closely associated with changes in the serum levels of associated lymphoid chemokines (CCL21 and CXCL13) and RANKL (a key regulator of LTi cell function). The administration of blocking antibodies for CCL21, CXCL13 or RANKL *in vivo* demonstrated i) LTi recruitment into tumors was dependent primarily on CCL21; ii) migration of LTi cells from the tumors to the draining lymph nodes was likely to be dependent on CXCL13; and iii) RANKL blocking was associated with significantly delayed onset of metastasis within the draining lymph node. Our *in vitro* studies demonstrate that an increase in stromal CXCL13 concentration within the tumor microenvironment following LTi recruitment promotes an EMT phenotype in the 4T1.2 cancer cell line, possibly via activation of the RANKL/RANK axis promoting an increase in tumor cell motility. **Conclusions:** We propose a pivotal role for LTi cells, through stromal cell interactions in the tumor microenvironment, in facilitating lymphatic invasion of tumor cells through modulation of the local lymphoid chemokine profile.

**11083 General Poster Session (Board #365), Sat, 1:15 PM-5:00 PM**

**PD-L1 specific tumor infiltrating lymphocytes occur frequently in melanoma and HNSCC patients.** *Presenting Author: Niels Junker, Department of Oncology and Center for Cancer ImmuneTherapy, Department of Hematology, Copenhagen University Hospital Herlev, Herlev, Denmark*

**Background:** Emerging immunotherapeutic strategies targeting the potent immune inhibitory PD-1/PD-L1 pathway in patients with advanced melanoma and squamous cell carcinoma of the lung, and TIL based adoptive therapy of patients with advanced melanoma are very promising. In order to identify relevant tumor associated targets of TIL based therapy our study aimed to identify the occurrence of PD-L1 specific T-cells in *ex vivo* expanded TIL from 30 patients, six of which were head and neck squamous cell carcinoma (HNSCC) patients and 24 were melanoma patients. The latter include 18 melanoma patients from our ongoing phase II trial NCT00937625. **Methods:** Upon PD-L1 peptide stimulation, TILs were screened for IFNgamma secretion using direct Elispot assays (Mabtech). In addition, PD-L1:tetramer (in house) analysis of TIL from selected patients was performed identifying PD-L1 specific cytotoxic T-cells. A standard $^{51}$Cr-release assay was used to assess killing of T2 cells presenting PD-L1 peptide. **Results:** In five of six HNSCC patients and in 17 of 24 melanoma patients, respectively, functional PD-L1 specific T-cells were identified in *ex vivo* expanded TIL, as determined by IFNgamma release. Moreover, it should be noted, PD-L1 responses were detected in four of five clinical responders (PR/CR), but in only two of five non-responders (SD/PD). Sequential analysis of specific binding to PD-L1:tetramers and the killing of PD-L1 presenting T2 cells confirmed the PD-L1 derived epitopes as a valid immunogenic target. **Conclusions:** These data demonstrate that counter immune inhibitory effector T-cells are present in tumors of different origin, and that they have the potential to effectively engage PD-L1, a known potent antitumor immune inhibitor. These findings may lead to the notion that effective immunotherapeutic approaches rely on the presence of effector T-cells specifically targeting both tumor and endogenous immune inhibitory pathways.

**11084 General Poster Session (Board #366), Sat, 1:15 PM-5:00 PM**

**Incidence and localization of tumor-infiltrating CD163$^+$ macrophages and T-cells in early breast cancer patients.** *Presenting Author: Anna Koumarianou, Fourth Department of Internal Medicine, Attikon University Hospital, Athens, Greece*

**Background:** CD163$^+$ macrophages (MΦ) infiltrate malignant tissue of breast cancer patients (BrCa) and suppress immunity, through a Th2 microenvironment characterized by high numbers of CD4$^+$ and low numbers of CD8$^+$ T-cells. We examined the associations between immune cell counts and clinicopathological characteristics. **Methods:** Serial sections of 59 paraffin-embedded BrCa tissues were immunohistochemically analyzed for the presence of total MΦ, their CD163$^+$ subpopulation, helper and cytototoxic T-cells by antibodies to CD68, CD163, CD4, and CD8 markers, respectively. Cells were counted in the intratumoral and peritumoral compartments by two independent observers, and expressed as number of cells for high power field. The medical records of the patients were retrospectively evaluated for various clinicopathologic parameters. Statistical analyses were performed by Tukey's multiple comparison tests and/or t-tests, or Spearman's correlation test. **Results:** Highly significant associations were found between the occurrence of CD163$^+$ MΦ cells and CD4$^+$ ($p<0.0001$) or CD8$^+$ ($p=0.0005$) T-cells as well as between total CD68$^+$ MΦ and CD4$^+$ T-cells ($p=0.01$), detected intratumorally. Importantly, intratumoral CD68$^+$ MΦ were positively correlated to relapse ($p=0.003$), and negatively correlated to survival ($p=0.01$) in patients treated only with chemotherapy ($n=19$). Among patients treated with both chemotherapy and hormonal therapy ($n=18$), relapse was positively associated with peritumoral CD163$^+$ MΦ ($p=0.04$) and negatively with intratumoral CD163$^+$ MΦ ($p=0.03$). The grade of the disease was correlated with the number of total CD4$^+$ T-cells peri- and intratumorally ($p<0.05$), while the CD4$^+$ peritumoral population was also associated with nodal disease ($p=0.03$). Moreover, a positive correlation was revealed between CD8$^+$peritumoral T-cells and p53 intense staining ($p=0.01$). **Conclusions:** Our study provides evidence that tumor associated macrophages, and specifically their CD163$^+$ subpopulation may serve as significant prognostic factors in BrCa, and supports the need for analysis also in terms of localization rather than solely incidence of infiltrating cells in the tumor tissue.

**11085 General Poster Session (Board #367), Sat, 1:15 PM-5:00 PM**

**Prognostic role of immune checkpoint-related genes in resectable lung adenocarcinomas.** *Presenting Author: Marta Usó, Fundación para la Investigación del Hospital General Universitario de Valencia, Valencia, Spain*

**Background:** Immune checkpoints blockade has demonstrated promising clinical results in NSCLC patients. In this study we have investigated the prognostic role of immune checkpoint markers (CTLA4, PD1 and PDL1) in resectable lung adenocarcinoma (ADC). **Methods:** RNA was isolated from fresh-frozen lung specimens (tumor and normal lung) from resectable ADC patients ($n=92$). RT-PCR was performed to analyze the expression of CTLA4, PD1 and PDL1 by the use of hydrolysis probes. Relative gene expression was assessed by Pfaffl formula and normalized by CDKN1B and ACTB as endogenous genes (selected by geNorm algorithm). Statistical analyses were considered significant at $p<0.05$. **Results:** Patient's median age was 64 [37-82], 77.2% were male, 73.9 % have a performance status of 0 and 58.7% presented stage I at the time of the diagnosis. We found a significant positive correlation between expression levels of PD1 and PDL1 ($r^2=0.436$; $p<0.0001$) and between PD1 and CTLA4 ($r^2=0.458$; $p<0.0001$). Survival analyses revealed that patients with higher levels of CTLA4, PD1 and PDL1 presented longer progression free survival (PFS) (Table 1), and in the case of CTLA4 also increased overall survival (OS) (median 32.30 *vs* 81.23 months $p=0.044$). Furthermore, the group of patients with high levels of both PD1 checkpoints (PD1$^{high}$ & PDL1$^{high}$) showed longer PFS (Table 1). The multivariate Cox regression analysis revealed that CTLA4 is an independent prognostic marker for PFS (HR 0.38 [0.19-0.79] p= 0.009) and OS (HR 0.38 [0.17-0.85] p=0.019]. **Conclusions:** Expression of immune checkpoint genes seems to have a prognostic role in lung ADC. Among these, CTLA4 has been found to be an independent prognostic marker highlighting the importance of these immune-markers in the prognosis of resectable lung ADC.

**PFS for CTLA4, PD1, and PDL1 in lung ADC patients.**

| | Median (months) | *p*-value |
|---|---|---|
| **CTLA4 (≤ median *vs* > median)** | 19.23 *vs* 81.23 | 0.008 |
| **PD1 (≤ median *vs* > median)** | 19.13 *vs* 49.30 | 0.048 |
| **PDL1 (≤ median *vs* > median)** | 19.23 *vs* 66.96 | 0.034 |
| **Combined checkpoints (Other combinations *vs* PD1$^{high}$ PDL1$^{high}$)** | 19.23 *vs* NR | 0.008 (0.048*) |

* *p* -value with Bonferroni correction.

**11086 General Poster Session (Board #368), Sat, 1:15 PM-5:00 PM**

**Gene-expression profiling to demonstrate select neutrophils from breast cancer patients versus healthy women as cytotoxic against breast cancer cells via novel chemokine-mediated mechanisms.** *Presenting Author: Elizabeth Anne Comen, Memorial Sloan Kettering Cancer Center, New York, NY*

**Background:** We have previously shown that neutrophils, entrained by a primary breast tumor, inhibit metastatic seeding and are cytotoxic to cancer cells in mouse models (Granot et al., 2010). We further demonstrated that neutrophils from human breast cancer patients are cytotoxic to breast cancer cells, and show a significantly higher cytotoxicity than neutrophils from cancer-free controls. We identified the cytokines IL1a, MCP-1, and TNF as being associated with neutrophil cytotoxicity and showed that these cytokines stimulate neutrophil cytotoxicity against breast cancer cells in cell culture assays. To further investigate neutrophil cytotoxicity, we preformed RNA-seq analyses on neutrophils from breast cancer patients and cancer-free controls. **Methods:** We purified neutrophils from 50 newly diagnosed pre-operative breast cancer patients and 25 cancer-free controls. Neutrophil cytotoxicity against MDA-MB-231 breast cancer cells was assessed in these samples by previously described methods. (Granot et al., 2010). RNA-seq was performed on 61 of these samples (36 breast cancer patients and 25 controls) using the Illumina HiSeq2500 platform. Comparative analyses were performed to identify genes differentially expressed between patients and controls and between samples showing high and low cytotoxicity. **Results:** Preliminary comparative analyses of the RNA-seq derived gene expression profiles identified 138 genes to be differentially expressed between patients and controls. Confirming our previous observations, IL1 family members and TNF were overexpressed in patient samples in comparison to cancer-free controls. Comparative analyses also identified 43 genes differentially expressed between patient samples with high cytotoxicity and those with low cytotoxicity. **Conclusions:** Our results have identified unique gene expression profiles associated with neutrophil cytotoxicity against breast cancer cells. We are currently evaluating the mechanism of action of neutrophil cytotoxicity as well as the prognostic and therapeutic roles of cytotoxic neutrophils in breast cancer patients.

**11087 General Poster Session (Board #369), Sat, 1:15 PM-5:00 PM**

**Prognostic and predictive value of tumor infiltrating lymphocytes (TIL) in two phase III randomized adjuvant breast cancer (BC) trials.** *Presenting Author: Maria Vittoria Dieci, University of Padua and Medical Oncology 2, Istituto Oncologico Veneto IRCCS, Padova, Italy*

**Background:** TIL have been proposed as a new prognostic factor for triple negative BC [Dieci MV, 2014]. Here we seek to evaluate the prognostic and predictive role of TIL in BC patients enrolled in two prospective adjuvant trials. **Methods:** The % of intratumoral (It) and stromal (Str) TIL were evaluated on H&E slides of tumors from 817 patients from two randomized trials comparing anthracycline-based to no chemotherapy [Arriagada R, 2005]. Samples were classified as High-TIL if ItTIL and/or StrTIL >=50%. CD3, CD8 and CD20 were also evaluated. Association with Disease-free survival (DFS) and interaction with chemotherapy were studied. **Results:** 781 of 817 cases were evaluable for TIL. High-TIL patients were more likely Grade 3 and ER-negative ($P<0.001$ for both). In multivariate analyses including age, tumor grade, tumor size, nodal status, ER, HER2 and treatment arm, both continuous It-TIL and Str-TIL variables were significantly associated with DFS. Each 10% increase in ItTIL or StrTIL was associated with 14% and 13% reduction in risk relapse (HR 0.86, 95%CI 0.78-0.94, P=0.001; HR 0.87, 95%CI 0.80-0.94, P<0.001), respectively. There was no prognostic effect in the ER+/HER2- subgroup, whereas both continuous ItTIL and StrTIL showed a significant prognostic value in multivariate analyses for both the ER-/HER2- and the HER2+ groups ($P=0.05$, $P=0.04$ for ItTIL and $P=0.02$, $P=0.01$ for StrTIL respectively). In the ER-/HER2- group 10yrs DFS rate was 85% and 53% for High-TIL and Low-TIL patients, respectively (HR 0.43 95%CI 0.20-0.94, $P=0.03$), whereas in the HER2-positive group 10yrs DFS rate was 74% and 54% for the High-TIL and Low-TIL groups, respectively (HR 0.48 95%CI 0.21-1.07, $P=0.07$). Either continuous ItTIL or StrTIL did not predict for the efficacy of anthracyclines, either in the whole study population or in different molecular subgroups (test for interaction: $P>0.2$). **Conclusions:** TILs did not predict anthracycline efficacy. We confirmed in prospective randomised trials the prognostic value of TIL for early triple negative BC patients and we suggested a prognostic impact in HER2+ patients. Analyses of TIL composition (CD3, CD8, CD20) are ongoing and will be presented at the meeting.

**11088 General Poster Session (Board #370), Sat, 1:15 PM-5:00 PM**

**Preclinical profile of ASPH_0047, a potent and selective antisense oligonucleotide targeting transforming growth factor beta 2 (TGF-β2).** *Presenting Author: Michel Janicot, Isarna Therapeutics GmbH, Munich, Germany*

**Background:** Transforming Growth Factor beta (TGF-β) proteins are members of a large family of related cytokines comprised of at least 33 members in mammals encoded by different genes, and which regulate a host of activities ranging from embryonic development to tissue homeostasis. The three bona fide TGF-β isoforms (TGF-β1, -β2 and -β3) play critical, pleiotropic roles in the pathophysiology of various human diseases. In cancer, correlations between TGF-β expression, disease stage and clinical parameters have been reported and linked to poor clinical outcome. TGF-β has been associated with a wide range of tumor-promoting processes, including tumor cell invasion and migration, angiogenesis, immunosuppression, as well as tumor stem cell maintenance and protection. More specifically, the TGF-β2 isoform has been reported to be a key molecular determinant of immunosuppression and invasiveness, and consequently playing a major role in metastasis. Therefore, inhibiting TGF-β2 appears as an attractive therapeutic intervention in Oncology. **Methods:** Based on the sequence of the human TGF-β2 mRNA, we have identified and engineered ASPH_0047, a LNA-modified antisense oligodeoxynucleotide gapmer, which shows potent and selective target mRNA and protein downregulation in various tumor cell-based assays, and promising anti-tumor activity in animal models. **Results:** In preclinical species, ASPH_0047 features plasma and tissue pharmacokinetics profile similar to previously reported profiles for LNA gapmers, strong metabolic stability and long-lasting tissue distribution with marked tissue penetration in liver, kidney and spleen. Preliminary safety assessment of ASPH_0047 in rats and *Cynomolgus* monkeys upon repeated 30-min infusion consistently points at dose-related stimulation of the immune system in several organs, including accumulation of distended macrophages in lymph nodes, and degenerative renal and liver changes at high doses. **Conclusions:** Key preclinical features of ASPH_0047 supporting rapid advancement to clinical development will be presented.

**11089 General Poster Session (Board #371), Sat, 1:15 PM-5:00 PM**

**Enabling a genetically informed approach to cancer medicine: A retrospective evaluation of the impact of comprehensive tumor profiling using a targeted next-generation sequencing panel.** *Presenting Author: Douglas Buckner Johnson, Vanderbilt-Ingram Cancer Center, Nashville, TN*

**Background:** Oncogenic genetic alterations "drive" neoplastic cell proliferation. An increasing number of potentially actionable alterations (PAAs) can be targeted by small molecules and antibodies. Since most patients (pts) do not have PAAs detectable by conventional clinical assays, NGS may identify these targets and increase treatment options. To determine the clinical impact of extensive genetic profiling, we reviewed our experience using a targeted NGS platform (FoundationOne) in advanced cancer pts. **Methods:** We retrospectively assessed demographics, NGS results, and therapies received for pts undergoing targeted NGS (exonic sequencing of 236 genes and selective intronic sequencing from 19 genes) from April 2012 to August 2013. PAAs were defined as somatic genetic changes inferred to confer sensitivity to approved or investigational agents. Co-primary endpoints were the proportion of pts with PAAs uncovered by NGS and the proportion who received genotype-directed therapy (GDT). **Results:** Samples from 103 pts were tested; most frequently breast carcinoma (26%), head and neck cancers (23%), and melanoma (10%). Most samples (83%) harbored ≥1 PAA; 6% had no detected mutations. Identified PAAs included alterations in the following pathways: cell cycle regulation (44%), PI3K-AKT (31%), and mitogen-activated protein kinase (19%); *TP53* was the most commonly altered gene (32%). With median follow up of 4.1 months, 21% received GDT. Of these, 61% were on clinical trials and 39% received approved or off-label GDT; several heavily pre-treated pts experienced significant benefit. Rationale for not administering GDT to pts with PAAs included assignment to standard therapy during follow up (35%) and clinical deterioration (13%).Additionally, a novel BRAF fusion was identified in melanoma. **Conclusions:** A targeted NGS panel identified PAAs in the majority of advanced cancer pts in our experience. The assay identified treatment options, facilitated enrollment in clinical trials, and identified novel PAAs. As time progresses, NGS results will be used to guide therapy in an increasing proportion of pts.

**11090 General Poster Session (Board #372), Sat, 1:15 PM-5:00 PM**

**$^{89}$Zr-bevacizumab PET imaging of disease manifestations in patients with Von Hippel-Lindau disease.** *Presenting Author: Sjoukje Oosting, University Medical Center Groningen, Groningen, Netherlands*

**Background:** Patients withvon Hippel-Lindau (VHL) disease develop benign and malignant vascular tumors. Local vascular endothelial growth factor (VEGF)-A production is likely involved in the development of disease manifestations and is a treatment target for antiangiogenic therapy. Bevacizumab binds VEGF-A. We aimed to assess whether $^{89}$Zr-bevacizumab positron emission tomography (PET) can visualize VHL manifestations and differentiate progressive from non-progressive lesions, and to compare PET results with plasma VEGF-A levels. **Methods:** Adult VHL patients with ≥ 1 measurable hemangioblastoma were eligible. The tracer $^{89}$Zr-bevacizumab (37 MBq) was injected 4 days before the PET scan. Maximum standardized uptake values (SUVmax) were calculated. PET scans were fused with routine MRI of the central nervous system (CNS) and abdomen. Progressive lesions were defined as new lesions, lesions that became symptomatic and lesions ≥ 10 mm that increased ≥ 10% and ≥ 4 mm on repeat anatomic imaging within 12 months. Plasma VEGF-A was measured before $^{89}$Zr-bevacizumab injection and with follow-up anatomic imaging. **Results:** Twenty-two patients were enrolled. $^{89}$Zr-bevacizumab PET visualized 59 known VHL manifestations (0-17 per patient, 24 in the CNS) with a median SUVmax of 8.5 (range 1.3-35.8) and a detection rate of 30.8% for lesions ≥ 10 mm. Two of 7 hotspots on PET without substrate on baseline anatomic imaging were detected as lesions on MRI during follow-up at 10 and 12 months. Nine out of 25 progressive lesions and 27 out of 175 non-progressive lesions were visible on PET (positive predictive value 25%, negative predictive value 90%). Progressive and non-progressive lesions had similar SUVmax (median 4.8, range 0.9-8.9 versus 6.7, range 1.3-35.8, $P$= .14). Plasma VEGF-A did not correlate with imaging results and was similar in patients with and without progressive lesions. **Conclusions:** VHL manifestations can be visualized with$^{89}$Zr-bevacizumab PET. $^{89}$Zr-bevacizumab uptake and plasma VEGF-A cannot be used to predict progression. High SUVmax in VHL lesions proves local bevacizumab accumulation and could potentially be used to select patients for bevacizumab treatment. Supported by the VHL Family Alliance. Clinical trial information: NCT00970970.

**11091 General Poster Session (Board #373), Sat, 1:15 PM-5:00 PM**

**Highly sensitive and quantitative detection of *EGFR* T790M mutationin tumor samples by nanofluidic digital PCR.** *Presenting Author: Eiji Iwama, Faculty of Medical Sciences Department of Comprehensive Clinical Oncology, Kyushu University, Fukuoka, Japan*

**Background:** Although treatment with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have a pronounced clinical benefit for patients with *EGFR* activating mutations, such patients inevitably develop drug resistances mainly due to the second mutation of T790M. In usual laboratory test, T790M emergence is reported qualitatively as presence or absence of the mutation. **Methods:** We evaluated the emergence of T790M with a highly sensitive and quantitative method, Nanofluidic Digital PCR. We compared digital PCR and Scorpion Amplification Refractory Mutation System (ARMS) in the sensitivity of detecting T790M. Digital PCR was used to calculate the ratio of T790M to the number of activating mutation alleles (T/A ratio) in 28 samples (15 pre- and 13 post-TKI treatment samples) obtained from 19 NSCLC with *EGFR*activating mutations. We also calculated the ratio of double-stranded DNA (dsDNA) to DNA concentration (dsDNA/DNA ratio) to evaluate the quality of each sample DNA. **Results:** Digital PCR detected T790M more sensitively compared with ARMS (pre-TKI: 14 of 15 samples, 93.3% *v* 2 of 15 samples, 13.3%, $p<0.001$; and post-TKI: 13 of 13 samples, 100% *v* 4 of 13 samples, 30.8%, $p<0.001$). In 8 patients whose both samples (pre- and post-TKI) were available, T/A ratios in post-TKI samples was higher than that in pre-TKI samples (37.3% *v* 5.4%; $p<0.01$). Digital PCR could not detect T790M only in one formalin-fixed, paraffin-embedded tissue (FFPE) sample. The dsDNA/DNA ratios were low in FFPE samples compared with those in cryopreserved cells (0.96 *v* 0.07; $p<0.001$). The possible explanation is that DNA extracted from FFPE samples used in this study was so fragmented that T790M could not be detected by PCR. **Conclusions:** This study indicates that T790M is present in all tumor samples before EGFR-TKI treatment. It is possible to calculate the ratio of T790M allele in well-preserved samples by digital PCR. This method is useful to develop treatment strategy to overcome the resistance to EGFR-TKI treatment.

**11092 General Poster Session (Board #374), Sat, 1:15 PM-5:00 PM**

**Quality assurance study of real-time targeted massive parallel sequencing (MPS) comprehensive cancer panel (CCP) and network pathway analysis in early breast cancer (EBC).** *Presenting Author: Paul N. Mainwaring, ICON Cancer Care, South Brisbane, Australia*

**Background:** We undertook a prospective quality assurance study in 63 women with early breast cancer (EBC) identifying technical issues that required modification for real-time integration of MPS with clinical and pathology parameters for clinical decision making. **Methods:** Pre-operatively, patients underwent a 2 step formal informed consent process. Samples were collected fresh into Qiagen PaxGene Tissue Container preserving both morphology and biomolecules with lysis of tissues overnight. Day 2 and 3; DNA extraction was performed using the Qiagen DSP kit over 1 hour. DNA and RNA MPS Ampliseq CCP was performed on Life technologies Proton P1 chip using in-house modifications in order to increase the fidelity of library preparation. Days 4-6 manually curated bioinformatics against publicly available mutation databases (e.g. COSMIC etc.) Day 7 communication of results. **Results:** The median age was 55, (32-84), 43 (66%) were postmenopausal. Histopathology IDC 47 (72%), ILC 8 (12%), NOS 5 (8%) metaplastic 2 (3%), mucinous 1 (2%). TNM Staging: Tis 1 (2%), T1a 2 (3%), T1b 13 (20%), T1c 25 (38%) T2 21 (32%); N0 48 (74%), N1mi 1 (2%), N1a 3 (45%), N2a 1 (2%), N3 5 (8%). Hormone receptors antibodies: ER (Roche SP1) Strong 46 (71%), Moderate 3 (5%), Weak 3 (5%), Negative 12 (18%); PR (Roche 1E2) Strong 25 (38%), Moderate 20 (31%), Weak 4 (6%), Negative 15 (23%); HER2 IHC (Ventana 4B5) Strong 2 (3%), Moderate 116 (17%), Weak 19 (29%), Negative 31 (48%); HER2 SISH (Ventana inform single probe); 2 SISH positive (mean copy number 20 & 29.6); 12 patients (18%) triple negative. Molecular aberrations identified included oncogenes TP53 7(13%), PIK3CA 16(29%) HRAS 2(4%), RUNX1 1(2%), STK11 1(2%), AKT1 1(2%) JAK2 1(2%); tumour suppressor genes MLL3 3 (5%), MSH6 1(2%), ARID1A 1(2%) UBR5 4(7%), and in the germline in tumour suppressor genes EPHB6 1(2%) NF1 1(2%) and LTK 1(2%). CNV, MethylSeq & RNASeq data will be presented in the context of network analysis. **Conclusions:** In summary, many challenges face the clinical laboratory developing high throughput desktop MPS. However, multilevel genomic information integration is possible within clinically relevant time-frames.

**11093 General Poster Session (Board #375), Sat, 1:15 PM-5:00 PM**

**Circulating tumor DNA (ctDNA) as a molecular monitoring tool in metastatic breast cancer (MBC).** *Presenting Author: Laura Katherine Austin, Thomas Jefferson University Hospital, Philadelphia, PA*

**Background:** MBC is an incurable disease with complex molecular features including somatic mutations that evolve in relation to genomic instability and selective treatment pressure. Circulating DNA fragments carrying tumor-specific sequence alterations (ctDNA) are found in blood and offer the possibility of longitudinal non-invasive molecular monitoring of the disease by detecting actionable mutations. **Methods:** This is a prospective evaluation of 18 patients with locally advanced or metastatic breast cancer who failed standard therapies and had plasma analyzed for ctDNA detection. Selection criteria: progression of disease after standard therapies, need to detect novel molecular abnormalities for possible therapeutic targeting, or confirmation of genomic abnormalities already demonstrated in tissue analysis. Guardant Health performed the plasma analysis; first ctDNA was isolated from plasma using a Qiagen circulating nucleic acid kit, then a panel of 54 gene mutations associated with solid tumors as reported in the COSMIC database were sequenced using single-molecule digital sequencing technology. **Results:** 89% of patients had metastatic disease; 55% of patients were ER+/HER2-, 6% ER+/HER2+, 22% ER-/HER2+, 17% ER-/HER2-, and 78% had IBC. All patients with MBC had ctDNA alterations. The most common mutations: *TP53* (44%), *PIK3CA* (44%), *ALK* (39%), *ERBB2* (33%), and *EGFR*(28%). Seven patients also had NGS analysis of tissue biopsy and 71% of these patients demonstrated having at least one concordant mutation. HER2 targeted therapy was continued in 3 patients with HER2+ disease after ctDNA confirmed ERBB2 alteration or amplification. Moreover, HER2 targeted therapy was initiated on two HER-2 negative patients that had ERBB2 mutations in ctDNA. Two patients were initiated on everolimus (Afinitor) combinations prior to ctDNA testing, had therapeutic benefit and ctDNA revealed alternations in PIK3CA. **Conclusions:** This is a sensitive test, 100% of patients with MBC had ctDNA alterations. ctDNA offers the possibility of non-invasive genomic analysis of MBC, providing tailored information on mutation status, new molecular targets for therapeutic interventions and allowing molecular monitoring of disease.

**11094 General Poster Session (Board #376), Sat, 1:15 PM-5:00 PM**

**Detection of EGFR mutations of serum circulating DNA.** *Presenting Author: Zongfei Li, MicroDiag Biomedicine Ltd. Co., Suzhou, China*

**Background:** As one of the EGFR-targeted drugs, EGFR tyrosine kinase inhibitors (TKI) play important roles in the treatment of NSCLC patients. It was established that EGFR mutation in tumor is a reliable marker for cancer response to EGFR-TKI. Herein, we assessed the concordance of EGFR mutations in serum circulating DNA (ctDNA) and tumor, and the possibility to predict the efficacy of EGFR-TKI by blood test. **Methods:** Samples (tissue and serum) from 404 NSCLC patients were analyzed retrospectively. EGFR mutations (exons 18-21) of tumor tissues and serum ctDNA were analyzed by sequencing and MCA-qASA assay respectively. MCA-qASA assay combines melting curve analysis and allele specific qPCR, which is expected to carry advantages of both. **Results:** We assess MCA-qASA assay first; the assay is capable to detect mutated DNA with low abundance (0.1 ng/$\mu$L) and low mutation rate (0.01%), probably the lowest ever. As summarized in the Table, among 123 tumor samples with EGFR mutations determined by DNA sequencing, we found 99 samples carrying EGFR mutations in their corresponding serum samples. We only found 15 serum samples carrying EGFR mutations among those whose corresponding tumor tissue samples did not carry EGFR mutations determined by DNA sequencing. The sensitivity and specificity for serum ctDNA EGFR mutation test using MCA-qASA assay as an alternative method for tumorous EGFR mutation test by DNA sequencing are 80.5% (99/123) and 94.7% (266/281) respectively. Kappa coefficient and Youden's index are 0.767 and 75.2% respectively. **Conclusions:** EGFR mutation occurrences are consistent in serum ctDNA and tumor tissues, with Youden index as high as 75.2%, which is the highest reported ever, which is ascribed to the high sensitivity and specificity of the MCA-qASA assay. We propose ctDNA EGFR mutation test for NSCLC patients without tumor tissues before the medication of EGFR-TKI.

**Comparison of EGFR-mutation status of NSCLC tumor tissues and serum ctDNA.**

| | | DNA sequencing - tumor | | |
|---|---|---|---|---|
| | | Mutation-positive | Wild-type | Total |
| MCA-Qaca - Serum | | | | |
| | Mutation-positive | 99 | 15 | 114 |
| | Wild-type | 24 | 266 | 290 |
| | Total | 123 | 281 | 404 |

**11095 General Poster Session (Board #377), Sat, 1:15 PM-5:00 PM**

**Phase I imaging study of the HER3 antibody RG7116 using $^{89}$Zr-RG7116-PET in patients with metastatic or locally advanced HER3-positive solid tumors.** *Presenting Author: Frederike Bensch, Department of Medical Oncology, University Medical Center Groningen, Groningen, Netherlands*

**Background:** Human epidermal growth factor receptor 3 (HER3) can play a critical role in tumor growth, proliferation and progression. The glycoengineered humanized monoclonal HER3-targeting antibody RG7116 is currently in phase I development (NCT01482377). Knowledge about whole body target expression, drug biodistribution and organ pharmacokinetics is lacking from many phase I designs. The aim of this imaging study is to determine *in vivo* biodistribution and tumor targeting characteristics of RG7116 by means of immunoPET using $^{89}$Zr-RG7116. **Methods:** Patients with HER3-positive metastatic or locally advanced solid tumors underwent $^{89}$Zr-RG7116-PET before treatment with RG7116. To determine optimal tracer dose and imaging schedule patients received $^{89}$Zr-RG7116 with increasing doses of unlabeled RG7116 followed by up to 3 PET scans until 7 days post injection (pi). Tracer uptake in organs of interest and tumor lesions was quantified as standardized uptake value (SUV) and tumor-to-background ratios (TBR) were calculated. **Results:** 13 patients participated without experiencing major safety issues. Initially, 7 patients received 37 MBq $^{89}$Zr-RG7116 containing 10, 50 or 100 mg unlabeled RG7116. The optimal dose was 100 mg and PET 2 days pi did not add valuable information. Subsequent patients (n=6) were evaluated at the 100 mg dose with PET scans 4 and 7 days pi. In all 13 patients tracer uptake in tumor lesions was seen, including in 12/13 biopsied HER3-positive lesions. In 3 of the 13 patients previously unknown brain and bone metastases were also detected. At the 100 mg dose 37 tumor lesions (9 patients) were quantifiable, with mean SUVmax 4 days pi of 4.2 ($\pm$1.8 SD). Normal antibody tissue distribution was seen with mean SUVmax 4 days pi for liver 8.1, intestine 6.5, blood pool 6.2, kidney 5.0, spleen 4.9, and low uptake in the vertebrae 2.7, lung 1.4, muscle 1.1 and brain 0.5, resulting in mean TBR of 3.60 (range 1.10-9.53). **Conclusions:** With $^{89}$Zr-RG7116-PET biodistribution of RG7116 was determined and tumor specific uptake of $^{89}$Zr-RG7116 was shown in patients with HER3-positive metastatic cancer. Analysis of HER3 saturation by repeated $^{89}$Zr-RG7116-PET scanning is ongoing. Clinical trial information: NCT01482377.

**11096 General Poster Session (Board #378), Sat, 1:15 PM-5:00 PM**

**Usefulness of I-[3-$^{18}$f]-$\alpha$-methyl tyrosine ($^{18}$F-FAMT) PET as therapeutic monitoring for patients with advanced lung cancer.** *Presenting Author: Kyoichi Kaira, Department of Oncology Clinical Development, Maebshi, Japan*

**Background:** L-[3-$^{18}$F]-$\alpha$-methyl tyrosine ($^{18}$F-FAMT) PET has a high specificity for detecting malignant lesions, and the high uptake of $^{18}$F-FAMT within tumor cells could be a useful marker for predicting worse outcome. However, it remains unknown whether $^{18}$F-FAMT PET has a potential of therapeutic monitoring after chemotherapy. Thus, we evaluated $^{18}$F-FAMT PET for therapy response and survival in patients with advanced lung cancer, as compared with $^{18}$F-FDG PET. **Methods:** $^{18}$F-FAMT PET and $^{18}$F-FDG PET were performed before and 4 weeks after chemotherapy in patients with untreated advanced lung cancer. Uptake of tracers was measured by standardized uptake value (SUV) in the primary tumor. The maximum SUV ($SUV_{max}$) on pre-treatment and post-treatment, and metabolic response (MR) were correlated with the survival time estimated by Kaplan-Meier method. **Results:** Of 111 enrolled patients, 95 patients eligible for post-treatment $SUV_{max}$ analyses on both $^{18}$F-FAMT PET and $^{18}$F-FDG PET. Seventy patients received systemic chemotherapy alone as first-line treatment, and 25 patients were treated with concurrent thoracic chemoradiotherapy. The histological type included 87 non-small cell lung cancers and 8 small-cell lung cancers. Post-treatment $SUV_{max}$ and MR on $^{18}$F-FAMT PET were significantly correlated with tumor response by Response evaluation criteria in solid tumor (RESCIST), but pre-treatment $SUV_{max}$ was not. In all patients (n=95), post-treatment $SUV_{max}$ on $^{18}$F-FDG and $^{18}$F-FAMT PET, and MR on $^{18}$F-FAMT PET were significant prognostic marker for predicting poor outcome by univariate analysis. Multivariate analysis confirmed that MR on $^{18}$F-FAMT PET was a significant independent prognostic factor. MR on $^{18}$F-FAMT PET was also an independent prognostic predictor in 70 patients who received chemotherapy alone. **Conclusions:** MR on $^{18}$F-FAMT PET may be a potential parameter to predict the prognosis after first-line chemotherapy in patients with advanced lung cancer.

**11097 General Poster Session (Board #379), Sat, 1:15 PM-5:00 PM**

**Copenhagen prospective personalized oncology (CoPPO): Sequencing and array-based pipeline for selection of patients to phase 1 studies.** *Presenting Author: Ida Elisabeth Viller Tuxen, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark*

**Background:** Advanced genomics technology can be used to characterize genomic alterations (GA) that potentially drive tumor growth. We have established a sequencing and array based pipeline to identify GA to select patients (pts) who might benefit from novel targeted treatments and to enrich the population in Phase 1 trials with pts that harbor specific targets. **Methods:** Pts with advanced solid tumors referred to a dedicated Phase 1 Unit were offered mapping of GA to identify pts who could benefit from a personalized treatment. Two ultrasound-guided biopsies were obtained and stored in RNA*later* for DNA and RNA purification. A third biopsy for histology was paraffin embedded. SNP-array from tumor and whole exome sequencing (WES) from DNA (tumor and blood) were performed using sequence capture and Illumina sequencing to call tumor specific mutations. Expression levels of therapeutic targets were revealed by expression Array and RNA-seq from tumor RNA. Results were reviewed by a tumor board. Patients with specific genetic profiles that could be targeted with marketed drugs or drugs in development, were, if possible, offered individualized treatment. **Results:** From May 2013 to December 2013, 30 heavily pretreated patients with solid tumors were included. In 28 patients (93%) a dedicated biopsy was obtained. An actionable target was identified in 15 patients (53%) and 6 patients (21%) were offered treatment according to the findings of either mutations or RNA expression levels of oncogenes. Median time from biopsy to result was 38 days. We were able to define a hypothetic driver for tumor growth in 80% of the cases. **Conclusions:** Establishing sequencing and array-based pipeline for enrichment of pts to phase 1 trials is feasible.

**11098 General Poster Session (Board #380), Sat, 1:15 PM-5:00 PM**

**Integrative whole-genome copy number analysis and mutation profiling of FFPE brain tumor specimens and potential in designing multi-arm clinical trials.** *Presenting Author: Shakti Ramkissoon, Dana-Farber Cancer Institute, Boston, MA*

**Background:** Multi-dimensional cancer genotyping has the potential to advance clinical diagnostics and improve results of clinical trials by identifying targetable genomic aberrations for glioblastoma (GBM). However, prospective use of formalin-fixed paraffin-embedded (FFPE) clinical samples for multiplex copy number and somatic mutation genotyping in clinical trials is not yet routinely performed. We evaluated feasibility and implemented a combined copy number and clinical research mutation-testing program (PROFILE) in a CLIA-certified laboratory. **Methods:** We collected molecular profiling results from clinical and clinical research testing on 250 GBM patients from the Brigham and Women's Hospital Center for Advanced Molecular Diagnostics. These data included array comparative genomic hybridization (OncoCopy, n=250), mass spectrometry-based mutation genotyping (OncoMap, n=86), and targeted cancer exome sequencing of 275 known cancer genes (OncoPanel, n=98). **Results:** We successfully reported OncoCopy profiles for 42 relevant loci in 97% of samples and demonstrated that analysis of 250 GBMs reliably detected amplifications or structural variations in common drug targets for clinical trials (*EGFR*, *EGFRvIII, MET*, *MDM2*, *MDM4*, *PDGFRA*, *CDK4*, and *CDK6)* at expected frequencies. OncoMap results for 86 GBMs revealed recurrent mutations in *IDH1*, *BRAF, PIK3CA,* and *PIK3R1* while less frequent mutations were detected in tumor suppressor genes *TP53*, *PTEN* and *RB1*. OncoPanel results were reported on >90% of patients and comprehensively detected known mutations of diagnostic, prognostic and therapeutic relevance (e.g. *IDH1* p.R132H, *BRAF* p.V600E). Tumor suppressor gene mutations and variants were robustly detected allowing for integrative OncoCopy and OncoPanel reporting in 65% of cases. **Conclusions:** These complementary clinical assays allowed efficient and reliable identification of diagnostic aberrations that serve as clinically actionable drug targets, which could be incorporated into genomically stratified multi-arm clinical trial design for GBM.

**11099 General Poster Session (Board #381), Sat, 1:15 PM-5:00 PM**

**Correlation of circulating miRNA levels with progression-free survival (PFS) and overall survival (OS) in early-stage lung adenocarcinoma.** *Presenting Author: Francesco Grignani, Department of Experimental Medicine, University of Perugia, Perugia, Italy*

**Background:** Surgically resected early-stage non-small lung cancer (NSCLC) display a highly variable outcome in terms of PFS and OS. Currently used clinico-pathological parameters may not precisely predict individual risk of relapse. Here, we correlated the levels of circulating miRNAs levels with PFS and OS in early stage fully resected NSCLCs. **Methods:** We analyzed the levels of the 84 most abundant circulating miRNAs (Qiagen PCR array) in sera from patients with stage IàIIIA resected NSCLC. All the sera were collected at the time of diagnosis. Total serum RNA was purified and miRNA levels were measured by real time PCR. Normalization was obtained by using a spike-in control miRNA and multiple endogenous unvariable control miRNAs. **Results:** We analyzed 94 sera, of which 44 were derived from patients who remained free of relapse for at least 2 years, while 50 sera from patients who relapsed within 2 years from the diagnosis. No significant correlation was found between miRNA levels and age, sex and smoking habits. In squamous cell lung cancer no significant correlation was found between miRNA levels and clinical outcome. Conversely, we were able to identify significant associations between the levels of a number of miRNA and PFS in samples from adenocarcinoma patients. The most significant ones were found in stage I and II patients where miR-15b levels were significantly higher in relapsed patients (p= 0.01). Also, high levels of serum miR-223 had a strong negative correlation with OS (p= 0.001). A miRNA signature could be derived which correlated with PFS with a specificity of 75% and a sensitivity of 84% (p<0.01) . The signature includes miR-15b, miR-27a, miR-106b, miR-191 and miR-223. The same miRNA signature gave similar data when OS was considered. Normalization with multiple endogenous miRNA levels was mandatory to obtain reliable statistics. **Conclusions:** The analysis of serum miRNA levels in resected early stage NSCLC seems to have limited usefulness as prognostic tool for early squamous cell carcinoma, whereas it may reliably predict clinical outcome in adenocarcinoma, with both high sensitivity and specificity. Prospective studies are warranted.

**11100 General Poster Session (Board #382), Sat, 1:15 PM-5:00 PM**

**Correlation of hypoxia measured by fluorine-18 fluoroerythronitroimidazole ($^{18}$F-FETNIM) PET/CT and the malignant progression of gliomas.** *Presenting Author: Man Hu, Shandong Cancer Hospital, Jinan, China*

**Background:** Hypoxia is important in the biology of human gliomas. PET offers a noninvasive method to differentiate individual tumor biology and modify treatment accordingly. The development of PET tracers provides further tools to evaluate the hypoxia of human tumors. The aim of this study was to determine whether hypoxia, as measured by fluorine-18 fluoroerythronitroimidazole ($^{18}$F-FETNIM) PET/CT, was associated with malignant progression of gliomas. **Methods:** Fifteen patients with suspected primary glioma and who were referred for surgical treatment were enrolled prospectively in this study. All patients had $^{18}$F-FETNIM PET/CT studies before surgery. PET/CT imaging was performed at 120 min after $^{18}$F-FETNIM injection. For semi-quantitative analysis, the maximum standardized uptake value (SUVmax) was obtained by drawing regions of interest (ROI) on the PET images for tumor tissues. Hypoxia, angiogenesis, aggression, and cellular proliferation related markers hypoxia-inducible factors-1alpha (HIF-1a), vascular endothelial growth factor (VEGF), matrix metallo proteinase 9 (MMP-9), and Ki-67 expression were estimated in tissue specimens by immunohistochemistry. **Results:** SUVmax, HIF-1a, VEGF, MMP-9, and Ki-67 expression in high-grade gliomas were significant higher than those in low-grade (2.03 ± 0.49 vs.1.04±0.37, 40.63% ± 11.16% vs. 20.71% ± 12.05%, 71.88% ± 15.57% vs. 37.86% ± 13.5%, 68.13% ± 17.92% vs. 35% ± 10.8%, and 28.13% ± 18.11% vs. 3.7% ± 1.25%, respectively. $p$ = 0.001, 0.006, 0.001, 0.001, 0.007, respectively). Furthermore, $^{18}$F-FETNIM uptake data were divided into 2 groups using the mean of SUVmax as a basis for the division. Significant differences were observed between high $^{18}$F-FETNIM uptake and low uptake in HIF-1a, MMP-9, VEGF, and Ki-67 expression ($p$= 0.004, 0.004, 0.001, 0.046, respectively). **Conclusions:** $^{18}$F-FETNIM PET/CT provides a noninvasive assessment of hypoxia in glioma. It is useful to understand the mechanisms by which hypoxia affect malignant progression of glioma. $^{18}$F-FETNIM PET/CT may have a role in evaluating novel therapeutic agent targeting tumor hypoxia in clinical trials.

**11101 General Poster Session (Board #383), Sat, 1:15 PM-5:00 PM**

**Sensitivity and specificity of an oral uracil-loading test dose for screening for DPD deficiency.** *Presenting Author: M C van Staveren, Scheper Hospital Emmen, Emmen, Netherlands*

**Background:** 5-fluorouracil (5FU) and capecitabine (CAP) are extensively metabolised by dihydropyrimidine dehydrogenase (DPD). DPD deficiency can lead to severe toxicity after 5FU or CAP. Uracil (U) can be used as a probe to determine the systemic DPD activity by measuring uracil and its metabolite dihydrouracil (DHU) in plasma. This study was performed to assess the sensitivity and specificity of an uracil loading dose for detecting DPD deficiency. **Methods:** All cancer patients who suffered from CTC grade III or IV toxicity after the first or second cycle of 5-FU or CAP-based treatment were asked to participate. Uracil 500 mg/m$^2$ was administered orally followed by multiple blood sampling, plasma concentrations of U and DHU in plasma were determined. DPD activity in PBMCs was determined and patients were divided in 2 groups: DPD activity in PBMCs $<$ 5 nmol/mg/hour (deficient group) and with activity $\geq$ 5 (normal group, controls: 9.9 ± 2.8 nmol/mg/hour). In the deficient group, PCR amplification of all 23 coding exons and flanking intronic regions of DPYD was performed. Plasma concentrations of U and DHU were determined by HPLC. A one-compartment uracil pharmacokinetics model was developed and used to determine $V_{max}$ of the DPD enzyme of each patient. Sensitivity and specificity of $V_{max,}$ U concentration and the U/DHU concentration ratio were determined using ROC analysis. **Results:** 47 patients were included (19 DPD deficient, 28 DPD normal). Sensitivity and specificity of the estimated pharmacokinetic parameters are displayed in the Table. PCR amplification in the DPD deficient group revealed the following pathogenic mutations: c.1129-5923C>G (n=4), c.2579delA (n=2), c.2846A>T (n=3), c.1905+1G>A (n=10), c.1679T>G (n=1). **Conclusions:** The sensitivity of 80% and specificity of 98% of the U/DHU ratio at t=120 min show that the oral uracil loading dose can effectively monitor DPD activity and can be used as a pre-emptive tool to identify patients with reduced DPD activity.

**Sensitivity, specificity, and cut-off levels for Vmax, U/DHU, and uracil concentration.**

| Test parameter | Cut-off level | Sensitivity (%) | Specificity (%) |
|---|---|---|---|
| Vmax (mg/h/1,85m$^2$) | 665 | 79 | 79 |
| U/DHU$_{120min}$ ratio | 2.4 | 80 | 98 |
| U$_{120\ min}$ (mg/l) | 6.4 | 80 | 96 |

**11102 General Poster Session (Board #384), Sat, 1:15 PM-5:00 PM**

**ImmunoPET imaging with $^{89}$Zr-cetuximab in patients with advanced colorectal cancer.** *Presenting Author: Catharina Wilhelmina Menke, Department of Medical Oncology, VU University Medical Center, Amsterdam, Netherlands*

**Background:** Inhibition of epidermal growth factor receptor (EGFR) with cetuximab is part of treatment for patients with wild type (wt) KRAS advanced colorectal cancer (mCRC). Sixty percent of these patients do not benefit from cetuximab treatment. Potential causes include mutations in the EGF signaling cascade or other RAS mutations. Alternatively, pharmacokinetic factors like sequestration of cetuximab in organs with high EGFR expression such as liver could lead to sub-therapeutic intratumoral drug levels. We performed an exploratory study to evaluate biodistribution and tumor uptake using Positron Emission Tomography (PET) with $^{89}$Zr labeled cetuximab in patients with wt KRAS mCRC. **Methods:** Eight patients with wt KRAS mCRC who were candidate for cetuximab monotherapy, received 37 ± 1 MBq $^{89}$Zr - cetuximab immediately after the first therapeutic dose of cetuximab. Serial whole body PET was performed from one hour to 10 days post injection (p.i.). Non-hepatic tumor lesions were visually assessed as positive or negative for uptake and quantified by Standard Uptake Value (SUV). Tumor response was analyzed every 8 weeks according to RECIST 1.1. **Results:** Sequential PET showed in 4 of 8 patients accumulation of cetuximab over time in non-hepatic tumor lesions. Visual tumor assessment was optimal with PET images acquired on day 6 p.i. with tumor $SUV_{peak}$ ranging from 2.3 to 7.5. Organ biodistribution was reproducible between patients, $SUV_{mean}$(CoV) levels observed were 7.8 (24) for liver, 2.2 (26) for the kidneys, 1 (44) for lung and 1.8 (34) for spleen. As expected, analysis of hepatic metastases was hampered due to high background activity in the liver. In two of 4 patients with cetuximab uptake clinical benefit was observed compared to progressive disease in 3 of 4 patients without uptake. EGFR-expression and RAS/BRAF mutation analyses on archival tumor material will be presented. **Conclusions:** PET-imaging with $^{89}$Zr-cetuximab is feasible and differential tumor uptake can be demonstrated. Further investigations are needed to determine whether the correlation between tumor uptake and the effect of dose escalation of cetuximab on tumor response in patients with wt RAS-mCRC can be used as an individualized treatment approach. Clinical trial information: NCT01691391.

**11103 General Poster Session (Board #385), Sat, 1:15 PM-5:00 PM**

**Preclinical evaluation of anti-MET antibodies for immunohistochemical staining.** *Presenting Author: Hartmut Koeppen, Genentech, Inc., South San Francisco, CA*

**Background:** The monovalent anti-MET antibody onartuzumab in combination with erlotinib showed clinical benefit in a phase II trial in advanced non-small cell lung cancer (NSCLC); this benefit was limited to MET-positive tumors as determined by immunohistochemistry (IHC) using the CONFIRM anti-total MET rabbit monoclonal antibody (Ventana). The trial results demonstrate the importance of a reliable IHC assay to distinguish MET-positive from MET-negative cancers. Therefore, it is important to gain a pre-clinical understanding of available antibodies that may warrant further investigation. The aim of this study was to evaluate nine anti-MET antibodies for sensitivity and specificity using various standard staining conditions. **Methods:** All antibodies were evaluated on eight formalin-fixed paraffin-embedded (FFPE) cell lines with known RNA and protein (ELISA) MET expression levels. Antibodies with adequate sensitivity and specificity were then analyzed on a NSCLC tissue microarray (TMA) and on whole sections of NSCLC and gastric adenocarcinoma (GAC) of known MET status. The antibody evaluation included four autostainers (Ventana Benchmark XT, Leica BOND-III, Dako Autostainer Plus and Dako Omnis), 14 antigen retrieval (AR) methods and 7 detection methods. **Results:** The SP44 and D1C2 antibodies showed staining on cell lines, NSCLC TMA, and large sections of NSCLC and GAC of adequate sensitivity and specificity when used under the following conditions: (1) Ventana Benchmark XT with CC1 standard and CC1 extended AR, (2) Leica BOND-III with ER2 AR, (3)DAKO Autostainer with EnVision FLEX Target High pH AR. All other antibodies and AR/detection methodologies showed inferior staining characteristics due to insufficient sensitivity and/or specificity. **Conclusions:** SP44 and D1C2 showed staining performance similar in sensitivity and specificity to the CONFIRM anti-Total MET antibody. Additional validation on larger cohorts of clinically annotated tissues is required prior to any clinical application.

**MET antibodies.**

| Vendor | Clone or product # |
|---|---|
| Spring Bioscience | SP44 |
| Cell Signaling | D1C2 |
| My Biosource | 3D4 |
| IBL | polyclonal #18321 |
| Santa Cruz | N-17; C-12; C-28 |
| Abcam | 8F11 |
| R&D Systems | polyclonal #AF276 |

**11104 General Poster Session (Board #386), Sat, 1:15 PM-5:00 PM**

**The NIH genetic testing registry: Hereditary, pharmacogenetic, and somatic tests for oncology practice.** *Presenting Author: Wendy S. Rubinstein, National Institutes of Health, Bethesda, MD*

**Background:** Oncology professionals need to access and gauge information about tests for hereditary cancer predisposition, biomarkers, pharmacogenetic dosing and risk-based chemoprevention. NIH has created the Genetic Testing Registry (GTR; http://www.ncbi.nlm.nih.gov/gtr/), a freely available, web-based resource to enable centralized access to comprehensive information about genetic tests and improve transparency. **Methods:** GTR was implemented by the National Center for Biotechnology Information (NCBI) with oversight by the NIH Office of the Director, extensive input from diverse stakeholders, and ongoing consultation with two advisory committees and other Federal agencies. Data are voluntarily submitted by laboratory providers (e.g., indications, methods, targets, FDA review status, CPT molecular pathology codes) and supplemented by NCBI (e.g., practice guidelines and informative web links to molecular, literature and other resources). **Results:** As of February 2014, GTR has 13,878 registered tests for 4,051 conditions offered by 395 labs from 39 countries. Next-generation sequencing (NGS), a component of 10% of molecular tests, is used in 113 tests to evaluate hereditary cancer syndromes, the largest a 107-gene panel. BRCA1 gene testing is a component of 32 clinical tests offered by 11 U.S. labs. Somatic test submission was enabled in late 2013; new test purposes include predictive, prognostic, recurrence, and therapeutic management. Registered tests include several targets used to guide treatment such as BRAF, BCR/ABL1, FLT3, KRAS, JAK2 and complex cytogenetic panels. GTR has 64 pharmacogenetic tests for 18 genetically influenced drug responses (e.g., tamoxifen, irinotecan, thioguanine, fluorouracil). Algorithm-based tests that employ variants discovered in genome-wide association studies to inform chemoprevention decisions are also in scope. **Conclusions:** GTR reflects trends in the genetic testing landscape such as the clinical use of NGS and the immediate effect of the U.S. Supreme Court patent ruling on the availability of BRCA testing. Growing participation in GTR by oncology test providers and clinicians will improve the utility of this resource to the community.

**11105 General Poster Session (Board #387), Sat, 1:15 PM-5:00 PM**

**Incorporation of FGFR1 and FGFR2 amplification status determination in routine molecular prescreening for targeted therapies.** *Presenting Author: Ludmila Prudkin, Molecular Pathology Laboratory, Vall d'Hebron Institute of Oncology, Barcelona, Spain*

**Background:** Enriching PhI trials with patients harboring alteration in the FGFR pathway is key to the successful development of FGFR pathway inhibitors. FGFR1 and 2 amplification (amp) are considered a driver event in many carcinomas. **Methods:** ISO-accredited FGFR1 and 2 FISH assays were run in samples from candidates to enter a PhI clinical study. FGFR amp status was defined as a ratio gene/centromere ≥2.2. FGFRs status was correlated with available PTEN expression (IHC) and mutations data (AKT, KRAS, BRAF, PIK3CA, among others). **Results:** From January 2012 we screened 272 samples for FGFR1 and 190 for FGFR2. Samples came from primary tumors in 196 cases (PT=71.8%), and 141 (PT=74.2%); and metastatic disease in 61 cases (MET=22.3%), and 41 (21.6%) for FGFR1 and FGFR2, respectively. Rest of cases was of unknown (UKN) origin. Overall, FGFR1 gene amp was observed in 11% and FGFR2 in 3% of cases with amplification rates similar between PT and MET. After subgrouping by tumor origin, FGFR1 ampl was most frequently observed in breast cancer (19%) followed by lung cancer (8%). FGFR2 was amplified in 5% of gastric and gynecological cancers, followed by breast cancer (2.5%). No associations were observed with FGFR1 and 2 amplifications and PTEN loss. Mutation results were available in 141 and 122 samples with FGFR1 and 2 amp data, respectively. Only one point mutation in AKT and one in PIK3CA genes were observed in FGFR1 amplified samples, while none in FGFR2 amplified cases. **Conclusions:** Incorporation of FGFRs gene amp status in a routine molecular prescreening is feasible and may provide clinicians with a tool to select patients to targeted therapies.

**FGFR1**

| Organ | PT (n.) | MET (n.) | PT FGFR1 ampl | MET FGFR1 ampl |
|---|---|---|---|---|
| Breast | 86 | 30 | 15 (17,5%) | 7 (23.3%) |
| Lung and pleura | 30 | 6 | 2 (6,7%) | 1 (16,6%) |
| Gyn | 23 | 1 | 1 (4.3%) | 0 |
| Stomach | 28 | 3 | 1 (3,6%) | 0 |
| Others / unknown* | 29 | 21 | 1 (3.5%) | 0 |
| FGFR1 | 196 | 61 | 20 (10,2%) | 8 (13,1%) |

**FGFR2**

| Organ | PT (n.) | MET (n.) | PT FGFR2 ampl | MET FGFR2 ampl |
|---|---|---|---|---|
| Breast | 60 | 21 | 1 (1.7%) | 1 (4,7%) |
| Lung and pleura | 2 | 3 | 0 | 0 |
| Gyn | 20 | 1 | 1 (5%) | 0 |
| Stomach | 38 | 4 | 1 (2,6%) | 1 (25%) |
| Others / unknown* | 21 | 12 | 0 | 0 |
| FGFR2 | 141 | 41 | 3 (2,1%) | 2 (4,9%) |

* Others = bone, CRC, esoph, liver, skin, soft tissues, thyroid.

**11106 General Poster Session (Board #388), Sat, 1:15 PM-5:00 PM**

**Identification of a rare germ-line variant in the *TP53* 3'UTR in individuals with the Li-Fraumeni-like phenotype: A new mechanism of cancer predisposition?** *Presenting Author: Gabriel de Souza Macedo, Universidade Federal do Rio Grande do Sul/ Hospital de Clínicas de Porto Alegre/CPE-Laboratório de Medicina Genômica, Porto Alegre, Brazil*

**Background:** Li-Fraumeni Syndrome (LFS) and Li-Fraumeni-like Syndrome (LFL), are inherited disorders characterized by increased predisposition to multiple early-onset cancers and are associated to *TP53* germline mutations. The rs78378222 (A>C) SNP, a rare variant located within the polyadenylation signal of *TP53*, was recently identified in a GWAS. It occurs at a frequency = 0.019 in Icelandic population and leads to impaired 3'-end processing of mRNA, conferring susceptibility to certain types of cancer. **Methods:** Considering that regulatory gene regions has not been considered in the *TP53* molecular diagnostic, the purpose of this study was to assess the allelic frequency of this variant in a patients group composed by LFS/LFL families with (n=57) and without (n=131) *TP53* germline mutation. To support the association, we also studied the evolutionary conservation of the *TP53* polyadenylation signal in vertebrate species and the p53 immunohisthochemical pattern in tumors from carriers of different *TP53* mutations. **Results:** The heterozygous genotype to rs78378222[C] was found in 7 patients fulfilling LFL criteria who tested negative for coding germline *TP53* mutations. In the group of patients with coding region *TP53* germline mutations we did not encounter rs78378222 [C] carriers. We also investigated the *TP53* sequence at the polyadenylation signal of 63 therian mammals. None of these organisms presented any variation in the locus of the variant, evidencing strong evolutionary conservation. Finally, we assessed p53 expression by immunohistochemistry in tumors of carriers of known germline pathogenic *TP53*mutations and of the 3´UTR variant. In the first group we observed intense nuclear accumulation of p53 and in the second weak and a focal p53 immunostaining was identified. **Conclusions:** This is the first description of rs78378222[C] in LFL families, and our findings suggest a new carcinogenesis mechanism associated to this variant. However, further functional characterization studies and analysis of larger series of families with the LFS/LFL phenotype should be undertaken to confirm the s78378222[C] as a pathogenic variant associated with this disorder.

**11107 General Poster Session (Board #389), Sat, 1:15 PM-5:00 PM**

**Subtype analysis from the GEICAM/2003-02 study: High-risk, node-negative breast cancer patients treated with adjuvant fluorouracil, doxorubicin, and cyclophosphamide (FAC) versus FAC followed by weekly paclitaxel.** *Presenting Author: Federico Rojo, Hospital Universitario Fundacion Jimenez Diaz, Madrid, Spain*

**Background:** Adding taxanes to standard anthracycline-based adjuvant therapy improves survival outcome in node-negative breast cancer (BC) patients (pts) with high risk of recurrence. Due to the small magnitude of the benefit and to avoid toxicity, biomarker analyses aimed to identify subpopulations benefiting the most from taxanes are warranted. **Methods:** After surgery, 1,925 node-negative BC pts with at least one high-risk factor for recurrence (St. Gallen 1998 criteria) were randomly assigned to receive 6 FAC cycles or 4 FAC cycles followed by 8 weekly paclitaxel doses (FAC-wP); 108 out of the 181 HER2+ pts did not receive trastuzumab. With a median follow-up of 63.3 months, 93% and 90.3% of pts receiving FAC-wP or FAC, respectively, remained disease free (hazard ratio [HR]: 0.73; 95% CI: 0.54-0.99; log-rank p= 0.04; Martin JCO 2013). We performed central immunohistochemistry (IHC) for ER, PR, Ki-67 and HER2/FISH; pts were grouped in intrinsic BC subtypes according to the Prat et al. classification (JCO 2012): Luminal A: RE+, PR>20%, HER2-, Ki67<14%; Luminal B1: RE+, HER2-, PR≤20% and/or Ki67≥14%; Luminal B2: RE+, PR+/-, HER2+; HER2: RE-, PR-, HER2+; TN: RE-, PR-, HER2-. We report here the correlation between these variables and Distant Metastases-Free Survival (DMFS). Cox regression and log-rank test were used for analysis. **Results:** Central biomarker expression and subtype classification is currently available for 1,084 and 946 pts, respectively. DMFS in the 1,084 pts were 97.8% vs 94.8% (HR: 0.52; 95% CI: 0.28-0.97; p=0.035). In the univariate analysis, FAC-wP therapy, ER and PR positive status, low Ki67 proliferation and Luminal A and B1 subtypes were significantly associated with better DMFS. Absence of PR and Luminal B1 were predictive for FAC-wP benefit. The multivariate analysis showed that intrinsic subtype classification was predictive of DMFS (p=0.010). **Conclusions:** Our study suggests that IHC-based intrinsic subtypes provide prognostic value and could identify a subpopulation of node-negative BC pts (the luminal B1) who obtains more benefit from FAC-wP adjuvant therapy.

**11108 General Poster Session (Board #390), Sat, 1:15 PM-5:00 PM**

**Development of a histology-guided gene expression tumor classifier for cancer of unknown primary (CUP).** *Presenting Author: Linda R. Mileshkin, Peter MacCallum Cancer Center, Melbourne, Australia*

**Background:** Accurate identification of the primary tumor in cases of cancer of unknown primary (CUP) is required for effective treatment selection and improved patient outcomes. Here we present the development and clinical validation of a histology-guided gene expression classifier. **Methods:** RNA from 450 formalin-fixed paraffin embedded tissue samples of known origin comprising 18 tumor groups were used to train and develop the classifier. Whole-genome expression data was collected from each sample using Illumina DASL bead-based arrays. A hierarchical tumor classifier utilizing both conventional histopathology and gene expression data was developed using a binary support vector machine, together with recursive feature elimination. The classifier was then validated on an independent cohort of 94 tumors of known origin and 58 CUP samples. **Results:** Based on the validation set of tumors, the classifier demonstrated an accuracy of 89% for the highest predicted tumor class, increasing to 98% for the correct prediction within the two highest similarity scores. When applied to CUP samples having a presumed final clinical diagnosis of a primary site six months following gene expression analysis (n=49), the classifier was found to improve the accuracy of histology alone from 33% to 78% for a single prediction and from 73% to 90% within the two highest predicted tumor class scores. **Conclusions:** This study demonstrates that combining gene expression data and conventional histopathology improves the accuracy of determining the primary site of origin in cases of CUP.

**11109 General Poster Session (Board #391), Sat, 1:15 PM-5:00 PM**

**Effect of clinical NGS-based cancer genomic profiling on physician treatment decisions in advanced solid tumors.** *Presenting Author: Fadi S. Braiteh, Comprehensive Cancer Centers of Nevada, Las Vegas, NV, and US Oncology Research, Houston, TX*

**Background:** Next generation sequencing (NGS) of routinely fixed tissue from pts with advanced solid tumors may inform treatment planning. Foundation Medicine has developed a CLIA-certified, CAP-accredited test (FoundationOne, F1) to simultaneously characterize all 4 classes of genomic alterations in 236 (originally 182) cancer genes. Primary study objective was to determine how many physicians would change treatment approach based on F1 results (switch rate=SR). An exploratory objective was to compare PFS impact of any switches. **Methods:** This was a prospective, multicenter, single-arm trial in pts with refractory metastatic solid tumors of any type. Eligible pts must have been receiving second- or third-line therapy (first-line for pancreatic) and were initially registered within 10 weeks of beginning a regimen and before response assessment reimaging. Tumors were assayed with F1 after initial registration. Upon progression and documentation of next proposed therapy, they were re-registered and results of F1 were provided to doctors. If F1 caused a change in proposed therapy, a switch was recorded. **Results:** 233 pts were eligible; 103 were not re-registered (pt died, investigator decision, withdrew consent). Two questionnaires were missing; 128 pts were included in this analysis. Median age 61 yrs; female (65.6%). Tumor types mainly included breast (20%), lung (16%), and colon (13%). The SR was 28.1% (36 switch, 92 no switch). For 95 treated pts, the SR was 27.4% (26 received switch drug, 69 received initial recommendation; [33 pts did not receive Rx due to PD, death, hospice, or pt decision]). All of the major tumor types above had switch rates above 20%. In 77% of nonswitch cases, physicians reported that there were "not enough" treatment options available. Data collection for PFS analysis and correlation of results to tumor genomic profiles are ongoing. **Conclusions:** Comprehensive NGS-based profiling resulted in altered therapeutic choice in 28% of advanced solid tumor patients in the community setting, highlighting the current broad applicability of this approach. As more targeted therapeutics advance to larger trials and become approved, the impact of comprehensive testing may be expected to increase.

**11110 General Poster Session (Board #392), Sat, 1:15 PM-5:00 PM**

**PET/CT assessment of tumor perfusion in metastatic renal cell carcinoma (RCC) before and during sunitinib: A comparison of $^{15}$O-water with $^{62}$Cu-ETS.** *Presenting Author: Theodore F. Logan, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN*

**Background:** RCC is a vascular cancer treated with antiangiogenic agents. Tumor perfusion (TP) can be measured by PET using $^{15}$O-water ($H_2{}^{15}O$), but its short physical half-life limits use to PET centers with a cyclotron. We studied a new "microsphere-like" perfusion agent with 9.7 min half-life, $^{62}$Cu-ETS, in RCC patients before and during sunitinib. As a generator-based agent, the kit-formulated $^{62}$Cu-ETS can be made available to virtually any PET camera from a central manufacturing site. And, since the $^{62}$Cu label is trapped after perfusion-rate-limited delivery, PET/CT whole-body imaging is possible, allowing evaluation of both primary tumor and distant metastases. **Methods:** Consented RCC patients were entered on this IRB approved protocol. PET/CT imaging was performed in 14 RCC patients with $H_2{}^{15}O$ and $^{62}$Cu-ETS, both before and during week 3-4 of Sunitinib (50mg/day X 4 wks on/2 wks off). PET/CT was performed after i.v. $H_2{}^{15}O$ (10-minute list mode), followed 10-minutes later by i.v. $^{62}$Cu-ETS, with the heart and at least one tumor in the PET field-of-view (6-min list mode). Whole body scan (WBS) of the $^{62}$Cu-ETS was then carried out from 6-20 min using 2-3 min/bed. Proportional Technologies, Inc. provided the $^{62}$Zn/$^{62}$Cu-generators, and kits for $^{62}$Cu-ETS preparation (IND #75,018). Blood flow ($k_1$) was quantified for both normal and malignant tissues in a 21.7 cm dynamic FOV. Arterial input functions were derived from the left atrium. **Results:** Paired $k_1$ data were available for 14 metastatic lesions before and post Rx. The average pre-Rx TP was similar with both $H_2{}^{15}O$ and $^{62}$Cu-ETS, (0.97 $\pm$ 0.51 and 0.97 $\pm$ 0.40 ml/min/g, respectively). The average TP for the two agents dropped significantly during Rx to 0.51 $\pm$ 0.35 and 0.56 $\pm$ 0.32 ml/min/g, p=0.010 and 0.0002 by paired T-tests. The correlation ($r^2$) between the $k_1$ values of both agents for normal and tumor tissues was 0.87 (y=0.88x+0.13). **Conclusions:** TP ($k_1$) measured by $H_2{}^{15}O$ and $^{62}$Cu-ETS using PET/CT in RCC was highly correlated. Sunitinib significantly decreases TP in metastatic RCC. $^{62}$Cu-ETS appears to be an excellent agent for the assessment in TP in RCC patients. Clinical trial information: NCI-2012-00051.

**11111 General Poster Session (Board #393), Sat, 1:15 PM-5:00 PM**

**First-in-human phase I study of a selective c-Met inhibitor volitinib (HMP504/AZD6094) in patients with advanced solid tumors.** *Presenting Author: Hui Kong Gan, Austin Health, Heidelberg, Australia*

**Background:** Volitinib is a selective oral small molecule inhibitor of cMet kinase with potent in vivo inhibitory effects on a variety of human tumor xenografts. **Methods:** This phase I, first-in-human dose-escalation study was conducted to determine the maximum tolerated dose (MTD), dose-limiting toxicities (DLTs), pharmacokinetics (PK) profile, and preliminary antitumor activity of volitinib. **Results:** By Dec 31, 2013, 32 patients (pts) had been enrolled and treated with volitinib at doses of 100-1000mg QD or 300-400mg BID. Pts had a median age of 61 (27-78) yrs, 66% were male. The most common tumor types were papillary renal cell carcinoma (PRCC, 6) and CRC (5). The most common adverse events were constipation, diarrhea, fatigue, nausea, vomiting, dizziness and peripheral edema, mostly grade (G) 1/2. Four pts reported 5 DLTs: 1 G3 elevated ALT (600mg QD), 1 G3 fatigue (800mg QD), and 2 G3 fatigues and 1 G3 headache (1000mg QD). 800mg was identified as MTD of the QD regimen. Dose-escalation in the BID cohort is currently ongoing at 400mg BID. PK analysis showed volitinib was rapidly absorbed with Tmax around 2 hours and half-life around 5 hours. Both Cmax and AUC displayed dose-proportional increase and no obvious accumulation occurred. Two PRCC pts in the 600mg QD cohort (one with ongoing treatment at 1 year) and 1 PRCC pt in the 300mg BID cohort achieved partial response. A CRC pt in the 600mg QD cohort achieved 29% tumor reduction. A PRCC pt in the 1000mg QD cohort achieved 27% tumor reduction and remains on study. Analysis of pre-treatment tumor sample showed that the responders had either gene copy number increase (Chromosome7 gains or MET gene amplification) or high MET protein expression. **Conclusions:** Volitinib was well tolerated at doses up to 800 mg QD and demonstrated promising anti-tumor activity in pts with evidence of dysregulated MET signaling. It demonstrated linear PK without marked drug accumulation. Further clinical studies are warranted. Clinical trial information: NCT01773018.

**11112 General Poster Session (Board #394), Sat, 1:15 PM-5:00 PM**

**Effect of adoptive T-cell therapy and intratumoral heat-killed bacteria on large tumors.** *Presenting Author: David C. Binder, The University of Chicago, Chicago, IL*

**Background:** Preventing tumor relapse as antigen-loss variants remains a challenge in T cell therapy. T cells eradicate tumors by secreting cytokines that mediate bystander killing of tumor stromal cells and antigen-negative cancer cells. However, when tumors express a lower "natural" level of antigen, T cells are unable to eradicate tumors due to insufficient antigen cross-presentation. We recently published that vaccination with live antigen-bearing bacteria can rescue T cell function in long-established tumors. Here, we studied the use of heat-killed (HK) bacteria to enhance adoptive T cell therapy. **Methods:** MC57 fibrosarcoma cancer cells expressing a low level of the SIYRYYGL (SIY) peptide were injected into OT-1 mice. Tumors were long-established (>14 days and >250 $mm^3$) prior to treatment with adoptively-transferred SIY-specific 2C T cells and/or intratumorally-injected HK *Salmonella* Typhimurium A1-R. Tumor stroma viability and composition were analyzed by flow cytometry. Cytokine analysis was conducted by cytometric bead array. **Results:** All tumors treated with only T cells or HK bacteria relapsed (antigen-loss variants were found in T cell-treated tumors). However, T cells and HK bacteria combined to eradicate tumors in 83% of mice, with eradication requiring cognate antigen recognition by T cells. HK bacteria alone induced tumor microenvironment changes by 1 day post-treatment including: (i) macrophage death, (ii) monocytes replaced by neutrophils, and (iii) higher levels of IFN-g, TNF-a, IL-6, and IL-10. **Conclusions:** HK bacteria synergize with T cells, allowing them to eradicate large tumors expressing a low level of antigen. By increasing release of pro-inflammatory cytokines into the tumor stroma and inducing macrophage death, HK bacteria likely make the tumor microenvironment more conducive for T cell-mediated destruction. These data support the idea that the addition of HK bacteria to adoptive T cell therapy protocols can lead to successful eradication of cancers expressing mutated antigens at a low level.

**11113 General Poster Session (Board #395), Sat, 1:15 PM-5:00 PM**

**First-in-human phase 1 dose-escalation study of AV-203, a monoclonal antibody against ERBB3, in patients with metastatic or advanced solid tumors.** *Presenting Author: John Sarantopoulos, Institute for Drug Development, Cancer Therapy and Research Center, University of Texas Health Science Center San Antonio, San Antonio, TX*

**Background:** AV-203 is an IgG1k humanized monoclonal antibody with high affinity and specificity for the anti-v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (ERBB3) receptor. Based on promising preclinical activity and resistance prevention data, a phase 1 study was conducted (NCT01603979). **Methods:** A phase 1 study using a 3+3 dose-escalation design evaluated the safety, tolerability, recommended phase 2 dose (RP2D), pharmacokinetics (PK) and pharmacodynamics of AV-203. AV-203 was given IV at 2, 5, 9, 14 or 20 mg/kg once every 2 wks (1 cycle = 28 days, 2 doses per cycle). Included patients (pts) had advanced solid tumors and progressed on standard therapies or had no proven treatment options. **Results:** AV-203 was administered to 22 pts (15M/7F; median age 68 y, range 31-82; ECOG PS 0/1: 8/13). Enrolled tumor types included colorectal (4), non–small-cell lung (NSCLC; 4), squamous cell carcinoma of the head and neck (2) and other solid tumors (12). There was a single dose-limiting toxicity of inability to tolerate the study drug (serious Grade 3 diarrhea and multiple concurrent adverse events [AEs]) at 2 mg/kg in an 80-y-old pt. The maximum administered dose of 20 mg/kg was well tolerated. All grade AEs observed in ≥25% of pts were: diarrhea (68%); decreased appetite (41%); hypokalemia, dry skin and hypomagnesemia (36% each); headache, dehydration, dizziness and dyspnea (27% each). Grade 3 and 4 AEs of anemia, diarrhea and hypokalemia occurred in ≥2 pts. The most common treatment-related AEs were diarrhea (59%), dry skin and decreased appetite (32% each), hypomagnesemia (27%) and pruritus (23%). No deaths were attributed to AV-203. Preliminary data show approximately dose proportional PK and no detection of anti-drug antibodies. Median time on treatment for all pts was 43 days (range: 1-491), with 15 pts discontinuing due to progressive disease during this time. There was one confirmed partial response (PR; 6 cycles) in a pt with squamous NSCLC which expressed high levels of neuregulin 1. **Conclusions:** AV-203 was well tolerated in the dose range tested; RP2D is 20 mg/kg IV every 2 wks. The PR in a pt with squamous cell NSCLC warrants further testing of AV-203 in this indication. Clinical trial information: NCT01603979.

**11115 General Poster Session (Board #397), Sat, 1:15 PM-5:00 PM**

**Clinical next-generation sequencing to identify actionable alterations in a phase I program.** *Presenting Author: Genevieve Marie Boland, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Due to affordable high-throughput technologies Clinical Laboratory Improvement Amendments (CLIA)-certified next-generation sequencing platforms for genomic characterization have emerged. Given the expansion of molecularly-targeted therapeutics, there is a huge opportunity to use genomic testing for patient selection in clinical trials. We sought to determine the frequency of alterations across tumor histologies in patients with advanced cancer using a deep sequencing approach to assess for mutations in hotspot regions of 46 cancer-related genes. **Methods:** We examined data from the first 500 patients with advanced cancer prospectively enrolled on an IRB-approved protocol through the Department of Investigational Cancer Therapeutics at MD Anderson Cancer Center. Archival tumor DNA was tested for hotspot mutations in 46 genes (Ampli-Seq Cancer Panel) using an Ion Torrent PGM Sequencer (Life Technologies, CA) at the clinical molecular diagnostics laboratory. The data were analyzed using R Statistical Software (R Foundation for Statistical Computing, Vienna, Austria). **Results:** Patients with 38 tumor types were enrolled. Of 500 patients analyzed, 293 had at least one detectable mutation. The most commonly mutated genes were *TP53* (38%), *KRAS* (11%), and *PIK3CA* (10%). Of tumor types tested (n ≥ 10), sarcoma (20%) and kidney (30%) had the fewest alterations, while pancreas (100%), colon (91%) and melanoma (87%) had the highest proportion. 46 patients had both primary tumors and metastases analyzed; of mutations seen in primaries or metastases, 91% were seen in both. Across all samples, there was a strong pattern of mutual exclusivity between *TP53* mutations and *PIK3CA* mutations. Alterations in potentially actionable genes were detected in 291 (58%) patients. Both rare mutations in common tumor types and potentially actionable (directly/indirectly druggable) mutations in rare tumor types were identified. **Conclusions:** Implementation of multiplex testing in the CLIA environment facilitates genomic characterization across multiple tumor types to identify novel opportunities for genotype-driven trials. Matching patients to molecularly targeted therapies is underway.

**11116 General Poster Session (Board #398), Sat, 1:15 PM-5:00 PM**

**A chemogenomic screening platform for identification of protein kinase CK2 as a novel target for prosenescence therapy in PTEN-null tumors.** *Presenting Author: Madhuri Kalathur, Institute of Oncology Research (IOSI), Bellinzona, Switzerland*

**Background:** *Pten* loss-induced cellular senescence (PICS) is characterized by the absence of hyper-replication, as well as lack of DNA damage response. Therapeutic enhancement of cellular senescence in tumors triggers an irreversible cell growth arrest and activation of a tumor immune response that can be used for cancer therapy. Currently, there are only a limited number of targeted therapies that act by increasing senescence in cancers but these therapies are not selective for cancer cells. **Methods:** We developed a combined chemical and shRNA screening platform to identify compounds that selectively enhance senescence in Pten deficient cells without affecting normal cells. By using this approach, we identified several Casein Kinase II (CK2) inhibitors as highly effective and selective pro-senescence compounds in Pten null cells and tumors. **Results:** We have identified CK2 inhibitors through our chemogenomic platform and furthur validated using shRNA kinase library. These compounds have enhanced the cellular senescence in Pten deficient cells. Mechanistically, we find that CK2 mRNA and protein levels are strongly up regulated in *Pten* null cells and PML is downregulated. Interestingly, CK2 transcription depends on the activation of signal transducer and activator of transcription 3, STAT3 that is highly phosphorylated in *Pten* null tumors. Treatment of *Pten* null prostate tumors with CK2 inhibitors has lead to the stabilization of PML thereby restoring its tumor suppressor activity; which then prompts more cells to enter senescence leading to tumor regression. **Conclusions:** Using our novel platform technologies we have discovered better pro-senescence compounds and systematically validating them *in vitro* and in *vivo.* We disocvered the possible mechanism behind the target based selective enhancement of senescence in *Pten* loss prostate cancer. These present findings for the first time showcase the proof-of-concept for the pro-senescence therapy.

**11117 General Poster Session (Board #399), Sat, 1:15 PM-5:00 PM**

**Frequency of concurrent gene mutations and copy number alterations in circulating cell-free DNA (cfDNA) from refractory metastatic CRC patients.** *Presenting Author: M. Pia Morelli, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** cfDNA allows non-invasive assessment of gene mutations, but has not been reported with copy number alterations. Methodologies to integrate mutation and copy number would allow improved insights into mechanisms of resistance and therapeutic opportunities. **Methods:** cfDNA extracted from metastatic CRC patient (pt) plasma samples were analyzed by GUARDANT sequencing technology for mutation and amplification of 54 genes. The lower limit of detection was 0.1% mutant alleles in a wild-type background. All patients were enrolled in the ATTACC program for mCRC patients who progressed on standard treatment, and had sequencing of the primary tumor performed for a 46-gene panel. **Results:** 71 pt plasma samples were analyzed. All pts were refractory to 5-FU-based therapy, with 49 pts previously treated with anti-EGFR monoclonal antibodies (mAbs). In patients treated with EGFR mAbs, 30% of pts (n=15) had detection of KRAS mutations not detectable in the primary tumor, compared to 5% (n=1) of pts without EGFR mAb treatment (odds ratio 8.6, P=0.027). In 6 of the 15 cases, newly detectable KRAS mutations were associated with KRAS gene amplification, compared to 0 of 16 cases with KRAS mutations detected in the primary tumor (P=0.007). 7 ectodomain mutations in EGFR that may alter binding affinity of EGFR mAbs were detected in EGFR mAb treated patients, including S492R (n=4) and three previously unreported mutations G465V, I491R, K467I; concurrent EGFR amplifications were present in 6 of the 7 cases. 14% of EGFR mAbs treated patients developed detectable MET amplifications, which co-existed with KRAS or EGFR mutations in 4 of the 7 cases. Amplifications in EGFR, BRAF, MYC, and SMO were detected in the plasma in 23%, 11%, 11%, and 4% of cases, respectively, representing rates higher than reported in untreated primary tumors. **Conclusions:** Advances in sequencing and bioinformatics allow detection of copy number alternations from cfDNA in plasma. Copy number alterations in treatment refractory mCRC are more common than previously described, and frequently co-exist with mutations after EGFR mAb treatment.

**11118 General Poster Session (Board #400), Sat, 1:15 PM-5:00 PM**

**Clinical significance of CD169-positive lymph node macrophages in human malignant tumors.** *Presenting Author: Koji Ohnishi, Department of Cell Pathology, Graduate School of Medical Sciences, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan*

**Background:** CD169 (sialoadhesin) is a sialic acid receptor that is expressed on specific macrophages such as lymph node sinus macrophages. Animal studies have suggested that $CD169^+$ macrophages have tumor-preventing activities, however, the role of these cells in human diseases has not been clarified. **Methods:** To examine the role of CD169 in anti-tumor immunity, we examined the expression of CD169 in regional lymph nodes (RLNs) and their relations with overall survival and clinicopathological factors in colorectal carcinoma (83 cases), melanoma (93 cases) and endometrial carcinoma (77 cases) by immunohistochemistry. To clarify the mechanism of CD169 expression in human macrophages, culture experiments were performed. **Results:** High density of $CD169^+$ cells was significantly associated with longer overall survival in these tumors ($p = 0.009$, $p = 0.001$ or $p = 0.007$, respectively). In colorectal carcinoma and melanoma, multivariate analysis showed that the density of $CD169^+$ cells was an independent prognostic factor. We also found that the density of $CD169^+$ macrophage was positively correlated with the number of $CD8^+$ cytotoxic T cells infiltrating into tumor tissues. The majority of $CD169^+$ macrophages were in direct contact with $CD8^+$ T cells expressing CD43, a major ligand of CD169, and many interferon (IFN) $\alpha$-producing cells were detected surrounding the $CD169^+$ cells. Furthermore, in our *in vitro* experiments with human macrophages, IFN$\alpha$ induced strong expression of CD169. These data suggest that $CD169^+$ macrophages in RLNs promote $CD8^+$ T-cell-mediated anti-tumor immunity and are associated with a better prognosis for cancer patients. **Conclusions:** $CD169^+$ macrophages in RLNs may thus be a useful marker for assessing clinical prognosis and monitoring anti-tumor immunity in patients with colorectal carcinoma, melanoma and endometrial carcinoma.

**11119 General Poster Session (Board #401), Sat, 1:15 PM-5:00 PM**

**Mesothelin expression as a predictive biomarker of breast cancer outcomes.** *Presenting Author: Yun Rose Li, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA*

**Background:** Mesothelin, previously-shown to be expressed in triple negative breast cancer (TNBC) tumors, is a potential therapeutic target and prognostic marker in breast cancer. **Methods:** We analyzed clinical data from two cohorts: a 141 patient-cohort treated between 2009 and 2011 at the UPHS (discovery) and the 844 patient-cohort from The Cancer Genome Atlas (TCGA) (validation). Mesothelin expression was quantified by immunohistochemistry (IHC) (discovery) or RNA transcript levels by whole-transcriptome sequencing (validation). **Results:** Median follow up for our discovery cohort was 3.54 years. Univariate analyses demonstrated that tumor size (HR=1.30, 95% CI 1.115-1.515, $p < 4.58 \times 10^{-4}$), number of positive axillary lymph nodes (HR=1.131; 95% CI 1.06-1.21; p-value $< 9.20 \times 10^{-5}$), tumor stage (HR (Grade III to I) = 21.294, 95% CI 2.69-168.69, $p < 3.40 \times 10^{-5}$), at least one lymph node removed (HR=1.07, 95% CI 1.021-1.116, $p < 2.45 \times 10^{-3}$), and most importantly, mesothelin expression (HR= 2.377; 95% CI 1.12-5.02; $p < 3.01 \times 10^{-3}$) were associated with both overall and disease-specific survival. We used a Cox-proportional hazard (Cox-PH) model to adjust for the only other independent predictors of survival, namely axillary lymph nodes involved and tumor size, and stratifying by African American race, we found a significant association between mesothelin expression and overall and disease-specific survival in the discovery cohort (HR = 3.138, 85% CI 1.38-7.10, $p < 6.14 \times 10^{-3}$). Using the TCGA dataset, we confirmed that, over a median follow-up of 16.0months, patients with mesothelin-expressing tumors had poorer overall survival (HR=1.463; 95% CI 1.053-2.033; p<0.021). On Cox-PH analysis, mesothelin-positivity was independently predictive of poorer survival, after adjusting for the number of involved axillary lymph nodes and tumor size (HR = 1.688; 95% CI 1.174-2.425; $p<4.67 \times 10^{-3}$). **Conclusions:** Our results suggest that mesothelin is a prognostic breast tumor marker and that its expression in a large proportion in TNBC holds promise that existing targeted therapy directed against mesothelin may be effective for the treatment of TNBC. Further work is needed to elucidate the mechanistic role of mesothelin in breast cancer.

**11120 General Poster Session (Board #402), Sat, 1:15 PM-5:00 PM**

**Hedgehog signalling in primary cervix xenograft (OCICx) models: A potential new therapeutic target in combination with chemoradiotherapy.** *Presenting Author: Naz Chaudary, Ontario Cancer Institute/The Campbell Family Institute for Cancer Research,Princess Margaret Cancer Centre Toronto, Ontario, Canada, Toronto, ON, Canada*

**Background:** Overcoming treatment resistance and repopulation in patients undergoing chemo-radiotherapy for primary treatment of cervical cancer is critical in order to improve long-term survival. Upregulation of Hh gene expression in women with cervical cancer prior to chemoradiotherapy is associated with a worse outcome. Aim: to investigate inhibition of the Hh pathway in combination with chemoradiotherapy in orthotopic primary cervical cancer xenograft models (OCICX). **Methods:** mRNA expression levels of Hh pathway members were characterized using qRT-PCR analysis in OCICx models. To simulate clinical treatment 5E1 (antibody blocking SHH and IHH ligand interaction with PTCH1) was administered to mice bearing cervix xenografts (20 mg/kg/weekly) with localized fractionated irradiation (15 x 2Gy fractions given 5 days/wk over 3 wks). Tumor growth delay, lymph node metastases, survival and toxicity were assessed. **Results:** The OCICX models exhibited matched levels of Hh gene expression compared to the patient tumor samples. The OCICX models recapitulate the stroma of the orginal tumor. OCICX models with higher tumor to stroma content showed higher human Hh gene expression. Higher mouse Hh gene expression was seen in tumors with more stroma. Combination radiochemotherapy plus 5E1 treatment caused greater growth delay than irradiation or 5E1 alone, reduced lymph node metastasis with increase in survival. No overt toxicity was observed in the mice treated with 5E1 or in combination with radiation. **Conclusions:** Combination treatment with fractionated irradiation and 5E1 shows increased efficacy consistent with an additive effect. In addition, inhibition of the Hh pathway significantly reduced lymphnode metastasis in the mice. Further investigation of Hh pathway inhibition in combination with chemo-radiotherapy in cervix cancer is warranted including exploration of predictive imaging markers of response.

**11121 General Poster Session (Board #403), Sat, 1:15 PM-5:00 PM**

**Reduction rate of the maximal value of the baseline standardized uptake value on fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography to predict response of breast cancer to neoadjuvant chemotherapy.** *Presenting Author: Takayuki Kadoya, Department of Surgical Oncology, Hiroshima University, Hiroshima, Japan*

**Background:** [18F]-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) is potentially useful to predict response of breast cancer to neoadjuvant chemotherapy. **Methods:** 114 breast cancer patients (mean age: 53.7±11.0) with clinical Stage I~III between January 2006 and December 2011, were prospectively evaluated. Patients underwent a whole-body FDG PET/CT before and after neoadjuvant chemotherapy. The reduction rate of maximal value of the baseline standardized uptake values (ΔmaxSUV) before and after neoadjuvant chemotherapy with sequential regimen of anthracyclines and taxanes were assessed for predicting pathological complete response (pCR). For the evaluation of relationship between ΔmaxSUV and prognostic factors, statistical analyses were performed using Student t test and log-rank test, and p values of less than 0.05 were considered to indicate statistically significant differences. **Results:** Clinical stage included were I (n =10), II (n=81) and III (n=23). Tumors with estrogen receptor (ER) positive and HER2 positive were 79 (69.3%) and 30 (26.3%), respectively. Patients were divided into two groups according to cut-off ΔmaxSUV established on the basis of receiver operating characteristic analysis (>80.4% vs 80.4% ≤, AUC=0.676). There was a significant difference in pCR between two groups (p=0.006) and, ER, progesterone receptor, HER2, clinical T factor were found strong relation to ΔmaxSUV. ER, HER2, tumor size and ΔmaxSUV were predictive factors with multivariable analysis using cox proportional hazard regression model (p<0.01, p<0.01, p=0.02 and p=0.04, respectively). **Conclusions:** The reduction rate of maxSUV on FDG PET/CT before and after neoadjuvant chemotherapy has a predictive value for pCR in operable breast cancer.

| Factors | Favorable | Unfavorable | Hazard ratio (95%CI) | p value |
|---|---|---|---|---|
| **Clinical T factor** | T1 | T2, T3, T4 | 0.200 (0.050-0.797) | 0.02 |
| **Clinical N factor** | N0 | N1,N2,N3 | 1.103 (0.319-3.818) | 0.88 |
| **ΔmaxSUV** | > 80.4% | 80.4%≤ | 3.816 (1.059-13.745) | 0.04 |
| **ER** | (+) | (-) | 0.068 (0.018-0.258) | <0.01 |
| **HER2** | (-) | (+) | 12.625 (3.295-48.375) | <0.01 |

**11122 General Poster Session (Board #404), Sat, 1:15 PM-5:00 PM**

**The CXCL12/CXCR4 pathway, bone marrow-derived myeloid cells, and survival in locally advanced cervical cancer.** *Presenting Author: Naz Chaudary, Ontario Cancer Institute/The Campbell Family Institute for Cancer Research,Princess Margaret Cancer Centre Toronto, Ontario, Canada, Toronto, ON, Canada*

**Background:** Cervical cancer is a global health problem. There is a need to improve standard treatment with radiotherapy (RT) and concurrent cisplatin (CT). Tumors are known to recruit myeloid cells from the bone marrow (BMDCs) via the CXCL12/CXCR4 and other chemokine pathways, which in turn influence tumor vascular function and RT response. The objective of this study was to explore the impact of the CXCL12/CXCR4-BMDC axis on clinical outcome in cervical cancer patients treated with RT, and ways of inhibiting this response. **Methods:** A total of 258 patients with cervical cancer (cT1b-T3b, N0-1, M0) were treated with RT +- concurrent CT. Tumor hypoxia, interstitial fluid pressure (IFP – a biomarker of abnormal vascular function) and CXCR4 expression were measured prior to treatment. The median follow-up was 5.3 years. Orthotopic cervical xenografts were developed from patient biopsies for evaluation of the chemokine inhibitor Plerixafor. **Results:** The pretreatment bloodpolymorphonuclear neutrophil (PMN) count was normal (<$7.5X10^9$/L) in 83% of cases.In patients treated with RT+CT, high pretreatment PMNs were associated with inferior disease-free survival (DFS) but only in the setting of high tumor IFP. This was independent of tumor stage, size and LN status, and was validated in a separate cohort of patients treated with RT alone. Patients with high PMNs displayed high peri-vascular tumor infiltration by CD11b+ or CD66b+ myeloid cells. There was 5-fold variation in CXCR4 mRNA expression by qRT-PCR, and 58% of cases showed high CXCR4 protein expression by IHC.Patient-derived orthotopic cervical tumors were treated with fractionated,image-guided RT and CT +- Plerixafor (5 mg/kg). Combined treatment with Plerixafor produced substantial tumor growth delay and prolonged survival compared to standard RT+CT alone. There was no difference in acute GI toxicity with the addition of Plerixafor to standard treatment. **Conclusions:** TheCXCL12/CXCR4 pathway and BMDCs influence RT response and clinical outcome in patients with cervical cancer via a vascular-dependent mechanism. Inhibition of CXCL12 signaling can mitigate this effect and should be considered for translation to phase I/II clinical trials.

**11123 General Poster Session (Board #405), Sat, 1:15 PM-5:00 PM**

**Investigations into the antiradition effects of BP-C2, a benzene-poly-carboxylic acid complex with molybdenum.** *Presenting Author: Stig Larsen, University of Oslo, Oslo, Norway*

**Background:** BP-C2 is an innovative oral radio-protective drug based on a benzene-poly-carboxylic acid complex with molybdenum with important detoxifying properties and a new globular polydentant ligand BP-Cx-1 known for its detoxifying, free radical scavenging and anti-oxidant activity. We have previously demonstrated that administration of BP-C2 results in highly significant survival advantage in animals receiving either lethal or sub-lethal doses of gamma irradiation. LD50/30 6.56 GY. No adverse side effects using BP-C2 have been observed *in vitro* (LDH release) or *in vivo*. **Methods:** In the skin radiation injury prophylactic group, age matched white mice were treated with BP-C2 on the day of irradiation and hereafter treated three times a week for 5 weeks. In the post irradiation treatment group the animals were treated with BP-C2 three times per week for five weeks after the occurrence of skin injuries**.** The effects on skin injuries were investigated by H and E histopathology, cytokine and gene expression by immunohistochemistry. Animals were irradiated at 30 GY in the one hind leg. **Results:** All control mice developed severe skin injury in the leg. In contrast no skin injury was observed in mice treated prophylactically with BP-C2. In the treatment group with BP-C2 all mice were cured after five weeks of treatment. The expression of several oncogenes were decreased significantly whereas tumor suppressing genes where increased. BP-C2also stimulated the innate immune system.The effect is properly mediated via several cytokines (TNF-alpha, INF-gamma, GM-CSF, IL-1 beta, IL-6, Il-25) and apoptotic genes. **Conclusions:** BP-C2 has a potential for clinical use to protect patients from radiotherapy injuries of the skin prophylactically as well as post irradiation treatment.

**11124 General Poster Session (Board #406), Sat, 1:15 PM-5:00 PM**

**WNT inhibitory factor-1 (WIF-1): A new role in carcinogenesis?** *Presenting Author: Tan Wei Chow, INFORMM USM, Pulau Pinang, Malaysia*

**Background:** Carcinogenesis is an orchestrated expression and depression of oncogenes and tumor suppressor genes at cellular level. The early involvement of epidermal growth factor receptor (EGFR) and wingless and integration site growth factor (WNT) signaling pathways in cell development has attracted much interest among researchers and clinicians. Aberrant activity in both signaling pathways may contribute to cancer formation. By tackling the potential key players in the study of cancer cell signaling pathways, alternative cancer treatment could be promoted in current cancer context. WIF-1 is a physiological inhibitor for WNT signaling pathway used to prevent carcinogenesis resulted from the activation of WNT signaling pathway. The structure of WIF domain is known to have a binding site that interacts with WNT molecules while the function(s) of its EGF-like domain is still unknown. **Methods:** To study the potential involvement of WIF-1 in EGFR signaling pathway, *in silico* protein-protein docking between WIF-1 and EGFR was carried out. Co-immunoprecipitation and western blot were designed to study the *in vitro* binding of EGFR/WIF1 and the potential resulting activation of EGFR downstream signaling pathways. **Results:** *In vitro* and *in silico* experimental results suggested that WIF-1 might play additional role in EGFR signaling pathway via its EGF-like domain. The binding energy of WIF-1/EGFR (-616.40 kcal/mol) was comparative to that of EGF/EGFR binding (-627.18 kcal/mol). Further results indicated that WIF-1 was bound to, and hence was co-immunoprecipitated with, EGFR. Downstream key factors in EGFR signaling pathway were found to be activated following the binding of WIF-1 to EGFR. In addition, the results obtained showed a prominent activation of downstream WNT signaling pathway via crosstalk from WIF-1 activated EGFR signaling pathway. **Conclusions:** As EGFR signaling pathway plays a crucial role in carcinogenesis, and the possibility to activate WNT signaling pathway via crosstalk between the WIF-1 activated EGFR signaling pathway and downstream of WNT signaling pathway, the use of WIF-1 in the treatment of cancer probably need to be reviewed for the safety of patients undergoing the treatment and prevent undesired outcomes from happening.

**11125 General Poster Session (Board #407), Sat, 1:15 PM-5:00 PM**

**Combined immunophenotyping of tumor-infiltrating lymphocytes as a prognostic factor in resected patients with non-small cell lung cancer.** *Presenting Author: Ross A. Soo, National University Health System, Singapore, Singapore*

**Background:** Current evidence has highlighted the potential role for tumor infiltrating lymphocytes (TILs) in determining the survival of non-small cell lung cancer (NSCLC) patients. Whilst multiple studies have investigated the prognostic role of various subtypes of TILs, data is limited on the co-expression of TILs subpopulations and its clinical relevance. Identifying immune prognostic markers may help select postoperative NSCLC patients with a poorer prognosis for treatment with immunotherapy. We aim to identify NSCLC subgroups according to combined immunophenotypes and investigate their clinical relevance. **Methods:** A tissue microarray was constructed from 105 cases of resected NSCLC. Immunohistochemistry for TILs with CD3, CD8, FoxP3 and Granzyme B (GZMB) Ab was performed with an autostainer. TILs were quantified using the Vectra Automated Multispectral Imaging System. Low (-) and high (+) densities of TILs were dichotomised by the medians. *EGFR* and *KRAS* mutations were determined with Sanger sequencing. Clustering was performed using the heatmap function of R v3.0.2. Associations with clinicopathological variables were assessed by Chi-square analysis, and association with disease-specific survival (DSS) was performed using Cox proportional hazards model analysis. **Results:** The median age of patients was 64 years, 70% were male, 59% were stage I, and 57% of tumors were adenocarcinoma. Unsupervised clustering revealed 4 major subgroups based on the co-occurrence of high and low densities: FOXP3+/CD3+ (29% of cases), FOXP3+/CD3- (11%), FOXP3-/GZMB+ (28%) and FOXP3-/GZMB- (31%). The FOXP3+/CD3+ phenotype was significantly associated with squamous cell histology (p=0.047). There was no association with other features, including *EGFR* or *KRAS* mutation status. Patients with FOXP3+/CD3+ phenotype had a worse DSS (HR 2.17, 95% confidence interval [1.08-4.36], p=0.034) compared to those in other subgroups. **Conclusions:** Combined immunophenotyping suggests NSCLC may be comprised of four major subgroups. The FOXP3+/CD3+ phenotype may indicate a worse prognosis for patients with resected NSCLC and thus identify patients for immune directed adjuvant therapy.

**11126 General Poster Session (Board #408), Sat, 1:15 PM-5:00 PM**

**The association of treatment-emergent proteinuria (TEP) with baseline/ treatment variables in patients (pts) treated with antiangiogenic tyrosine kinase inhibitors (AA-TKIs): A pooled analysis of NCIC Clinical Trial Group (NCIC CTG) trials.** *Presenting Author: Maria Bonomi, NCIC Clinical Trials Group, Kingston, ON, Canada*

**Background:** TEP is an expected effect of AA-TKIs. This pooled analysis of NCIC CTG trials aimed to assess its incidence, risk factors and clinical impact. **Methods:** 423 pts with baseline (BL) and ≥ 1 on treatment urinalysis were included in 2 cohorts: 1) AA-TKI (VEGFR2/PDGFR/KIT; VEGFR2/MET) ± other targeted agent; 2) AA-TKI (panVEGFR/KIT) + chemotherapy (CT; platinum based regimens capecitabine). Cohort 1 (138 pts) included ovary, cervix, mesothelioma, lymphoma, breast, non small cell lung cancer (NSCLC); cohort 2 (285 pts) colorectal and NSCLC. BL uncontrolled HTN and abnormal renal function were always excluded; BL > G1 proteinuria only in cohort 2 (all but 1 trial). Dose modifications and algorithms for treatment emergent (TE) HTN or TEP were provided. TEP was defined as any value > BL and ≥ G2. BL/treatment variables considered were age, PS, sex, proteinuria, HTN, diabetes, obesity, nephrotoxic and nephroprotective drugs, TE HTN, increased creatinine, hypoalbuminemia. **Results:** Incidence of TEP in cohort 1 and 2 was 10.1% and 18.2% (p .03 Fisher's exact test). Median onset of TEP was 12.4 vs 6.4 weeks (wks) in cohort 1 and 2 (p 0.005 log rank). Only TE HTN and increased creatinine were significantly associated with TEP in a stratified logistic regression (table). Median time on AA-TKIs in pts with (TEP +) and without TEP (TEP-) was 19.3 vs 16.0 wks (cohort 1), and 23.5 vs 20.6 wks (cohort 2). Neither renal nor cardiovascular nor thromboembolic complications were more common in TEP + vs TEP – pts. G3 TEP caused treatment discontinuation in 2 pts (cohort 1). **Conclusions:** In this population, TEP was more common and began earlier if CT was added to AA-TKIs . TEP was associated with other AA-related effects but was not predicted by BL variables evaluated. It rarely caused treatment discontinuation, did not affect time on treatment, and had little clinical impact.

| | TE hypertension | | ↑ Creatinine | |
|---|---|---|---|---|
| | OR (CL) | p | OR (CL) | p |
| **Univariate** | 3.32 (1.90 - 5.80) | <0.0001 | 1.92 (1.06 - 3.48) | 0.03 |
| **Multivariate** | 4.00 (2.18 - 7.35) | <0.0001 | 2.41 (1.23 – 4.72) | 0.01 |

Abbreviations: OR, odds ratio; CL, 95% confidence limits.

**11127 General Poster Session (Board #409), Sat, 1:15 PM-5:00 PM**

**Essential experimental steps and estimates of renal carcinoma initiating cells.** *Presenting Author: Craig Gedye, Ontario Cancer Institute, Toronto, ON, Canada*

**Background**: Rare cancer stem cells (CSC), proposed to be solely responsible for tumor propagation and re-initiation, are functionally identified as tumor-initiating cells (TIC) from *ex vivo* tumors using xenotransplantation and clonogenic limiting dilution assays (LDA). TIC have not previously been described from *ex vivo*human clear cell renal cell carcinoma (ccRCC). **Methods**: Primary human ccRCC samples (n=120) from patients undergoing nephrectomy were processed and implanted as subcapsular fragments or cell suspension injection LDAs with Matrigel in NOD/SCID/IL2R$\gamma^{-/-}$ (NSG) mice, and observed for at least 6 months. *In vitro* clonogenic LDAs assays were performed from primary cell suspensions and ccRCC cell lines. LDAs were supplemented with human stromal cells and proteins, and the Y-26732 ROCK inhibitor. Multiparametric flow cytometry and immunofluorescence were used to investigate tumor heterogeneity and cell viability. **Results**: ccRCC TIC appeared rare from injected suspensions, but xenografts engrafted frequently from tiny fragments, and clonogenic frequencies were $10^3$-$10^4$greater than TIC frequencies, suggesting that LDAs underestimated ccRCC tumor cell potential. We systematically identified multiple methodological steps that distort quantitation and identification of ccRCC TIC. For example cell viability was highly variable prior to processing, disaggregation itself destroyed up to 99% of tumor cells, standard assays substantially overestimated tumor cell viability in suspensions, and supplementation with human extracellular cells or proteins, or inhibition of anoikis by Y-26732 increased clonogenic and TIC frequencies in cell lines and primary ccRCC suspensions. Annexin-V staining revealed that tumor cells were more apoptotic then normal stromal cells, and that tumor cells positive for CD44 (a putative CSC marker) were more viable than CD44- tumor cells. **Conclusions**: We describe multiple, unappreciated and largely unavoidable observational errors in essential methods used to study TIC in ccRCC. ccRCC TIC may be more common than appreciated. Re-examination of the CSC hypothesis in other solid tumors is warranted in view of these previously unexplored methodological biases.

**11128 General Poster Session (Board #410), Sat, 1:15 PM-5:00 PM**

**RANKL circulating levels in the evaluation of bone response in breast cancer (BC) patients.** *Presenting Author: Toni Ibrahim, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) s.r.l., IRCCS - Osteoncology and Rare Tumors Center, Meldola, Italy*

**Background:** Bone Metastases (BM) are responsible of the high morbidity, low quality of life and poor prognosis of patients with BC. The evaluation of bone response to treatment is still controversial. **Methods:** This is a prospective study on 36 consecutive BC patients with BM for the evaluation of RANK, RANKL and OPG transcripts by Real-Time PCR and NTX levels by ELISA. Patients enrolled had at first diagnosis of bone metastases and had not previously undergone bone targeted treatment. They underwent the standard Zoledronic Acid schedule of a 4-mg infusion every 28 days and standard antitumor therapy. Patients were monitored for about 1 year and blood samples were collected before the first infusion of ZA and every 4 months. The primary aim was to study the predictive role of different circulating markers in the response to ZA respect to objective response (MD Anderson criteria). **Results:** The NTX levels were not different in patients that underwent to progression respect to those with stable disease or partial response to ZA Treatment. Instead a decrease of 30% and 15% was observed in OPG and RANKL levels in non responders patients. ROC curves evaluation for all markers showed RANKL was the most accurate, with an AUC of 0.70 (95%CI 0.48-0.93). We observed for RANKL/OPG an AUC of 0.64 (95%CI 0.44-0.84) and for NTX an AUC of 0.60 (95%CI 0.38-0.82). Considering as a cut off a variation of markers of at least 25%, the positive predictive value (PPV) for RANK was 26.6%, 9.1 for RANKL, 30 for OPG and 13.3 for the ratio RANKL/OPG. NPV for these markers ranged from 79.2 to 84.6 %. NTX PPV and NPV were respectively 0 and 84.6%. **Conclusions:** The most accurate marker for the evaluation of bone response was RANKL, the key molecule in the pathogenesis of BM and the target of Denosumab. NTX, the marker most used up to now, failed to show a predictive power of response with aspecific decrease both in responder and non responder patients. Further research should be done to improve our knowledge in this field.

**11129 General Poster Session (Board #411), Sat, 1:15 PM-5:00 PM**

**Association of stromal cell gene expression with response to neoadjuvant chemotherapy in locally advanced breast cancer.** *Presenting Author: Rene Aloisio da Costa Vieira, Hospital de Cancer de Barretos, Barretos, São Paulo, Brazil, São Paulo, Brazil*

**Background:** There is increasing evidence that breast cancer behavior is a reflection of an interactive signaling between the malignant epithelial compartment and the surrounding microenvironment. A high stromal gene expression, characterizing a reactive stroma, was associated with resistance to neoadjuvant chemotherapy, in indirect analysis. Our aim was to detect a stromal cell signature associated with response to neoadjuvant chemotherapy in locally advanced breast cancer, using a direct approach, consisting of stromal cell selection, through laser microdissection. **Methods:** Twenty one patients treated at Hospital de Câncer de Barretos were included. Patients were diagnosed with invasive ductal carcinoma, except one (lobular invasive carcinoma); median age was 44.5 years; all presented stage III disease; mean tumor dimension was 6.89 cm. Eleven tumors were luminal HER2 negative; 5 HER2 positive [3 ER(+); 2 ER(-)] and 5 triple negative. All patients were submitted to neoadjuvant chemotherapy (4AC followed by paclitaxel). Response was defined as down staging to a maximum pT1pN0 and according to these criteria, seven patients had a responsive disease. Pre-chemotherapy samples, after stromal cell selection through LCM, were analyzed in an Agilent microarray platform. Expression levels were evaluated using MEV software (t-test with Bonferroni correction). **Results:** Twenty three sequences were found differentially expressed, 16 more expressed in stromal cells from down staging samples (responsive) and 7 more expressed in stromal cells from non-down staging (non-responsive) samples, including 17 known genes. Unsupervised hierarchical clustering and bootstrapping using these sequences identified two branches with high confidence, one including 6/7 down staging (responsive) samples and the other including all non-down staging (non-responsive) samples. **Conclusions:** Breast cancer stromal cells transcriptional profile may separate tumors with major response from non-responsive to neoadjuvant chemotherapy, indicating these cells may be involved in chemosensitivity. These findings however, need to be confirmed in an extended group of samples.

**11130 General Poster Session (Board #412), Sat, 1:15 PM-5:00 PM**

**Patient-derived xenografts from breast cancer patients before and after neoadjuvant chemotherapy: A prospective study.** *Presenting Author: Judy Caroline Boughey, Mayo Clinic, Rochester, MN*

**Background:** Use of next generation sequencing (NGS) in the neoadjuvant setting results in identification of drug targets/pathways associated with chemotherapy resistance. PDX may be superior to cell line models for validation given their similarity to parental tumors. There are no data on PDX from percutaneous needle biopsy (PNB) prior to chemotherapy or from residual disease after neoadjuvant chemotherapy. **Methods:** The Breast Cancer Genome Guided Therapy Study (BEAUTY) is a prospective study of high-risk breast cancer patients (pts) treated with neoadjuvant paclitaxel +/- trastuzumab followed by anthracycline based chemotherapy. PNB at baseline and surgical residual disease after chemotherapy are obtained for NGS and PDX. Tumors were implanted in flanks of estradiol supplemented NOD-SCID or NSG mice. Definitions: outgrowth rate - % pts with 1+ PDX tumor volume >50 mm3, take rate - % pts with 1+ stably transplanted PDX. **Results:** Pretreatment PNB from 83 unique pts were implanted in 266 mice (2-4 mice/pt) from 3/2012-7/2013. PDX outgrowth rate was 37.3% (31/83) and take rate 31.3% (26/83) Take rates were triple negative (TN) 51.9% (14/27), ER+/Her2+ 41.7% (5/12), ER-/Her2+ 27.3% (3/11), Luminal B 17.4% (4/23) and Luminal A 0% (0/10) and did not differ by Ki67. Histological assessment of the first 8 PDX demonstrated similarity to parent tumor in histology (ductal tumors-8/8) and grade (7/8). Tumor subtype in the PDX was concordant in TN tumors (5/5); however ER expression was lost in PDXs from Luminal B tumors (2/2). Residual tumor at surgery from 17 pts was injected into 83 mice (median 5 mice/pt). Outgrowth rate was 35% (6/17) and take rate 17% (3/17). All were TN grade III tumors with Ki67 ≥90% at surgery. PDXs generated were concordant with the residual disease histology, tumor subtype and grade. **Conclusions:** These are the first data to show PDX generated in the neoadjuvant setting both before and after chemotherapy. PDX take rate varies by tumor subtype with highest take in TN and ER+/Her2+ tumors. Early data suggest that the ER expression may be lost in PDX from luminal B tumors. The generation of PDX from tumors resistant to chemotherapy may provide an important resource for drug testing and development. Clinical trial information: NCT02022202.

**11131 General Poster Session (Board #413), Sat, 1:15 PM-5:00 PM**

**Immune responses induced by the TLR-4 agonist-based adjuvant prothymosin alpha.** *Presenting Author: Pinelopi Samara, Department of Animal and Human Physiology, Faculty of Biology, University of Athens, Athens, Greece*

**Background:** The immunomodulator prothymosin $\alpha$ (proT$\alpha$) stimulates immune subpopulations via generating an optimized cytokine milieu. The decapeptide proT$\alpha$(100-109) restores the deficient immune responses of cancer patients *in vitro* equally well to proT$\alpha$. ProT$\alpha$(100-109) and proT$\alpha$ ligate TLR-4, signal through TRIF- and MyD88-dependent pathways, promote the phenotypic and functional maturation of dendritic cells. These elicit $T_H1$-type immune responses and prime tumor antigen-reactive T cell functions. We assessed whether proT$\alpha$(100-109) and proT$\alpha$ can function similarly *in vivo*. **Methods:** PBMCs and cells from various cancer lines incubated with proT$\alpha$(100-109) or proT$\alpha$ were tested for induction of toxicity/apoptosis by MTT and Annexin V/PI staining. C57BL/6 mice were subcutaneously inoculated with syngeneic melanoma B16.F1 cells and upon palpable tumor formation were intraperitoneally treated with 2 cycles of GM-CSF, proT$\alpha$(100-109) or proT$\alpha$, in conjunction with a B16.F1-specific peptide extract (AWE). Tumor growth and animal survival were monitored. Splenocytes from selected animals were tested for their *ex vivo* cytotoxicity by $^{51}$Cr-release assay and CD107 expression. Serum concentrations of IFN-$\gamma$ and IL-4 were determined. **Results:** ProT$\alpha$(100-109) and proT$\alpha$ are not cytotoxic to normal or cancer cells and do not induce PBMC or cancer cell apoptosis/necrosis. In agreement with our *in vitro* data, both peptides when administered therapeutically in melanoma-bearing mice in the presence of cancer antigens, retard tumor growth and prolong animals' survival by 25 days. *Ex vivo* cytotoxicity of mouse splenocytes verified the induction of B16.F1-specific and non-specific responses, mediated by activated cytotoxic T and NK/LAK lymphocytes, respectively. Sera from proT$\alpha$(100-109) or proT$\alpha$-treated animals contained more IFN-$\gamma$, whereas IL-4 concentration was marginally increased. **Conclusions:** We propose that the TLR-4 ligands proT$\alpha$ and its immunoactive decapeptide proT$\alpha$(100-109), induce $T_H1$-biased immune responses to coadministered tumor antigens, both *in vitro* and *in vivo*. As they are non-toxic to normal cells, their adjuvanticity to orchestrate anti-tumor immune responses may eventually be used therapeutically.

**TPS11132 General Poster Session (Board #414A), Sat, 1:15 PM-5:00 PM**

**DETECT III/IV: Two combined clinical trials based on the phenotype of circulating tumor cells (CTCs).** *Presenting Author: Susanne Albrecht, Universitätsfrauenklinik Ulm, Ulm, Germany*

**Background:** Although the prognostic value of CTC enumeration in metastatic breast cancer (MBC) is well understood, the value of taking into account the molecular characteristics of CTCs in treatment decision requires further investigation. Trial Design: The DETECT studies are prospective, multicenter, open-label clinical trials designed for patients with HER2-negative MBC and CTCs in the peripheral blood. DETECT III is a two-arm, phase III study for patients with HER2-positive CTCs, randomized to physician's choice chemotherapy with or without additional HER2-targeted treatment with lapatinib. DETECT IV is a single-arm phase-II study including postmenopausal women with hormone-receptor-positive, HER2-negative MBC and HER2-negative CTCs that will be treated with the mTOR-inhibitor everolimus in combination with an endocrine therapy of physician's choice. Specific aims: The primary objective of both trials is to estimate the clinical efficacy of treatments, assessed by the CTC clearance rate for DETECT III and progression-free survival (PFS) for DETECT IV. Present and target accrual: Overall, about 2000 MBC patients with a HER2-negative primary tumor will have to be screened to be able to include 120 patients with HER2-positive CTCs for DETECT III (started in February 2012) and 400 patients with HER2-negative CTCs for DETECT IV (started in December 2013). So far, 751 patients have been screened for CTCs. **Methods:** Prevalence of CTCs at various time points as well as the HER2 status of CTCs will be determined using the FDA-approved CellSearch System (Veridex, USA). Survival endpoints will be estimated using the Kaplan-Meier method. Perspectives: The DETECT III trial is the first study in which treatment is based on phenotypic characteristics of CTCs. If this trial succeeds in proving efficacy of lapatinib in patients with HER2-negative primary tumor but HER2-positive CTCs, it may lead to new treatment strategies for MBC. DETECT IV complements DETECT III with regard to additional therapy indications. The innovative study concept of these clinical trials with therapy decisions being based on prevalence and molecular phenotypes of CTCs is an important step towards a more personalized cancer treatment for MBC. Clinical trial information: NCT01619111/ NCT02035813.

**TPS11133 General Poster Session (Board #414B), Sat, 1:15 PM-5:00 PM**

**Pharmacist-led lung cancer biomarker detection.** *Presenting Author: Emer Ann Sheridan, University of Huddersfield, Huddersfield, England*

**Background:** Patients at risk of lung cancer may have subclinical disease present for years before diagnosis. Exhaled breath condensate (EBC) is water vapour which contains aerosolized particles in which a large number of metabolites are detectable. Lung malignancy, inflammation and therapeutic intervention influence these biomolecules. This project aims to use EBC as a non-invasive means of detecting biomarkers, differentiating between lung malignancy, lung inflammatory disorders and the generally healthy population. In doing so, there is potential for early diagnosis of lung cancer in a public health setting. This will involve the design of a novel care pathway where pharmacists administer non-invasive breath tests to at-risk patients and flag up and distinguish early signs of malignant or inflammatory lung disease. **Methods:** A cohort of histologically confirmed lung cancer patients (both SCLC and NSCLC) a cohort of patients with inflammatory lung disease (asthma and COPD) and a control cohort of volunteers from the general population will be recruited to a proof of principle study aiming to collect breath samples. These will be profiled for mRNA expression of a range of candidate biomarkers using both custom and commercially available qRT-PCR pathway arrays. This will be extended to both genomic and proteomic analysis. A putative biomarker signature has been identified in silico using Gene Expression Omnibus and Oncomine databases. To aid differentiation between stable or progressing COPD/asthma and early signs of lung cancer, we have incorporated groups of tumour biomarkers with increased expression in lung cancer e.g., those associated with the hypoxic tumour microenvironment. This theoretical signature comprises approximately 100 genes. These genes have all been mined with a threshold of at least a two fold change and statistical significance of $P = 10^{-4}$. For this comparative study a multiple ANOVA approach will be utilised. Potentially a large number of outcomes may be considered, variable reduction techniques (e.g. principal component analysis) will be utilised to reduce the dimensionality of the study. The study will run alongside chemical analysis, working towards a highly specific, selective and combined biological and chemical signature.

**TPS11134 General Poster Session (Board #415A), Sat, 1:15 PM-5:00 PM**

**GEFCAPI 04: A phase III trial comparing a treatment oriented by a molecular analysis with CancerTYPE ID test to cisplatin-gemcitabine in patients with carcinoma of an unknown primary (CUP).** *Presenting Author: Geraldine Martineau, Clinical Research Department, Institut Gustave Roussy, Villejuif, France*

**Background:** Despite advances in tumor imaging and pathology, patients with CUP still account for about 2-3% of all cancer patients in European registries. Two randomized phase II trials: GEFCAPI01 (Culine, J Clin Oncol 2003) and GEFCAPI02 (Gross-Goupil, Eur J Cancer 2012) demonstrated that the combination of cisplatin and gemcitabine has anticancer activity and can be regarded as an acceptable comparator for new treatments. Recently, several groups have shown that molecular analysis can identify a likely primary cancer in up to 80% of patients with CUPs. This trial aims to assess whether the use of a molecular test-oriented systemic treatment improves progression-free survival (PFS) over cisplatin-gemcitabine in patients with CUPs. **Methods:** GEFCAPI04 is a European randomized, phase III study comparing a diagnostic and therapeutic strategy based on molecular analysis followed by suspected primary cancer tailored specific therapy, to an empiric strategy by cisplatin and gemcitabin (NCT01540058). It was initiated in March 2012. Eligibility criteria include: patients presenting with CUP, confirmed by histo-pathological analysis, diagnostic work-up in keeping with guidelines (Lesimple et al., 2003), good or poor prognosis CUP, CUP not belonging to a subgroup requiring a specific treatment, no previous chemotherapy. Patients are stratified by prognostic factors (performance status and serum LDH level) and center. 223 patients will be randomized 1:1 to cisplatin-gemcitabine (A) or treatment according to the result of the molecular analysis (B). The primary endpoint is PFS based on central independent review. Imaging will be undertaken every 6 weeks, in each arm. A 0.05 level two-sided log-rank test for equality of PFS curves will have 80% power to detect a 3 months difference between PFS medians (5 months in group A and 8 months in Group B, (HR=0.62). Secondary endpoints include: overall survival, objective response rate, tolerance, and economic evaluation. The study is recruiting patients and 30 patients are included. Clinical trial information: NCT01540058.

**TPS11135 General Poster Session (Board #415B), Sat, 1:15 PM-5:00 PM**

**A phase I study of the safety and activation of a cathepsin-activatable fluorescent cancer-specific probe LUM015.** *Presenting Author: Melodi Javid Whitley, Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC*

**Background:** Local recurrence is a common mode of failure for patients with cancer. Intra-operative detection of microscopic residual disease in the tumor bed could be used to decrease the risk of a positive surgical margin, reduce the rate of re-excision, and tailor adjuvant therapy. Previously, we utilized a primary mouse model of soft tissue sarcoma (STS) to develop a novel imaging system to detect cancer (*Cancer.* 2012). Because cathepsin proteases are preferentially expressed in tumors compared to normal tissue, we used cathepsin-activatable fluorescent imaging agents with a novel imaging device for intra-operative assessment of residual cancer within tumor beds of mice. We demonstrated that residual fluorescence detected in the tumor bed by the imaging system correlates with local recurrence and that image guided surgery improves outcomes for mice with positive residual fluorescence. LUM015 is a pegylated cathepsin-activated imaging agent containing a Cy5 fluorophore attached to a quencher by a polypeptide linker. Upon cleavage of the linker by cathepsin proteases, the quencher is released, allowing fluorescence to be detected. A phase I clinical trial is open at Duke to test the safety of LUM015 (NCT01626066). **Methods:** This open-label nonrandomized trial compares up to four dose cohorts of LUM015 (cohorts -1 to 3: 0.25, 0.5, 1 and 1.5 mg/kg) in order to determine a safe and recommended phase II dose of LUM015 that labels tumors in human patients. Subjects with STS or breast cancer receive LUM015 by peripheral intravenous injection 2-72 hours prior to scheduled surgical resection. Safety evaluations prior to and during the 24-hour period after injection consist of vital signs, ECG, PFTs, blood and urine studies and documentation of any adverse pharmacological activity (APA). This evaluation is repeated at 2, 7 and 14 days after study agent delivery and an end of study APA assessment occurs 30-35 days after surgery. Pharmacokinetic parameters are also determined. Correlative studies include quantitative imaging as well as histological and biochemical analyses of the resected tissues. To date, cohorts 1 and 2 (n=9 patients) have been enrolled without APA. Enrollment in cohort 3 began in January 2014. Clinical trial information: NCT01626066.

**TPS11136 General Poster Session (Board #416A), Sat, 1:15 PM-5:00 PM**

**A prospective study to compare qPCR to IHC and FISH for the detection of anaplastic lymphoma kinase (ALK) fusions in FFPE specimens from NSCLC patients (*PCRTALK*).** *Presenting Author: David Richard Hout, Insight Genetics, Inc., Nashville, TN*

**Background:** Lung cancer is the most common cause of cancer-related deaths in North America. A number of pharmaceutical firms currently have therapies that target ALK-driven lung cancers in development, with the first-in-class FDA-approved ALK inhibitor Xalkori (crizotinib, Pfizer) demonstrating excellent anti-tumor responses without significant toxicities. There is now substantial interest in ensuring the accurate identification of those NSCLC patients who harbor ALK fusions. The *ALK qPCR assay* is a quantitative real-time PCR assay that offers high throughput, 24-48 hour TAT, and easily interpretable results. We are performing a clinical diagnostic trial, PCRTALK (PCR tumor ALK), with the primary objective of this trial being to unequivocally demonstrate the performance of the *ALK qPCR assay*against current ALK testing modalities in screening FFPE lung cancer biopsy specimens. The study is recruiting multiple clinical centers throughout Canada for patient enrollment. Once PCRTALK has been completed, our goal is to accomplish the following: (1) the trial will provide clinically relevant data on which types of lung cancer biopsies (bronchoscopy, FNA, CNB, pleural fluid thoracentesis) provide sufficient tissue for the different modalities of ALK testing and report on the number of cases rejected for ALK testing by IHC and FISH due to insufficient tissue; and (2) provide therapeutic outcome data for cases with discordant ALK diagnostic results. A second arm of the study is to conduct a correlative study analyzing both matched FFPE and blood collected from NSCLC patients using various non-invasive methodologies. **Methods:** The study will proceed according to the following work flow: (1) ALK IHC (ALK IHC-5A4, Leica Biosystems) conducted by BCCA laboratories; (2) 72 individual ALK IHC 5A4-positives and 72 ALK IHC 5A4-negatives selected according to their respective IHC scores and reflexed to 3 - 5; (3) ALK FISH (Abbott Diagnostics) performed on all 144 specimens; (4) The ALK qPCR assay performed on all 144 specimens; and (5) Sanger and/or NGS to determine true status. Initial PCRTALK clinical trial data will be presented together with conclusions based on the results. Clinical trial information: NCT02010047.

## Publication-Only Abstracts

Publication-only abstracts, which are selected to be published in conjunction with the 2014 Annual Meeting, but not to be presented at the Meeting, can be found online in full-text, fully searchable versions at abstract.asco.org and JCO.org.

The publication-only abstracts are not included in the print volume, but are citable to this *Journal of Clinical Oncology* supplement. Please refer to the following example when citing publication-only abstracts:

J Clin Oncol 32, 2014 (suppl; abstr e12000)

# Abstract Author Index

## Numerals refer to abstract number

*Accepted abstracts not presented at the meeting (designated by e) are available in full-text versions on ASCO.org.*

## B

## C

## D

## E

## F

## G

## H

## I

## J

## K

## L

## M

## N

## O

## P

## Q

## R

## S

## T

## U

## V

## W

## X



## Y

## Z

## Ö

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# Errata

The Editor of the *2014 ASCO Annual Meeting Proceedings* has authorized correction of the following errors:

**Abstract 5509**

After publication of the abstract, the authors discovered an error in matching clinical data to molecular subgroups. The changes are as follows:

1. The proliferative and mesenchymal molecular subgroups have the largest improvement of PFS when treated with bevacizumab. The mesenchymal and differentiated groups showed the largest improvements in the original abstract.
2. Patients in the proliferative group who received bevacizumab had a 10-month improvement in PFS, which is statistically significant. This difference was not statistically significant in the original abstract.
3. Analysis of overall survival was added, and shows the greatest advantage in the proliferative and mesenchymal groups, similar to PFS results. OS was not included in original abstract.
4. Non-ovarian cancer cases have been removed based on centralized pathology review. All cases were included in original analysis.

**Abstract 8043**

After publication of the Proceedings Part I, it was discovered that abstract 8043 was not included in the body of the printed edition. The abstract appears below:

**E7080 (lenvatinib) in addition to best supportive care (BSC) versus BSC alone in third-line or greater nonsquamous, non-small cell lung cancer (NSCLC).** *Presenting author: Libor Havel, 3rd Medical Faculty, Charles University, Hospital Bulovka, Czech Republic*

**Background:** Lenvatinib (E7080; LEN) is an oral, tyrosine kinase inhibitor targeting VEGFR1-3, FGFR1-4, RET, KIT, and PDGFR$\beta$ with evidence of antitumor activity in a broad range of solid tumors. Currently there is an unmet medical need for treatments in third-line or greater NSCLC patients (pts). **Methods:** This study was a double-blind, placebo-controlled, multicenter, randomized Phase II study of LEN 24 mg PO once daily + BSC vs. placebo (PBO) + BSC (2:1 randomization). Pts with nonsquamous NSCLC who had failed $\geq$ 2 two systemic anticancer regimens were enrolled. Prior erlotinib or gefitinib was required for pts with known EGFR-activating mutations. The primary endpoint was overall survival (OS). Progression free survival (PFS), overall response rate (ORR), and disease control rate (DCR) were based on investigator assessment. Efficacy endpoints were estimated via Kaplan-Meier. **Results:** 135 pts enrolled in the study. Per protocol, the study was unblinded and analyzed after 90 deaths. 76% received $\geq$ 3 prior anti-cancer regimens and 85% received prior erlotinib or gefitinib (similar rates in each arm). A summary of efficacy and safety is presented by study arm (Table). In a post hoc analysis, a similar treatment effect was observed among subjects with wild-type EGFR. **Conclusions:** LEN in addition to BSC demonstrated a clinically meaningful improvement in both OS and PFS ($\sim$ 3 months) in heavily pretreated patients with NSCLC, including those who received prior EGFR inhibitors. LEN was generally well-tolerated, with an AE profile consistent with observed LEN monotherapy studies. These data warrant additional evaluation of LEN in this population.

| Median value or percentage | LEN + BSC (n=89) | PBO + BSC (n=46) | P value |
|---|---|---|---|
| OS, wks (95% CI) | 38.4 (26.57, 47.86)<br>N=58 events | 24.1 (15.29, 36.43)<br>N=37 events | p = 0.065 |
| PFS, weeks (95% CI) | 20.9 (15.86, 23.86)<br>N=73 events | 7.9 (7.43, 8.14)<br>N=45 events | p < 0.001 |
| ORR | 10.1% | 2.2% | 0.1635 |
| DCR | 42.7% | 19.6% | 0.0079 |
| Treatment duration (days) | 113 | 58 | Not compared (NC) |
| Serious adverse events (AEs) | 52% | 46% | NC |
| Grade 3/grade 4 AEs: | 69% | 50% | NC |
| Hypertension | 17% | 0% | |
| Dyspnea | 9% | 13% | |
| Pneumonia | 9% | 6.5% | |
| Study discontinuation due to AE | 24.7% | 17.4% | NC |

*All errors have been corrected in the online versions of the abstracts on JCO.org and ASCO.org. This errata is updated on a rolling basis, as needed, and is available online at http://meetinglibrary.asco.org/errata.*

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16